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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

e-Therapy Interventions for the Treatment of Post-Traumatic Stress Disorder: A Review of Clinical Evidence

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	June 13, 2018
Report Length:	31 Pages

CADTH

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Cite As: *e-Therapy Interventions for the Treatment of Post-Traumatic Stress Disorder: A Review of Clinical Evidence.* Ottawa: CADTH; 2018 Jun. (CADTH rapid response report: summary with critical appraisal).

Acknowledgments:

ISSN: 1922-8147 (online)

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

Abbreviations

AUDIT	Alcohol Use Disorders Identification test
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BSI	Brief Symptom Inventory
CAPS	Clinician-Administered PTSD scale
CBT	cognitive behavioral therapy
iCBT	internet based cognitive behavioral therapy
CES-D	Center for Epidemiological studies – Depression scale
FDAS	Four Dimensional Anxiety Scale
GSE	General Self Efficacy scale
PCL	PTSD checkllist
PCL-C	PTSD checklist – Civilian version
PDS	Posttraumatic Diagnostic Scale
PHQ	Patient Health Questionnaire
PSS-I	PTSD Symptom Scale Interview
PTSD	posttraumatic stress disorder
QoL	quality of life
SDS	Sheehan Disability Scale
SMD	Standardized mean difference
SSQ	Social Support Questionnaire
TAU	Treatment as usual
WL	waitlist

Context and Policy Issues

Posttraumatic stress disorder (PTSD) is a debilitating condition which generally results from exposure to a traumatic event or a series of traumatic events.[1,2] It is characterized by intrusive thoughts, hyperarousal, avoidance of reminders of trauma, negative thoughts or feelings.[3-5] It has been reported that the lifetime prevalence rates of PTSD vary between 5% and 55%.[3] Military service members and first responders are found to be at high risk of PTSD.[1]

Psychotherapies have been used for the treatment of PTSD. The majority of these therapies were designed to be provided face-to-face by trained therapists and some of the therapies are trauma-focused.[4,6] These therapies may involve substantial input from the therapist, require substantial time commitments, and may be associated with the stigma of attending a mental health clinic.[7] In recent times, psychotherapies that can be offered remotely have been investigated for the treatment of mental health conditions. These include therapies with telecommunication offered via videoconferencing, telephone, e-mail, and internet.[8]

It has been suggested that for treatment of PTSD, internet based treatment options may have several advantages such as increased accessibility for individuals residing in remote areas and those with mobility restrictions; acceptability by individuals with fear of stigmatization; opportunity to avail the treatment at one's own time; and several individuals can avail the treatment at the same time.[1,6]

The purpose of this review is to assess the comparative clinical effectiveness of e-therapies (such as interventions that are based on the use of the internet, e-mail, or smartphone) for the treatment of PTSD.

Research Question

What is the clinical effectiveness of e-Therapy interventions for the treatment of post-traumatic stress disorder?

Key Findings

There is a suggestion that e-Therapy with therapist support when compared to waitlist, treatment as usual, or other active treatment, may be a promising treatment option of managing PTSD symptoms. However, the between group differences were not always statistically significant. Findings need to be interpreted in the light of limitations such as small sample size, variable study quality, and limited quantity of studies for a particular comparison.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, Medline via OVID, PsycINFO via OVID, 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. No filters were applied to limit the retrieval by study type. The search was also limited to English language documents published between Jan 1, 2015 and May 15, 2018.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

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 post-traumatic stress disorder (PTSD) with or without co-morbid mental health conditions.
Intervention	e-Therapy interventions that are not solely videochat or telephone-based but that include therapist contact: - Online, internet, web, mobile based therapy for PTSD
Comparator	In person treatment Videochat or videoconference therapy Telehealth Wait list Treatment as Usual
Outcomes	Improvements in symptoms (based on psychometric scales, based on self-report and clinician report) Reductions in symptoms, improved functioning, drop-out rates/attrition rates (particularly compared to in-person treatment) Reliable treatment Recovery
Study Designs	Health technology assessments, systematic reviews, meta-analyses, and randomized controlled trials (RCTs)

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2015. Systematic reviews with all included relevant studies included in a selected systematic review, unless it presented additional relevant information were also excluded. Individual studies that were included in an included systematic review were excluded unless a later publication of the study reported long term results. Studies on telehealth and video conferencing and without an e-therapy program were excluded. Studies were excluded if they did not report a diagnosis of PTSD or a PTSD measure for the study population. Studies on e-therapy combined with other treatments were excluded. e-therapies that did not include therapist support were excluded also.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using AMSTAR 2[9] and randomized controlled trials were critically appraised using the Downs and Black checklist.[10] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were narratively described.

Summary of Evidence

Quantity of Research Available

A total of 370 citations were identified in the literature search. Following screening of titles and abstracts, 324 citations were excluded and 46 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 38 publications were excluded for various reasons, while eight publications met the inclusion criteria and were included in this report. These eight publications comprised two systematic reviews[4,6] and six RCTs.[7,11-15] Appendix 1 presents the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Two relevant systematic review[4,6] and six relevant RCTs[7,11-15] were identified.

Study characteristics are summarized below and details are available in Appendix 2, Tables 2 to 4.

Study Design

The two included systematic reviews[4,6] both had a broad objectives and included e-therapies with and without therapist assistance; only RCTs relevant (i.e. with therapist assistance) for our report are included here. One systematic review[4] included 24 relevant RCTs, of which 22 RCTs were published between 2001 and 2016, and two RCTs were reported as unpublished. The second systematic review[6] included nine relevant RCTs published between 2001 and 2014. Of note, although all RCTs included in this systematic review[6] were included in the more recent systematic review,[4] this systematic review[6] was included as it presented some additional information.

Six relevant RCTs[7,11-15] were identified. Due to the nature of the studies, blinding of patient and therapist were not possible.

Country of Origin

One systematic review,[4] from the UK, was published in 2017; and the second systematic review, from the Netherlands, was published in 2016.

Of the six RCTs, four RCTs were published in 2017, one each conducted in Germany,[13] Sweden, [11] the UK,[7] and the USA;[12] and two RCTs were published in 2016, and both were conducted in the USA.[14,15]

Patient Population

One systematic review[4] included adult patients who had experienced trauma and had symptoms of PTSD. The patient number in the individual RCTs ranged between 25 and 600, with majority of the studies having fewer than 100 patients. The mean age of the patients ranged between 22 years and 58 years and the proportion of female participants ranged between 14% and 100%. The second systematic review[6] included adult patients with diagnosis of PTSD based on clinician assessment or self-report instrument. The patient number in the individual RCTs ranged between 28 and 228. The mean age and proportion of female patients were not presented.

The six selected RCTs[7,11-15] included adults with PTSD diagnosis. The number of patients in the RCTs ranged between 20 and 94. In the RCTs, mean ages of the patients ranged between 38 years to 71 years; and proportions of female patients ranged between 5% and 100%. Two RCTs[12,15] specifically included veterans.

Interventions and Comparators

The two included systematic reviews[4,6] investigated a variety of treatments. Both systematic reviews included RCTs on e-therapies with therapist assistance, and the e-therapies were compared with waitlist (WL), treatment as usual (TAU), or an active treatment. In addition, the systematic review by Simblett et al.[4] included RCTs on e-therapies with feedback from a discussion forum compared with WL, TAU, or an active treatment. One systematic review[4], including 24 RCTs, reported that in five RCTs the therapist feedback was asynchronous, in one RCT both synchronous and asynchronous therapist feedback was included, and in the remaining RCTs it was not mentioned whether the therapist feedback was synchronous or asynchronous. In the second systematic review,[6] it was not mentioned whether the therapist feedback was synchronous or asynchronous in the included RCTs. In one systematic review[4] the number of sessions varied between three and 18, and the treatment duration varied between six weeks and 12 weeks. In one systematic review[6] } the number of sessions varied between six sessions and 10 sessions, and duration of treatment was not mentioned.

Of the six RCTs, four RCTs[7,11-13] compared therapist guided e-therapy interventions with WL or TAU; and two RCTs[14,15] compared therapist guided e-therapy interventions with a different active treatment. Treatment duration varied between six weeks and 14 weeks, and follow-up times varied between one and 12 months. In one RCT[13] it was mentioned that therapist feedback was asynchronous, and in five RCTs[7,11,12,14,15] it was not mentioned whether therapist feedback was synchronous or asynchronous.

Outcomes

The RCTs in the included systematic reviews[4,6] reported outcomes using several measures for PTSD symptoms and the results in the systematic review were reported as standardized mean differences (SMD),[4] and Hedges' g.[6]

In the included RCTs, various outcome measures were used Measures used for PTSD symptoms include Clinician-Administered PTSD scale (CAPS),[7,12] PTSD checklist – Civilian version (PCL-C),[11,12] Posttraumatic diagnostic scale (PDS),[12,13] and PTSD Symptom Scale – Interview (PSS-I).[14] Measures used for depression include: Beck Depression Inventory (BDI),[7,11,12] Center for Epidemiological Studies – Depression (CES-D).[14] Measures used for anxiety include: Beck Anxiety Inventory (BAI),[7,11,12] and Four Dimensional Anxiety Scale (FDAS)),[14] Measures of several other outcomes include: Alcohol Use Disorder Identification Test (AUDIT),[7] EUROHIS-QoL,[13] General Self-Efficacy scale (GSE),[13] Patient Health Questionnaire (PHQ),[15] PTSD Symptom Scale – Interview (PSS-I),[14] Sheehan Disability Scale (SDS),[7] Social Support Questionnaire (SSQ),[7] and WHO-QoL.[15] Details of these measures are presented in Appendix 2, Table 4. Effect sizes were reported as SMD and Cohen's d. Effect sizes of 0.2, 0.5, and 0.8 are considered as small, medium and large effect respectively.[11]

Summary of Critical Appraisal

Critical appraisal of the studies is summarized below and details are available in Appendix 3, Tables 5 and 6.

Systematic Reviews

In both systematic reviews,[4,6] the objective and inclusion criteria were stated; multiple databases were searched; selection of articles was described; list of included studies was provide; quality assessment was conducted and the studies were found to be of variable quality; and it was mentioned that there were no conflicts of interest. In both systematic reviews, a list of excluded studies was not presented; study characteristics were reported but details were lacking; and it was unclear if data extraction was done in duplicate. Article selection was done in duplicate in one systematic review,[4] and was unclear in one systematic review.[6] Both systematic reviews conducted meta-analysis. However pooled estimates from one systematic review[4] could not be presented in our report as the pooled estimates presented in the Forest plots included RCTs that were not relevant for our report. Though pooled estimates for the subgroup with therapist feedback were reported, the number of comparisons stated for this subgroup analysis did not appear to match the relevant number of comparisons presented in the Forest plots of all included studies. As the Forest plot for the subgroup analysis was not presented, it was therefore not possible to determine which RCTs were included or the reason for the differences in the number of comparisons, hence this pooled estimate was not reported in this review.

Considering that quality of the included studies in the systematic reviews were variable and the study characteristics were not described in detail, findings need to be interpreted with caution.

RCTs

All six RCTs[7,11-15] stated the study objective and inclusion criteria; and described patient characteristics, intervention and outcomes. Exclusion criteria were reported in five RCTs,[7,12-15] and not explicitly mentioned in one RCT.[11] Randomization was done by using various computer generated or statistical methods in five RCTs,[7,11-14] and randomization method was not described in one RCT.[15] Due to the nature of the studies, blinding of patient and therapist were not possible. One RCT[7] mentioned that the assessor was blinded, and in the remaining five RCTs[11-15] it was unclear if the assessor was blinded, hence potential for detection bias cannot be ruled out. In three RCTs[12-14] it was unclear if sample size calculations were undertaken, in two RCTs[11,15] the sample size was reported to be underpowered, and in one RCT[7] the sample size was appropriate. In all RCTs, drop-out rates were reported and appeared to be substantial (Appendix 3, Table 6). Four RCTs[7,11,14,15] conducted ITT analysis, one RCT[12] conducted repeated measures analysis, and one RCT[13] conducted linear mixed-effects analysis. Three RCT reports[11,13,15] mentioned that there were no conflicts of interest. In one RCT[7] conflicts of interest were declared and based on the conflicts, there appeared to be potential for bias. In two RCTs[12,14] there was no mention of conflicts of interest.

Summary of Findings

Findings are summarized below and details are available in Appendix 4, Table 7.

What is the clinical effectiveness of e-Therapy interventions for the treatment of post-traumatic stress disorder?

Patient population: various

The systematic review by Simblett et al.[4] showed that compared with WL or TAU or active treatment, e-Mental Health interventions with therapist feedback resulted in greater

improvements in PTSD symptoms, however the between group difference was not always statistically significant. Between group differences were more often statistically significant in studies comparing e-therapies with WL or TAU, than in studies comparing e-therapies with other active treatments. The SMD in individual RCTs varied between 0.12 and 1.05 (from 14 RCTs). The systematic review by Sijbrandij et al.[6] showed that compared with WL or TAU, e-therapy plus therapist support resulted in better outcomes with respect to PTSD symptoms; the pooled estimate (based on Hedges' g) was 0.89 and was statistically significant, favoring e-therapy. This systematic review[6] showed that there was no statistically significant difference between e-therapy and another active treatment (based on 2 RCTs). Both systematic reviews[4,6] did not report on drop-out rates.

The systematic review by Simblett et al.[4] showed that compared with WL, TAU, or active treatment, e-Mental Health interventions with feedback from a discussion forum (comprising therapist or peer coach) resulted in improvements in PTSD symptoms, however the between group difference was not always statistically significant. The SMD varied between 0.24 and 0.66 (in 3 studies) and was zero (in one study).

The RCT by Cernvall et al.[11] involved parents of children with cancer who had a PTSD diagnosis. This RCT[11] compared internet-based self-help program plus therapist guidance versus WL and there was statistically significant improvement in PTSD symptoms with the internet based program, at post treatment and at 12-month follow up. At posttreatment, drop-out rates were 45.1% in the internet intervention group and 25.9% in the WL group.

The RCT by Knaevelsrud et al.[13] involving older individuals who had experienced childhood trauma, and comparing iCBT with WL, showed a between group difference for PTSD symptoms, GSE and EUROHIS-QoL, favoring iCBT (Cohen's d = 0.42 for PTSD symptoms, 0.38 for GSE, and 0.39 for EUROHIS-Qol). The effects were maintained up to 12 months. Drop-out rates were reported to be 12.8% in iCBT group, and 6.4% in the WL group but were not significantly different between the groups (P = 0.29).

The RCT by Lewis et al.[7] involved patients with diagnosis of PTSD of mild to moderate severity and compared therapist guided internet-based self-help intervention program versus control (delayed treatment). It showed statistically significant between group improvements with respect to PTSD symptoms, anxiety, depression, and functional impairment, favoring the intervention. There were no statistically significant between group differences with respect to alcohol misuse or perception of social support. Drop-out rates at post-treatment were 28.6% in the immediate treatment group and 19.1% in the delayed treatment group.

The RCT by Littleton et al.[14] involved female students (university or college) with diagnosis of rape-related PTSD, and examined two online treatment programs: therapist-guided interactive program and self-help psychoeducational program. Both programs resulted in reductions in PTSD symptoms, depressive, and general anxiety symptoms at post-treatment and at 3-months follow-up. Regression analysis indicated that in terms of PTSD symptoms and general distress there were no statistically significant differences between the two treatment groups in change from pre- to post-treatment, although the change in symptoms was numerically greater among the patients assigned to the therapist-guided program. It was reported that post-treatment assessments were completed by 72.6% of the participants who started the programs.

Patient population: veterans

The RCT by Franklin et al.[12] involved veterans with PTSD diagnosis**,** and compared prolonged exposure (PE) therapy using iPhone based teleconferencing, PE using computer-based teleconferencing (TMH), and TAU (included psychotherapy or medication management). This study showed significant differences in PDS total scores and CAPS total scores between the PE groups and the TAU group, favoring the PE groups. No significant differences were reported between the two PE groups. Drop-out rates were 70% in the iPhone group, 43% in the TMH group and 0% in the TAU group.

The RCT by Possemato et al.[15] included veterans with significant PTSD symptoms resulting from military-related trauma. This study compared the mobile app (PTSD Coach) plus clinician support (CS), with self-managed PTSD Coach (SM). Both treatments (CS and SM) resulted in reduction in PTSD symptoms. Improvements with CS appeared to be greater than that with SM, however the between group difference was not statistically significant. It was reported that 70% of CS group patients and 38% of SM group patients had clinically significant improvements in PCL scores (i.e. reduction of ≥ 10). Patient retention at posttreatment was 100% in the CS group and 80% in the SM group.

In summary, e-therapies with therapist support when compared to WL, TAU, or other active treatment, appear to improve PTSD symptoms, however the between group differences were not always statistically significant.

Limitations

There are several limitations to this review.

There appears to be variability in the way PTSD diagnosis is reported in the systematic reviews. Details of clinical status of patients at treatment initiation was lacking in the in the RCTs included in the systematic reviews. Hence the impact of severity if any, on findings could not be determined.

No systematic review exclusively investigating therapist-guided e-therapy was identified. Pooled estimates from the meta-analyses in one included systematic review[4] could not be reported here, as this systematic review had a broad objective and included in the pooling also studies that were not relevant for our review, hence only SMDs from individual relevant studies in the meta-analysis were reported.

There were variations in the patient populations and the therapies investigated, hence comparison across studies was difficult. Furthermore, the number of RCTs investigating a particular patient population and a particular type of intervention was limited.

Majority of the studies had small sample size (< 100) and were of variable quality.

Findings need to be interpreted in the light of the limitations.

Conclusions and Implications for Decision or Policy Making

Two relevant systematic reviews[4,6] and six relevant RCTs[7,11-15] were identified. e-therapy with therapist support when compared to WL, TAU, or other active treatment, appear to be a promising treatment option for managing PTSD symptoms. However, between treatment group differences were not always statistically significant. Between group differences were more often significant in studies comparing e-therapies with WL or TAU, than in studies

comparing e-therapies with other active treatments. In the majority of studies it was not mentioned if therapist feedback was synchronous or asynchronous, hence impact of synchronicity on outcomes could not be determined. In the majority of studies drop-out rates were substantial and this could impact the findings, the direction of impact is unclear. Definitive conclusions with respect to effectiveness of e-therapies for veterans, is not possible due to the limited quantity of evidence available.

Findings need to be interpreted in the light of limitations reported. Additional studies investigating the use of e-therapies plus therapist support and their associated outcomes in specific populations, are needed to make definitive conclusions.

Extent of treatment success may depend on patient characteristics such as age, type of trauma experienced, level of computer literacy, and educational level, hence a personalized approach may be needed for better outcomes.[7]

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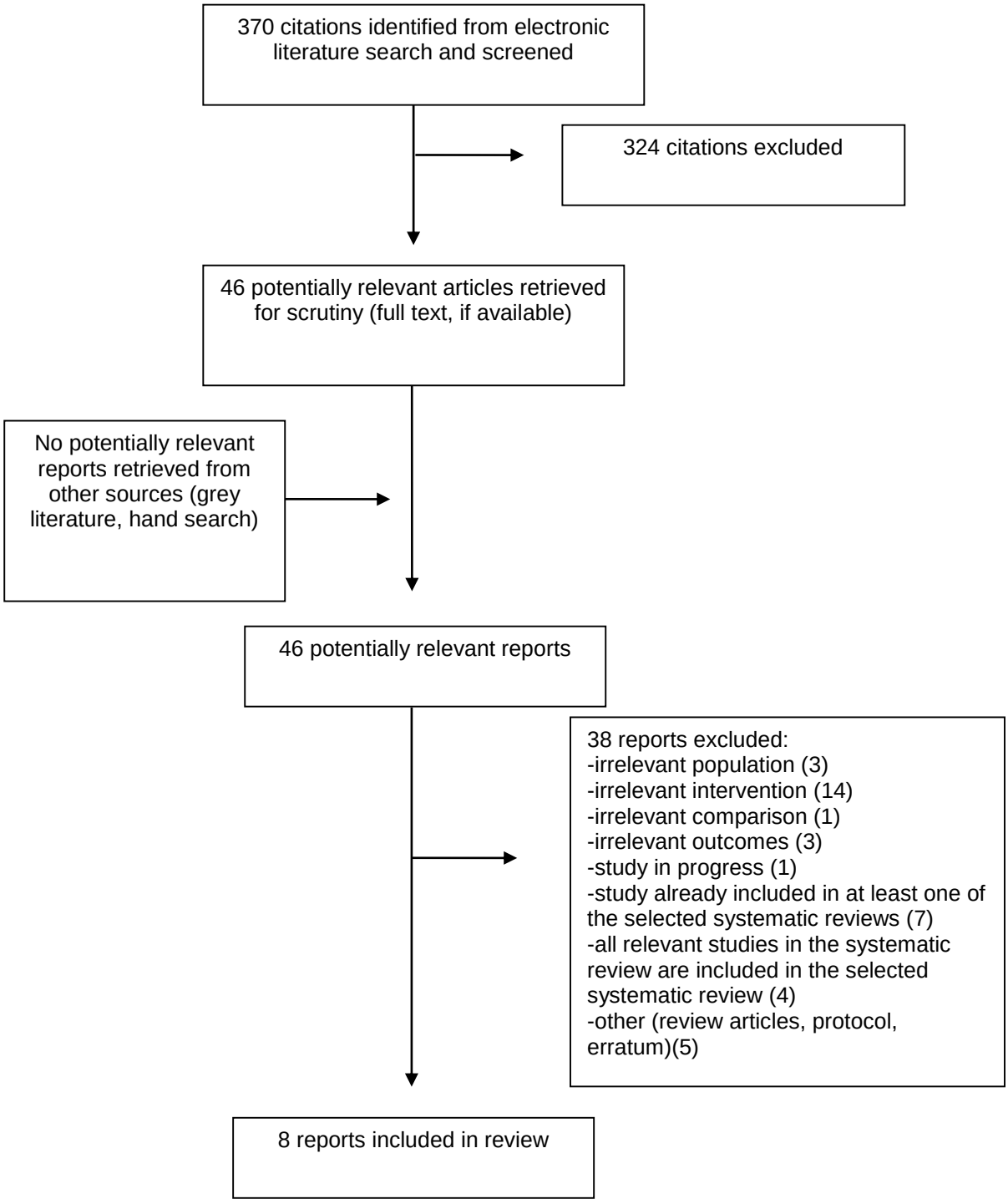
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

Author, year, Country	Study Design	Population Characteristics	Comparison	Outcomes
Sijbrandij,[6] 2016, The Netherlands (Of note, although all RCTs included in this systematic review[6] were included in the more recent systematic review[4], this systematic review[6] was included as it presented some additional information.)	Systematic review and meta-analysis It had a broad focus considering various interventions and included 12 RCTs of which 9 RCTs were relevant for our report and are described here. These RCTs were published between2001 and 2014; with wo RCTs from Australia, 4 RCTs from Europe, 3 RCTs from USA. Aim: To assess the internet-based cognitive behavioral therapy (iCBT) with control therapy (WL or TAU) or other active therapy	Adults with diagnosis of PTSD based on clinician assessment or self-report instrument. Number of patients in the individual studies ranged between 18 and 228 Age: NR (mentioned as adults) % Female: NR Types of trauma experienced by the individuals (in the RCTs) were pregnancy loss (1), bereavement (1), combat or terrorism, (1) and mixed (6) In 5 RCTs the patient group had clinical PTSD diagnosis, and in 4 RCTs the patient group had elevated levels of PTSD symptoms	Intervention (iCBT) versus comparator (WL, TAU or other active therapy) Interventions were internet delivered and based on CBT and were therapist assisted. Session ranged between 6 and 10 sessions. Treatment period not specified.	Outcome measures (CAPS, IES-R, PDS, BDI-II, BSI, IES, SCL-90, PSS-IV, PCL-C, PHQ-9, PSS-IV) (Results reported as Hedge's g) Number of sessions: 6 to 10 Treatment duration: NR
Simblett,[4] 2017, UK	Systematic review and meta-analysis It had a broad focus considering various interventions and included 39 RCTs of which 24 RCTs were relevant for our report and are described here. Of these, 22 RCTs were published between 2001 and 2016 and two studies were indicated as	Adults with experience of a single-event trauma who were administered psychological therapy to treat symptoms of PTSD. Number of patients in the individual studies: 25 to 600 (with majority of studies having <	Interventions included web-based treatments (EW, non TF-CBT, TF-CBT, mindfulness-based treatment) with tailored feedback (delayed or immediate), online discussion forum, or face-to-face session. (Tailored feedback was defined as feedback from a trained facilitator that directly related to the content of the therapeutic intervention. Feedback from licensed clinicians such as psychologist, psychotherapist, psychiatrists or in training clinician.	Severity of PTSD. Measures used: IES, IES-D, IES-R, PCL-5, PCL-C, PCL-M, PDS, PSS, TES (SMD reported) Number of sessions 3 to 18. Treatment duration 6 weeks

Table 2: Characteristics of Included Systematic Reviews

Author, year, Country	Study Design	Population Characteristics	Comparison	Outcomes
	unpublished. Countries in which the RCTs were conducted was not mentioned Aim: To assess e-Mental Health interventions (both web-based and mobile-based) to treat symptoms of PTSD in adults.	100 participants). Mean age in the individual studies (years): 22 to 58 % Female (range): 13.7% to 100%. The patient population comprised : individuals with traumatic experience (3), patients with cancer (4) parents of children with cancer (1), patients who had experienced death or loss of a family member (5), women with postpartum PTSD (1), community-based patients with PTSD (6), and veterans (4)	Online discussion forum was defined as a message board where individuals could post messages and receive tailored feedback from a trained facilitator or peers.) Feedback was from licensed clinical psychologist, other mental health professional or trained peer coach). Number of sessions varied between 3 and 10. Treatment period ranged between 6 weeks and 24 weeks Comparators included waitlist or active controls such as web-based treatments (time-management writing, psycho-education, non-TF CBT, non-specific support), psychosocial treatment, or behavioral activation. There was no therapist feedback except in three studies there was therapist feedback.	to 12 weeks

CBT = cognitive behavioral therapy; CSOSI = Calgary symptoms of stress inventory; EW = expressive writing; IES = impact of events scale; IES-D = impact of events scale Dutch version; impact of events scale revised; NR = not reported; PCL-5PTSD checklist 5; PCL-C = PTSD checklist civilian version; PTSD-M = PTSD checklist military version; PDS = posttraumatic diagnosis scale; PSS = posttraumatic stress scale; PTSD = posttraumatic stress disorder; TF-CBT = trauma focused CBT; nRCT = non-randomized trial; RCT = randomized controlled trial; SMD = standardized mean, TES = traumatic event scale difference, TF-CBT = trauma focused cognitive behavioral therapy

Table 3: Characteristics of Included Randomized Controlled Studies

Author, year, Country	Study Design	Population Characteristics	Comparison	Outcomes
Cernvall,[11] 2017, Sweden	RCT, no blinding (therapist nor participants were blinded) Setting: Individuals were recruited from five Swedish pediatric oncology centers, between April 2010 and May 2014.	Individuals (parents of children on cancer treatment) fulfilling the modified symptom criteria on PCL-C corresponding to DSM-IV criteria for PTSD. N = 58 (31 in internet group and 27 in TAU group) Age (mean ± SD) (years): 38 ± 7.2 % Female: 67% PCL-C score at baseline 49.1 ± 10.3 (score ≥ 44 indicates diagnosis of PTSD)	Internet-based guided self-help program versus WL. The internet program was based on CBT-principles. Participants worked with 1 module each week and completed assignments. Each participant was assigned a therapist who provided written feedback via the portal. The three therapist included in the study comprised one licensed psychologist and two psychologists with Masters in Psychology who were supervised by the licensed psychologist. The WL group received treatment after the 12-month follow up. All participants were allowed to avail psychological services from the regular health care.	Outcomes (PCL-C, BDI-II, BAI) Effect size was calculated using Cohen's d, for changes between groups Treatment duration 10 weeks Follow up: 12 months
Franklin,[12] 2017, USA	RCT Setting: Veterans who were seeking treatment at five rural Veteran's Administration (VA) community-based outpatient clinics in the Southeast were recruited	Veterans with PTSD diagnosis according to DSM-IV-TR. Majority were from the war zones: Vietnam, Operation Desert Storm, or operation Enduring Freedom/ Operation Iraqi freedom. Individuals with low intellectual capacity, drug or alcohol addiction, self-injurious behavior, suicidal or homicidal ideation, or active psychosis were excluded N = 27 randomized (25 entered treatment; 10 in iPhone, 7 in TMH, and 8 in TAU) Age: (mean ± SD) (years):	PE delivered using smartphone (iPhone 4) (iPhone group) versus PE using computer based teleconferencing equipment (TMH group) versus TAU. Psychologists trained in PE provided the therapy. There were 10 sessions over 12 weeks. TAU included supportive psychotherapy or medication management provided by psychiatrists, psychologist, psychology interns or fellows, or masters level social workers. Treatment duration 12 weeks.	Outcomes (PDS, BDI, BAI, CAPS scores) Treatment duration: 12 weeks. 1-month follow-up post-treatment

Table 3: Characteristics of Included Randomized Controlled Studies

Author, year, Country	Study Design	Population Characteristics	Comparison	Outcomes
		46.1 ± 15.5 % Female: 7.4% PDS score (mean) at baseline: 37 in iPhone group, 36 in TMH group, and 36 in TAU group.		
Knaevelsrud,[13] 2017, Germany	RCT Setting: Patients were recruited between May 2008 and May 2012, from primary care practices, clinician referrals, and through radio, newspaper and an open access web site	Older patients (with childhood traumatization) with clinically meaningful (i.e., subsyndromal or greater) PTSD symptoms. Patients with severe depression, suicidal risk, alcohol or drug abuse, or receiving psychological treatment were excluded N = 94 (47 in iCBT, 47 in WL) Age (mean ± SD, range) (years): 71.4 ± 4.7, range 63 to 85. % Female: 64.9% PDS total score (mean ± SD): 22.3 ± 8.4; indicating moderate to severe symptom severity. The authors reported that there were no significant differences between the groups, except greater proportion of females and smaller proportion of patients who were married or in partnership in iCBT group compared to WL group.	Therapist guided iCBT versus control (WL) Treatment comprised structured writing assignments and therapist feedback through a secured web-based platform. Patients were requested to complete two 45-minute writing assignments each week for 6 weeks. Therapists were licensed clinical psychologists. Therapist and patients communicated asynchronously; therapist provided feedback within 24 hours. Each feedback took 45 to 50 minutes on average.	Outcomes (PDS, BSI-18, GSE, EUROHIS-QoL) Effect size was calculated using Cohen's d, for changes between groups Duration of treatment: 6 weeks. Follow-up post treatment up to 12 months
Lewis,[7] 2017, UK	RCT, single-blind (assessor [post-doctoral researcher] blinded to group allocation). Therapist had no role in assessments.	Patients of age 18 years or older and diagnosed according to DSM-5 as mild to moderate severity of PTSD (CAPS-5 score 55 or less)	Therapist guided internet self-help intervention program versus control (delayed treatment). The intervention program	Outcomes (CAPS, PCL, BAI, BDI, SDS, AUDIT, SSQ). Adverse events.

Table 3: Characteristics of Included Randomized Controlled Studies

Author, year, Country	Study Design	Population Characteristics	Comparison	Outcomes
	Setting: Patients were recruited between March 2013 and June 2014 from specialist secondary care Traumatic Stress Service and mental health services at the primary care level.	Patients with psychosis, previous or concurrent psychological therapy, severe major depressive episode, substance dependence, suicidal intent were excluded. Patients unable to fluently read or write in English were also excluded N = 42 (21 in each group) Age (mean SD) (years): 39.3 ± 12.7 % Female: 59.5% Time since trauma (mean, range) (months): 37.3, 3 to 228. Majority of the traumatic events were related to transportation accident, witnessing death, traumatic childbirth, sexual assault or physical attack. CAPS score (mean) at baseline: 36 in the internet intervention group, and 37 in the control (delayed treatment) group	included 8 online steps, and each step activated a “tool” in the toolkit area of the website. At start, guidance was provided with 1-hour face-to-face session with a therapist and thereafter followed by 30-minute appointments, either face-to-face or by telephone according to the patient’s preference. There was telephone or e-mail contact between appointments if needed. Therapists were psychiatrist, clinical psychologist, or cognitive behavioral therapist. The delayed treatment group did not have any therapist contact until they crossed over to receive the internet based intervention program.	Duration of treatment: 10 weeks. Follow-up up to 22 months (i.e. 3 months after posttreatment)
Littleton,[14] 2016, USA	RCT Setting: Patients were recruited via advertisements at four institutions (university and college campuses)	Women students (from four institutions - university or community college) with diagnosis of rape-related PTSD. PSS-I was used for PTSD diagnosis. Patients receiving psychotherapy, or with lack of stability on; psychotropic medication, suicidal tendency, or substance use disorder were excluded N = 87 randomized, of	Therapist-facilitated cognitive behavioral program for rape-related PTSD (Survivor to Thriver interactive program) versus psychoeducational self-help website The interactive program had nine modules and needed to be completed sequentially, one module at a time. In the interactive program group, the program therapist provided written feedback to each answer provided as well as embedded video	Outcomes (PSS-I, FDAS, CES-D) Duration of treatment: 14 weeks (patients had 14 weeks to view content of the online programs. Follow-up : 3 months

Table 3: Characteristics of Included Randomized Controlled Studies

Author, year, Country	Study Design	Population Characteristics	Comparison	Outcomes
		which 74 completed baseline online questionnaire and logged into assigned program at least once (39 in interactive program and 35 in psychoeducational self-help program) Age (mean, range) (years): 22, 18 to 42/ % Female: 100% Occurrence of patients' index rape was on average 4 years ago with range 1.5 months to 21 years ago PSS-I score (mean) at baseline: 24 in the intervention group, and 23 in the control (self-help) group	messages containing more extensive feedback on the interactive exercise page in the program (asynchronous communication). In the psycho-educational website group, the patients had access to all the website contents and could use the content in whatever manner and however frequently they wanted to do so. Patients in both groups received scheduled check-in phone calls from study staff (doctoral students in psychology) generally once every two weeks.	
Possemato,[15] 2016, USA	RCT Setting: Patients were recruited from the VA primary care, over 4 months	Patients (veterans) with significant PTSD symptoms arising from a military-related trauma as indicated by a PCL score of greater than 40. Majority (90%) had served in Iraq and/or Afghanistan. Participants were excluded if they had gross cognitive impairment, or had any of the following in the previous two months: suicidal tendency, additional health counseling for PTSD outside the VA primary care, change or new psychotropic medication. N = 20 Age (mean ± SD) (years): 42 ± 12 % Female: NR	Clinician supported PTSD coach (CS) versus self-managed PTSD Coach (SM). PTSD Coach is a mobile App. CS: Patients received four 20-minute sessions over 8 weeks; session 1 was in-person, and sessions 2 to 4 were in-person or by phone. Each session followed a CBT structure. Sessions focused on setting symptom reduction goals and helping veterans to be engaged with the application content. SM: Patients received one 10-minute session that was guided by a handout providing basic information about the App. Sessions provided by PC-MHI clinicians, including a licensed psychologist, a	Outcomes (PCL, PHQ-9, WHO-QoL) Duration of treatment: 8 weeks. Follow up: at 12 weeks and 16 weeks

Table 3: Characteristics of Included Randomized Controlled Studies

Author, year, Country	Study Design	Population Characteristics	Comparison	Outcomes
		PCL score (mean) at baseline: 51 in CS group and 56 in SM group.	licensed social worker, and a pre-doctoral psychology intern.	

AUDIT = Alcohol Use Disorders Identification Test; BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory-II; BSI-18 = Brief Symptom Inventory -18;CAPS = Clinician-Administered PTSD scale; CBT = cognitive behavioral therapy; CES-D = Center for Epidemiological Studies – Depression Scale; DSM = Diagnostic and Statistical Manual; DSM-IV-TR = DSM, Fourth Edition, Text Revision; EOROHIS-QoL assess QoL; FDAS = Four Dimensional Anxiety Scale; GSE = General Self-Efficacy scale; iCBT = internet-based CBT; NR = not reported; PCL = PTSD checklist; PCL-C = PTSD Checklist – Civilian version; PCL-M = PTSD Checklist – Military version; PDS = posttraumatic diagnostic scale; PE = prolonged exposure; PHQ-9 = Patient Health Questionnaire – 9; PSS-I = PTSD Symptom Scale Interview; PTSD = posttraumatic stress disorder; QoL = quality of life; RCT = randomized controlled trial; SD = standard deviation; SDS = Sheehan Disability scale; SSQ = social support questionnaire; TAU = treatment as usual; VA = Veteran's Affair; WL = waitlist

Table 4: Explanation of outcome measures

Outcome measure	Reference (First Author)	Explanation
BAI (anxiety)	Cernvall,[11] Franklin[12]	Consists of 21 items each rated on a 4-point scale (0 to 3). Scores indicate: 0 to 7, minimal; 8 to 15, mild, 16 to 23, moderate, and 24 to 63 severe anxiety. Considered to have good test-retest reliability and convergent validity. Higher scores indicate more symptoms.
BDI=II (depression)	Cernvall,[11] Franklin[12]	Consists of 21 items each rated on a 4-point scale (0 to 3). Scores indicate: 0 to 13, minimal; 14 to 19 mild; 20 to 28 moderate; and 29 to 63 severe depression. Considered to have good concurrent validity with the BDI and Hamilton psychatric rating scale. Higher scores indicate more symptoms.
BSI (depression, anxiety, somatization)	Knaevelsrud,[13]	Consists of three subscales (depression, anxiety, somatization) each with six items rated on a 5-point Likert scale (0 = not at all, 4 = extremely). Higher scores indicate more symptoms.
CAPS (PTSD symptom)	Franklin,[12]Lewis,(29)	Considered to have excellent reliability; convergent and discriminant validity; and sensitivity. Considered gold standard. Higher scores indicate more symptoms.
CES-D (depression)	Littleton,[14]	Consists of 21 items. Total score ranges from 0 to 60. A score of 21 or higher indicates clinically significant depression. Internal consistency and convergent validity similar to other self-report depression symptom measures. Higher scores indicate more symptoms.
EUROHIS-QoL (QoL)	Knaevelsrud,[13]	Consists of eight items, each rated on a 5-point Likert scale (1 = not at all, 5 = completely)
FDAS (anxiety)	Littleton,[14]	Consists of a 35 items. Score range 35 to 175. Internal consistency and convergent validity similar to other self-report anxiety symptom measures.
GSE (perceived self-efficacy)	Knaevelsrud,[13]	Consists of eight items, each rated on a 4-point Likert scale (1 = not at all true, 4 = exactly true)
PCL-C (PTSD symptoms)	Cernvall,[11]	Consist of 17 items rated on a 5-point scale (1 = not at all and 5 = extremely) with respect to items: re-experiencing, avoidance and numbing, and hyperarousal. Considered to have adequate internal consistency; test-retest reliability; convergent and discriminant validity, as compared to other wll-established measures of posttraumatic stress symptoms, depression and general anxiety
PCL-S (PTSD symptoms)	Possemato,[15]	Consists of 17-item self-report measure of severity of PTSD symptoms. Higher scores indicate greater symptoms. Considered to have good psychometric properties.
PDS (PTSD symptoms)	Franklin,[12]	Consists of a 49-item self-reported measure of severity of PTSD symptoms with total scores ranging from 0 to 51. Higher scores indicate more symptoms.
PDS (PTSD symptoms)	Knaevelsrud[13]	Consists of a 49-item self-reported measure of severity of PTSD symptoms with total scores ranging from 0 to 51. Scores indicate: 1 to 10mild, 11 to 20 moderate, 21 to 35, moderate to severe and > 36 severe

Table 4: Explanation of outcome measures

Outcome measure	Reference (First Author)	Explanation
PHQ (depression)	Possemato,[15]	Consists of 17-item self-report measure of depression. Considered to have strong psychometric properties.
PSS-I (PTSD symptoms)	Littleton,[14]	Consists of 17 items each rated on a scale of 0 to 3 (0 = does not interfere at all, and 3 = interferes very much. Total score ranges from 0 to 51. Considered a reliable measure.
WHO-QoL (QoL)	Possemato,[15]	Consists of 26-item self-report measure of QoL. Considered to have strong psychometric properties.

BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; BSI= Brief Symptom Inventory; CAPS = Clinician-Administered PTSD scale; CES-D = Center for Epidemiological Studies – Depression Scale; EUROHIS-QoL assess QoL; FDAS = Four Dimensional Anxiety Scale; GSE = General Self-Efficacy scale; PCL-C = PTSD checklist Civilian version; PDS = Posttraumatic Diagnostic Scale;Public Health Questionnaire; PHQ = PSS-I = PTSD Symptom Scale – Interview; PTSD = posttraumatic stress disorder; PTSS = Post traumatic stress symptoms; QoL = quality of life.

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR2[9]

Strengths	Limitations
Sijbrandij,[6] 2016, The Netherlands	
• The objective was clearly stated. • The inclusion criteria were stated. • Multiple databases were searched (PubMed, Embase, PsychINFO, Cochrane Central Register of Controlled Trials, Web of Science). In addition reference list of relevant meta-analysis and reviews were searched. Search period was not specified. • Study selection was described • Flow chart of study selection was provided • List of included studies was provided • Quality assessment was done by two independent reviewers using the four criteria of the Cochrane Handbook for Systematic Reviews of Interventions. Study quality was variable (1 RCT satisfied all 4 criteria, 4 RCTs satisfied 3 criteria, and 4 RCTs satisfied 2 criteria). • Characteristics of the individual studies were provided but some details were lacking. • Publication bias was explored using Funnel plot and Egger's test and the authors reported that potential for publication bias was not indicated • Meta-analyses were conducted • The authors mentioned that there were no conflicts of interest	• The exclusion criteria were not explicitly stated • List of excluded studies was not provided • Unclear if article selection or data extraction were done in duplicate, however quality assessment was done by two independent reviewers.
Simblett,[4] 2017, UK	
• The objective was clearly stated. • The inclusion criteria were stated. • The exclusion criteria were stated • Multiple databases were searched until November 2016 (Medline, Embase, PsycINFO). In addition trial registries, and reference list of relevant publications were searched • Study selection was described • Flow chart of study selection was provided • List of included studies was provided • Article selection was done independently by three reviewers • Quality assessment was done using the Effective Public Health Practice Project Quality Assessment Tool. Quality of the studies was judged to be low or moderate. • Characteristics of the individual studies were provided but some details were lacking. • Meta-analyses were conducted • The authors mentioned that there were no conflicts of interest	• List of excluded studies was not provided • Unclear if data extraction was done in duplicate • Unclear if publication bias was explored

Table 6: Strengths and Limitations of Randomized Controlled Trials using Downs and Black checklist[10]

Strengths	Limitations
Cernvall,[11] 2017, Sweden	
• The objective was clearly stated • The inclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • Randomization was conducted by an independent consultant using a statistical program to generate the randomization schedule and sealed envelopes were provided by the consultant to the research group. • Lost to follow up was reported (Lost to follow at 12-month follow up was 48.4% in the internet intervention group, and 40.7% in the control [WL] were) group. Reasons for drop-out were reported. • ITT analysis was conducted and missing data was assumed to be missing at random • Authors mentioned that there were no conflicts of interest to declare	• The exclusion criteria were not explicitly stated • Neither participant nor therapist were blinded. Unclear if assessor (if other than therapist) was blinded • Sample size was calculated. However the required sample size could not be reached. • Drop-out rates were substantial (48% and 41%)
Franklin,[12] 2017, USA	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • Randomization was performed using permuted block procedure • Dropouts were reported (70% in iPhone, 43% in TMH, 0% in TAU) • A repeated measures analysis was conducted for each outcome using mixed models and including terms for treatment group, time and time * treatment interaction.	• There was no mention of blinding. Blinding of patient and therapist was not possible in this study. Unclear if assessor was blinded • Unclear if sample size calculations were undertaken • Dropouts were substantial in the intervention groups and also variable (70% in iPhone, 43% in TMH, 0% in TAU). Differences in dropout rates between groups were statistically significant (P = 0.016). Reasons for dropout were not reported • There was no mention of conflicts of interest
Knaevelsrud,[13] 2017, Germany	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • Randomization was based on computer generated randomization list • Drop-out rates were reported (12.8% in iCBT, and 6.4% in WL). Authors mentioned that dropout rates did not differ significantly between the groups (P = 0.29) • Linear mixed-effects analyses were conducted. Treatment, time and interaction term (treatment * time) were entered in the model. Cohen's d was used for effect size determination • Authors mentioned that there were no disclosures to report	• There was no mention of blinding. Blinding of patient and therapist was not possible in this study. Unclear if assessor was blinded • Unclear if sample size calculations were undertaken • Reasons for dropout were not reported.

Lewis,[7] 2017, UK	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • Randomization was based on use of sealed opaque envelopes containing an allocation code, generated by an independent statistician • Sample size calculations were undertaken and the appropriate number of patients recruited. • Drop-out rates were reported (28.6% in the immediate treatment group and 19.1% in the delayed treatment group) Reasons for drop-out were provided. • ITT analysis undertaken (Missing data was imputed using various methods: multiple imputation, last observation carried forward, and missing at random) • Conflicts of interest were reported.	• Blinding of patient and therapist was not possible, however assessor was blinded • Drop-out rates were substantial (28.6% in the immediate treatment group and 19.1% in the delayed treatment group) • Conflicts of interest were reported. The study was undertaken in collaboration with a software company producing the interactive online version of the treatment program. If the program was marketed, five of the seven authors would receive royalties, and the remaining two authors had no conflicts of interest.
Littleton,[14] 2016, USA	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • Randomization was based on a computerized coin flip • Drop-out rates were reported (For interactive program group: 28.3% at post treatment and 37% at 3-m FU; for psycho-education group: 14.6% at post treatment and 34.1% at 3-m FU based on the number randomized). A few patients failed to initiate the programs and reasons for the other drop-outs were not mentioned. • ITT analysis and completer analysis undertaken. For missing data imputations were done using the R package mice.	• Blinding of patient and therapist was not possible in this study. Unclear if assessor was blinded • Unclear if sample size calculations were undertaken • Drop- out rates were substantial • There was no mention of conflicts of interest
Possemato,[15] 2016, USA	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. Details of the assessment scales sparse. Patient characteristics were not reported separately for each of the two groups. • Randomized. Randomization was stratified • Retention was reported. 100% in the CS group and 80% in the SM group • ITT analysis. Missing data was imputed using an Estimation Maximization algorithm. • Authors mentioned that there were no conflicts of interest	• Details of randomization were lacking • There was no mention of blinding. Blinding of patient and therapist was not possible in this study. Unclear if assessor was blinded • This was a pilot study and was not powered to detect statistically significant differences

CBT = cognitive behavioral therapy; iCBT = internet CBT;

Appendix 4: Main Study Findings and Author's Conclusions

Table 7: Summary of Findings of Included Studies

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusion</th></tr>
<tr><td colspan="2">Systematic Review</td></tr>
<tr><td colspan="2">Sijbrandij,[6] 2016, The Netherlands</td></tr>
<tr><td>Population studied: Adults with diagnosis of PTSD based on clinician assessment or self-report instrument.

Results from individual studies
Impact of iCBT combined with therapist assistance compared with WL or TAU for PTSD symptoms (7 studies):
Hedge's g ranged between 0.44 and 1.33 favoring iCBT but the between group differences were not always statistically significant

Impact of iCBT combined with therapist assistance compared with other active treatment for PTSD symptoms (2 studies):
Hedge's g was 0.24 and 0.40 but the between group differences were not statistically significant.

Results from meta-analysis
Comparison of outcomes with iCBT compared with WL or TAU
<table>
<tr><th>Outcome</th><th>Number of RCTs</th><th>Effect size for iCBT compared with WL or TAU</th></tr>
<tr><td>PTSD symptoms</td><td>7</td><td>0.89 (0.70 to 1.08</td></tr>
<tr><td>Depressive symptoms</td><td>6</td><td>0.66 (0.36 to 0.96)</td></tr>
</table>
</td><td>The authors mentioned that "The findings of this systematic review and metaanalysis supplement understanding of Internet-delivered interventions by showing that iCBT, particularly with some component of therapist-support, is an effective treatment for individuals with PTSD symptoms." Page 790</td></tr>
<tr><td colspan="2">Simblett,[4] 2017, UK</td></tr>
<tr><td>Population studied: Adults with actual diagnoses of PTSD or having PTSD symptoms.

Results from individual studies
Impact of e-Mental Health interventions combined with therapist feedback compared with WL or TAU, for PTSD (from 9 studies):
SMD ranged between –0.12 to -0.92, and was not always statistically significant.

Impact of e-Mental Health interventions combined with therapist feedback compared with active treatment, for PTSD (from 5 studies):
SMD ranged between -0.13 to -1.05, but the between group difference was not always statistically significant.

Impact of e-Mental Health interventions combined with feedback from discussion forum compared with WL or TAU, for PTSD (from 3 studies):
SMD ranged between 0.00 to -0.66, and the between group difference was not always statistically significant

Impact of e-Mental Health interventions combined with feedback from discussion forum compared with active treatment, for PTSD (1 study):
SMD was -0.24, and the between group difference was statistically significant</td><td>The authors mentioned that "Replications of findings are needed to investigate the use of similar e-Mental Health interventions across diagnostics groups and health settings and could benefit from research to better understand which specific intervention packages or components work best and for whom. [….]There is far to go in terms of gathering the same level of evidence base as therapist-delivered approaches. However, the results presented in this systematic review take a small step forward in understanding how technology such as e-Mental Health resources may offer additional opportunities for increasing access to effective psychological support for people suffering from PTSD, to improve well-being." Page 12</td></tr>
</table>

Table 7: Summary of Findings of Included Studies

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusion</th></tr>
<tr><td>SMD < 0 favors the intervention.</td><td></td></tr>
<tr><td colspan="2">Randomized Controlled Trials</td></tr>
<tr><td colspan="2">Cernvall,[11] 2017, Sweden</td></tr>
<tr><td>Population studied: Individuals (parents of children on cancer treatment) with diagnosis of PTSD

Outcomes with internet intervention group compared with control (waitlist [WL])

<table>
<tr><th>Outcome</th><th>Time point</th><th>Between group difference, Cohen's d (95% CI)</th></tr>
<tr><td>PCL-C</td><td>Posttreatment</td><td>0.89 (0.35 to 1.43)</td></tr>
<tr><td></td><td>12-month FU</td><td>0.78 (0.25 to 1.32)</td></tr>
<tr><td>BDI-II</td><td>Posttreatment</td><td>0.52 (-0.003 to 1.04)</td></tr>
<tr><td></td><td>12-month FU</td><td>1.25 (0.69 to 1.82)</td></tr>
<tr><td>BAI</td><td>Posttreatment</td><td>0.12 (-0.39 to 0.64)</td></tr>
<tr><td></td><td>12-month FU</td><td>0.92 (0.38 to 1.46)</td></tr>
</table>
Attrition:
At posttreatment, drop-out rates were 45.1% in the internet intervention group and 25.9% in the WL group.
At 12-month follow up, the drop-out rates were 48.4% in the internet intervention group and 40.7% in the WL group.</td><td>The authors mentioned that "Using the Internet to provide psychological interventions shows promise as an effective mode of delivery for parents reporting an increased level of PTSS and who consider Internet-based interventions as a viable option. Future research should corroborate these findings and also develop and evaluate interventions and policies that may help ameliorate the economic burden that parents may face during their child's treatment of cancer." Page 2 of 18</td></tr>
<tr><td colspan="2">Franklin,[12] 2017, USA</td></tr>
<tr><td>Population studied: Veterans with PTSD diagnosis according to DSM-IV-TR.

Outcomes in the three groups (PE groups [iPhone, or TMH], and TAU):
Assessment scores by treatment group were reported; and repeated measure analysis was conducted, and F statistics and P values for the time * treatment interactions were reported; P values were 0.21 for BDI, 0.31 for BAI, 0.01 for PDS and 0.02 for CAPS. Significant differences in PDS total scores and CAPS total scores were reported in the PE groups compared to the TAU group. No significant differences were reported between the two PE groups.
For patients completing treatment, at 1-month follow-up posttreatment, all participants in the iPhone group had their PTSD symptoms offset below the DSM-IV-TR PTSD diagnostic cutoffs; whereas 33.3% in the TMH group and 28.6% in the Tau group had their PTSD offset on the CAPS.

Attrition
Dropout rates were 70% in iPhone group; 43% in the TMH group and 0% in the TAU group. (Patients who entered treatment in each group, were 10 in iPhone group, 7 in the TMH group, and 8 in the TAU group; numbers completing the treatment were 3, 4, and 8 in the iPhone, TMH, and TAU groups respectively)</td><td>The authors mentioned that "Results indicated decreases in PTSD symptoms in veterans who completed PE therapy via teleconferencing; however, there was significantly more attrition in these groups than in the TAU group." Page 116</td></tr>
</table>

Table 7: Summary of Findings of Included Studies

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusion</th></tr>
<tr><td colspan="2">Knaevelsrud,[13] 2017, Germany</td></tr>
<tr><td>Population studied: older patients who experienced childhood traumatization

Comparison of outcomes with iCBT and WL

The linear mixed effects analyses showed a significant interaction effect between treatment (iCBT versus WL) and time (pre versus post) for PDS-total, PDS-hyperarousal, PDS-avoidance, GSE, and EUROHIS-QoL, indicating improvement in in iCBT group compared to the WL group, (P values ranged between <0.001 to 0.015).

<table>
<tr><th>Outcome measure</th><th>Effect size for iCBT compared to WL, at posttreatment.
Cohen's d</th></tr>
<tr><td>PDS - intrusion</td><td>0.09</td></tr>
<tr><td>PDS - hyperarousal</td><td>0.47</td></tr>
<tr><td>PDS - avoidance</td><td>0.54</td></tr>
<tr><td>PDS - total</td><td>0.42</td></tr>
<tr><td>BSI-18 - anxiety</td><td>0.04</td></tr>
<tr><td>BSI-18 - depression</td><td>0.36</td></tr>
<tr><td>GSE</td><td>0.38</td></tr>
<tr><td>EUROHIS-QoL</td><td>0.39</td></tr>
</table>
Resource-oriented variables: GSE, EUROHIS.

Stability of effects in the iCBT group over time

There were no significant differences in symptom scores from posttreatment to 12-month follow up for PDS-total, PDS – hyperarousal, PDS – avoidance, as indicated by overlapping 95% Cis. Only for PDS – intrusion there was a significant decrease of symptoms, as indicated by non-overlapping 95% CI.
There were no significant differences from posttreatment to 12-month follow up with respect to the outcome measures: GSE, EUROHIS, and BSI-18 as indicated by overlapping 95% Cis.

Attrition:
Drop-out rates were reported as 12.8% in iCBT, and 6.4% in WL. Authors mentioned that dropout rates did not differ significantly between the groups (P = 0.29)</td><td>The authors mentioned that
"Results suggest that therapist guided Internet-based CBT is associated with a substantial reduction in PTSD symptoms, and increase in resource-related variables in older adults with (subsyndromal) PTSD." Page 878

"Combined with its limitations, however, further studies are needed to extend the current findings." Page 887</td></tr>
<tr><td colspan="2">Lewis,[7] 2017, UK</td></tr>
<tr><td>Population studied: Adults with diagnosis of PTSD (mild to moderate severity).

Comparison of outcomes with immediate treatment (internet-based therapist guided self-help program) versus delayed treatment

<table>
<tr><th>Outcome</th><th>Outcome measure</th><th>Between group difference in outcomes (at posttreatment, i.e., 10 weeks), mean (95% CI)</th></tr>
</table></td><td>The author concluded that "Internet-based trauma-focused guided self-help for PTSD is a promising treatment option that requires far less therapist time than current first line face-to-face psychological therapy." Page 555

The author also mentioned that "Large multicentre effectiveness trials with nested process evaluation are needed to confidently recommend internet-based guided selfhelp</td></tr>
</table>

Table 7: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion

PTSD symptoms	CAPS	18.60 (-24.65 to -13.41)
	PCL	25.79 (NR)
Depression	BDI	10.83 (-16.66 to -5.14)
Anxiety	BAI	13.40 (-19.91 to -6.35)
Functional impairment	SDS	9.36 (-13.56 to -3.93)
Alcohol misuse	AUDIT	2.13 (-6.02 to 1.63)
Perceived social support	SSQ	-0.18 (-5.37 to 5.33)

At 22 weeks (i.e. after treatment in both groups) there was no significant difference in the two groups with respect to PTSD symptoms (CAPS: mean difference 0.97; 95% CI, -7.48 to 8.44)

Therapist time needed
Time (minutes) taken for therapist input per patient (mean ± SD): 147.53 ± 57.01

Adverse events
Therapists were asked to record adverse events if any during the study. No adverse events were reported.

Attrition
Drop-out rates after treatment in both groups were 28.6% in the immediate treatment group and 19.1% in the delayed treatment group. Reasons for dropout included did not log into the program, perceived lack of time to dedicate to the program, difficulty with the program, or symptoms had improved.

as an evidence-based treatment option for PTSD. Further trials are also required to ascertain the optimal balance between minimizing therapist input and maximizing outcome." Page 563

Littleton,[14] 2016, USA

Population studied: Women students (university or community college) with diagnosis of rape-related PTSD

Outcomes with therapist-guided online interactive program and self-help online psychoeducational program

Outcome measure	Assessment time point	Effect size (d) (change from pre-treatment)			
		ITT analysis		Completer analysis	
		Therapist-guided program	Self-help program	Therapist-guided program	Self-help program
PSS-I	posttreatment	0.88	0.86	2.22	1.10
	3-month FU	1.80	1.80	2.60	2.26
CES-D	posttreatment	0.68	0.39	0.76	0.86
	3-month FU	0.84	0.62	0.95	1.03
FDAS	posttreatment	0.75	0.63	0.70	0.87
	3-month FU	0.78	0.68	1.50	1.05

Reliable change index (RCI) scores with therapist-guided online interactive program and self-help online psychoeducational program

Outcome measure	Assessment time point	Percentage of participants with statistically significant RCI scores	
		Therapist-guided program	Self-help program
PSS-I	posttreatment	73.9	75.0

The authors mentioned that *"[…] results provide support for the efficacy of tailored cognitive-behaviorally oriented online interventions for rape-related PTSD presented in either a self-help or therapist-facilitated format. Future trials are necessary to evaluate the efficacy and effectiveness of such interventions when delivered to more diverse populations and when delivered in multiple practice settings*" Page 16

The authors mentioned that "*Findings of the present study must be placed within the context of the study's strengths and limitations*." Page 15

Table 7: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion

	3-month FU	80.0	70.0
CES-D	posttreatment	40.0	37.5
	3-month FU	40.0	52.9
FDAS	posttreatment	55.0	52.2
	3-month FU	68.4	52.9

Analysis: For direct comparison between the two groups with respect to reduction in PTSD symptomology and general distress a regression analysis was conducted. It was reported that there were no significant differences between the groups in change from pre- to post-treatment, although the change in symptomology was more among the patients assigned to the therapist-guided program . Further as determined from simple slopes, the authors reported that for women with low PTSD symptomology at pre-treatment, women assigned to the therapist-guided program had higher post-treatment PTSD symptom scores compared to those assigned to the self-help program. On the other hand, for women with high PTSD symptomology at pre-treatment, women assigned to the therapist-guided program had lower post-treatment PTSD symptom scores compared to those assigned to the self-help program.

Attrition
It was reported that 72.6% of the participants who initiated one of the two programs completed the post-treatment assessment.

Possemato,[15] 2016, USA

Population studied: Patients (veterans) with significant PTSD symptoms arising from a military-related trauma

Outcomes with clinician-supported PTSD Coach (CS) and self-managed PTSD Coach (SM)

Outcome	Group	Effect size (Cohen's d) (Change from pre- to post-treatment)	P value
PCL (PTSD)	CS	1.4	≤0.01
	SM	0.41	0.02
PHQ-9 (Depression)	CS	0.33	0.09
	SM	0.27	0.12
WHO-QoL (Psychological)	CS	0.28	0.11
	SM	0.00	0.98
WHO-QoL (Social)	CS	0.52	0.02
	SM	0.37[a]	0.07

[a]This effect represents worsening

Comparison of outcomes with clinician-supported PTSD Coach (CS) and self-managed PTSD Coach (SM)

Outcome	Group * Time effect[a]
	Between group change Mean (95% CI)
PCL (PTSD)	-4.8 (-9.7 to 4.1)
PHQ-9 (Depression)	0.4 (-3.5 to 4.3)

The authors mentioned that "*Both PTSD Coach interventions are feasible and potentially helpful. The addition of clinician support appears to increase the effectiveness of self-management alone. A larger-scale randomized controlled trial is warranted to confirm these encouraging preliminary findings.* " Page 94

Table 7: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
<table><tr><td>WHO-QoL (Psychological)</td><td>6.4 (-4.6 to 17.3)</td></tr><tr><td>WHO-QoL (Social)</td><td>21.0 (7.5 to 34.4)</td></tr><tr><td colspan="2">[a]Group by time effect were calculated using: ([$CS_{baseline}$ – $CS_{post\text{-}treatment}$] - [$SM_{baseline}$ – $SM_{post\text{-}treatment}$])/ SD of pooled change scores. Mean values were used</td></tr></table> **Clinically significant results**: 70% of CS group patients and 38% of SM group patients had clinically significant improvements` in PCL scores (i.e. reduction of ≥ 10). **Follow up at 12 weeks and 16 weeks**: The 12-week and 16-week follow up results were not reported as following treatment with PTSD Coach, majority of the patients sought specialty mental healthcare, hence outcomes would likely reflect the efficacy of this specialty care and not that of PTSD Coach. **Attrition**: Retention of patients in the study was high. All participants in the CS group and 80%of patients in the SM group completed the posttreatment assessment.	

BSI-18 = Brief Symptom Inventory -18;CAPS = Clinician-Administered PTSD scale; CES-D = Center for Epidemiological Studies – Depression Scale; CI = confidence interval; DSM = Diagnostic and Statistical Manual; DSM-IV-TR = DSM, Fourth Edition, Text Revision; EUROHIS-QoL assess QoL; FDAS = Four Dimensional Anxiety Scale; FU = follow up; GSE = General Self-Efficacy scale; iCBT = internet-based CBT; ITT = intention to treat; PDS = Posttraumatic Diagnostic Scale; PE = prolonged exposure; PSS-I = PTSD Symptom Scale – Interview; PTSD = posttraumatic stress disorder; PTSS = Post traumatic stress symptoms; QoL = quality of life; RCI = Reliable Change Index; SMD = standardized mean difference; TAU = treatment as usual; TMH = PE delivered via traditional teleconference; WL = waitlist