Number of figures: 3
Number of tables: 2

Internet-based cognitive behavioural therapy (i-CBT) for post-traumatic stress disorder (PTSD): systematic review and meta-analysis

Catrin Lewis Ph.D. (Research Associate)[1], Neil P. Roberts D.Clin.Psy. (Consultant Clinical Psychologist)[1,2], Natalie Simon BSc. (Research Assistant)[1], Andrew Bethell (Trainee Clinical Psychologist)[3], Jonathan I. Bisson D.M. (Professor in Psychiatry)[1]

[1] Division of Psychological Medicine and Clinical Neurosciences, Cardiff University School of Medicine, UK

[2] Directorate of Psychology and Psychological Therapies, Cardiff & Vale University Health Board, UK

[3] Institute of Psychology, Health and Society, University of Liverpool, Liverpool, UK

Work conducted at the Division of Psychological Medicine and Clinical Neurosciences, Cardiff University School of Medicine, Hadyn Ellis Building, Maindy Road, Cardiff, CF24 4HQ

Correspondence to: Dr. Catrin Lewis – LewisCE7@Cardiff.ac.uk; Division of Psychological Medicine and Clinical Neurosciences, Cardiff University School of Medicine, Hadyn Ellis Building, Maindy Road, Cardiff, CF24 4HQ

Acknowledgements: We would like to acknowledge the input and support of the Cochrane Collaboration.

Funding: This work was unfunded.

Declaration of interest: CL, JB and NR are the authors of one of the included RCTs (Lewis et al 2017).

Abstract

Objective: To determine whether internet-based cognitive behavioural therapy (i-CBT) is an effective treatment for those who meet diagnostic criteria for post-traumatic stress disorder (PTSD).

Method: A systematic review was undertaken according to Cochrane Collaboration Guidelines. The primary outcome measures were reduction in PTSD symptoms and dropout. Categorical outcomes were meta-analysed as risk ratios (RRs), and continuous outcomes as mean differences (MDs) or standardised mean differences (SMDs).

Results: Ten studies with 720 participants were included. Evidence showed that i-CBT may be associated with a clinically important reduction in post-treatment PTSD symptoms compared with waitlist (SMD-0.60, 95% confidence interval -0.97 to -0.24; N=560), however only three studies reported follow-up data and there was no evidence to support the maintainance of symptom improvement at follow-up of three to six months. There was no evidence of a difference in PTSD symptoms between i-CBT and internet-based-non-CBT post-treatment. There was evidence of greater treatment effect from trauma-focused i-CBT than i-CBT without a trauma-focus, as well as evidence that treatment effect was increased by the provision of guidance.

Conclusions: While the review found some beneficial effects of i-CBT for PTSD post-treatment, the quality of the evidence was very low due to the small number of included trials and there was insufficient evidence to support the maintainance of improvement at follow-up of three to six months. Further work is required to establish non-inferiority to current first-line interventions; to determine long-term efficacy; to explore mechanisms of effect; and to establish optimal levels of guidance.

Keywords (MeSH): Cognitive Behavioural Therapy; Guided Self Help; Stress Disorders, Post-Traumatic;

Summations and Limitations

Summations
i-CBT may be associated with a clinically important reduction in PTSD symptoms post-treatment, but there is currently a lack of evidence to support maintainance of the effect at follow-up.
There was evidence of greater treatment effect from trauma-focused i-CBT than i-CBT without a trauma-focus, as well as evidence that treatment effect was increased by the provision of guidance.
Further work is required to establish non-inferiority to current first line interventions.

Limitations
Only ten studies were eligible for inclusion and sample sizes were often small.
Participants included in the ten studies were predominantly from the USA and Western Europe, employed, and had relatively high levels of education. It is not possible to determine whether similar results would have been obtained from participants with more representative demographic characteristics.
There was a lack of independent evaluation. All but one of the programmes were evaluated by the programme developers themselves.

Introduction

There is robust evidence that therapist-delivered trauma-focused cognitive behavioural therapies (CBTs) are effective for the treatment of post-traumatic stress disorder (PTSD) (1-3). Although these interventions have become accepted first-line therapies for PTSD (4-6), many factors limit the availability and uptake of treatment. These factors include the cost of delivering treatment (4); the limited number of suitably trained therapists (7); the perceived stigma associated with psychological therapy (8); and geographical variations in service provision (9).

Internet-delivered CBT (i-CBT) is an increasingly popular alternative to therapist-delivered CBT (10, 11), which has the potential to address the factors described above. I-CBTs are structured online interventions that deliver therapy interactively with or without guidance from a trained professional (12). The content of existing therapies is not usually altered, deviating from traditional psychological treatment only in terms of the method of delivery (13). I-CBTs have been developed for a range of disorders with the aim of reducing health care expenditure and widening access to effective treatment (11, 14). An established evidence base supports the use of i-CBT for the treatment of anxiety disorders and depression, for which they are routinely used in clinical practice (11, 15, 16). However, the development and evaluation of similar interventions for PTSD has received less attention (15). As a consequence, systematic reviews to date have included studies focused on the reduction of sub-clinical traumatic stress symptoms among participants recruited from the general population (17, 18), resulting in uncertainty regarding the clinical utility of the approach in treatment seeking populations.

Driven by positive findings in sub-clinical trauma-exposed samples, there has been a recent proliferation of studies evaluating the efficacy of i-CBT for those who meet diagnostic criteria for PTSD, creating the rationale for a systematic review and meta-analysis of the studies to date.

Aims of the Study

We aimed to systematically review the available evidence to determine whether i-CBT is effective in the reduction of traumatic stress symptoms for those with a clinical diagnosis of PTSD. We also aimed to review the evidence in relation to rates of dropout and reduction in secondary symptoms of depression and anxiety, and to establish whether any characteristics of the i-CBTs evaluated to date are associated with efficacy.

Method

A systematic review and meta-analyses were undertaken according to a protocol prostectively registered with the Cochrane Collaboration (19).

Selection Criteria

Eligible studies were randomised controlled trials (RCTs); randomised cross-over trials; and cluster-randomised trials of i-CBT for the treatment of PTSD. Participants were required to be adults aged 16 years or older. At least 70% of study participants were required to meet full diagnostic criteria for PTSD according to DSM or ICD criteria, assessed by clinical interview or a validated questionnaire. We included RCTs that used validated questionnaires on the basis that many studies of internet-based interventions recruit participants via the internet and do not incorporate face-to-face assessments. Studies were included regardless of the index trauma; the severity or duration of symptoms; or the length of time since trauma. No restrictions were applied on the basis of co-morbidity as long as PTSD was the primary diagnosis and reduction in traumatic stress symptoms was the main aim of the intervention. I-CBTs were defined as interventions that delivered therapy based on cognitive behavioural principles via the internet by means of an interactive programme. I-CBTs with or without therapist guidance were eligible, including therapies delivered online and through mobile applications (apps). Programmes that provided up to a maximum of 5-hours of therapist guidance (i.e. input from a therapist to facilitate use of the internet-based programme) were included, as well as programmes that provided therapist guidance delivered face-to-face or remotely. There were no restrictions related to the number of interactions with a therapist or length of the online programme. Eligible comparator interventions were face-to-face psychological therapy; waitlist/minimal attention/repeated assessment/usual care; and non-CBT internet-delivered psychological therapy. Sample size and publication status were not used to determine inclusion. Only English language studies were eligible.

Search Strategy

A systematic search of the Cochrane Common Mental Disorders Group (CCMDG) clinical trials registers databases was performed for studies published up to using predefined search terms up to 2nd March 2018 (see appendix 1). These databases are updated weekly from searches of OVID MEDLINE (from 1950), Embase (from 1974), and PsycINFO (from 1967), quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), and review-specific searches of additional

databases. We checked reference lists of studies identified in the search and of relevant systematic reviews. We searched the World Health Organization's, and the U.S. National Institutes of Health's trials portals to identify additional unpublished or ongoing studies. We contacted experts in the field with the aim of identifying unpublished studies and studies that were in submission. A complementary search of the Published International Literature on Traumatic Stress (PILOTS) was also conducted. Two authors independently screened the abstracts of studies identified by the search and the full-text publications of all potentially eligible studies. Any disagreements were resolved with the input of a third reviewer.

Data Extraction

A data extraction form (piloted on one of the included studies), was used to extract study characteristics and outcome data. The primary outcome measures for the review were (1) severity of PTSD symptoms measured using a standardised scale such as the Clinician-Administered PTSD Scale (CAPS)(20); and (2) dropout from treatment. The secondary outcome measures were (1) severity of depressive symptoms (using a standardised scale, such as the Beck Depression Inventory (21)); (2) severity of anxiety symptoms (using a standardised scale, such as the Beck Anxiety Inventory (22)); and (3) quality of life (using a standardised scale such as the Quality of Life Inventory (QOLI) (23)). When both a clinician-administered scale and a self-report measure were adopted by a study, the clinician-administered measure was used in the meta-analysis. Hierarchies of standardised measures were produced that were based on their frequency of use within included studies. When a trial reported data from two or more measures of the same outcome, we used only data from the measure ranked highest. We categorised outcome measures according to the length of follow up, grouping together measures taken: post-treatment; at follow up of 3 - 6 months; at follow up of 6 - 12 months; and follow up of over a year. Only data from the first randomisation period of cross-over trials was included.

Data Synthesis

Data were entered into the Cochrane Collaboration’s Review Manager 5 (RevMan-5) software (24). Categorical outcomes were analysed as risk ratios (RRs). Continuous outcomes were analysed as mean differences (MDs) if all studies used the same outcome measure and standardised mean differences (SMDs) otherwise. All outcomes were presented using 95% confidence intervals. Clinical heterogeneity was assessed by looking at variability in the experimental and control interventions, participants, settings, and outcomes. To further assess heterogeneity, both the I^2 statistic and the chi-

squared test of heterogeneity, as well as visual inspection of the forest plots were used. An I^2 of less than 30% was taken to indicate mild heterogeneity and a fixed effects model was used. When the I^2 was greater or equal to 30%, a random-effects model based on the DerSimonian and Laird method was used (25). We planned to generate funnel plots to assess reporting bias if a meta-analysis included more than 10 studies. Sub-group analyses were conducted to explore the impact of trauma-focus and the provision of guidance (whether or not i-CBT was facilitated by a therapist), on the reduction in traumatic stress symptoms.

All included studies were assessed for risk of bias using Cochrane criteria (26). This comprised: sequence allocation for randomisation (the methods used for randomly assigning participants to the treatment arms and the extent to which this was truly random); allocation concealment (whether or not participants or personnel were able to foresee allocation to a specific group); assessor blinding (whether the assessor was aware of group allocation); incomplete outcome data (whether missing outcome data was handled appropriately); selective outcome reporting (whether reported outcomes matched with those that were pre-specified); and any other notable threats to validity (for example, baseline imbalances between groups or premature termination of the study). Two researchers independently assessed each study and any conflicts were discussed with a third researcher with the aim of reaching a unanimous decision.

Results

The initial searches identified 983 potentially eligible studies. Abstracts were reviewed and full text copies obtained for 66 potentially relevant studies. Ten RCTs of 720 participants met inclusion criteria for the review. Figure 1 presents a flow diagram for study selection.

Figure 1: Flow diagram for study selection here

Study Characteristics

Study characteristics are summarised in table 1. Eight of the studies compared i-CBT to a wait-list control group/ treatment-as-usual / minimal attention control group. Two studies compared i-CBT with i-non-CBT-based psychological interventions targeting PTSD symptoms. It is worth noting that

the non-CBT interventions also included several components that are also commonly included in CBT-based protocols, such as psychoeducation and stress management strategies. Descriptions of the experimental and control interventions are provided in table 2. Studies evaluated the following i-CBT programmes: Delivery of Self Training and Education for Stressful Situations (DESTRESS) (2 studies); PTSD Coach (2 studies); From Survivor to Thriver (1 study); Spring [29] (1 study); Warriors Internet Recovery & Education (WIRED) (1 study); Interapy (1 study); and unnamed i-CBT programmes (2 studies). All interventions delivered therapy predominantly on the internet with therapist guidance aiming to facilitate progress and maximise engagement with the online programmes. Only one study reported regular face-to-face therapist-guidance (27), with the remainder of studies that reported therapist guidance indicating that it was delivered over the phone or via email / messaging service. Duration of treatment ranged from four (28) to fourteen weeks (29). Five of the included studies evaluated trauma-focused interventions; the remainder were non-trauma focused. The number of randomised participants ranged from 34 (30) to 159 (31). Studies were conducted in the USA (6 studies) (28-30, 32-34), Australia (1 study) (35), Iraq (1 study) (31), Sweden (1 study) (36) and the United Kingdom (1 study) (27). Studies included individuals traumatised by military combat (30, 32, 34); living in a war zone (1 study) (31); and rape (1 study) (29). The remainder of the studies included individuals traumatised by various traumatic events (27, 28, 33, 35, 36). Six of the included studies determined PTSD dignosis with a clinician-administered scale (27, 29, 32, 34-36), and four adopted a self-report measure (28, 30, 31, 33).

Outcomes

Methodological Quality of Studies

Risk of bias assessments for the included studies are illustrated in figure 2. Seven studies reported a method of sequence allocation judged to pose a "low" risk of bias, with the remainder reporting insufficient details, and therefore rated as “unclear”. One study reported adequate allocation concealment, representing a "low" risk of bias, with the remainder rated as “unclear”. The outcome

assessor was aware of the participant's allocation in two of the included studies, with the remaining studies using blinded-raters or self-report questionnaires delivered in a way that could not be influenced by members of the research team. Four studies were judged as posing a "high" risk of bias in terms of incomplete outcome data (due to high rates of dropout without adequate explanation or not having dealt with dropout appropriately in statistical analyses). The remainder were felt to have dealt with dropouts appropriately. The majority of studies failed to reference a published protocol, however there was little evidence of reporting bias. We could not rule out potential researcher allegiance, since treatment originators evaluated i-CBT in all but one of the included studies. All studies presented objectives, but sample sizes were often small.

Efficacy

i-CBT versus waitlist/ treatment as usual/ minimal attention

Full results of the meta-analyses are presented in table 3. There was evidence that i-CBT was more effective than waitlist/ treatment as usual/ minimal attention in the reduction of PTSD symptoms post-treatment (8 studies; n=560; SMD -0.60; CI -0.97 to -0.24; see figure 3 for Forest plot). This was not maintained at follow-up of 3 - 6 months (3 studies; n=146; SMD -0.0; CI -0.64 to 0.04). The post-treatment effect size was greater for studies in a sub-group analysis of only trauma-focused i-CBT (trauma focused: 4 studies; n=177; SMD -1.04; CI -1.57 to -0.51 versus non-trauma-focused). There was also evidence for greater effect in a sub-group analysis of only therapist guided i-CBT (6 studies; n=391; SMD -0.86; CI -1.25 to -0.47). There was evidence of greater drop-out from i-CBT than waitlist/ treatment as usual / minimal attention (8 studies; n=585; RR 1.39; CI 1.03 to 1.88). The results should be interpreted with caution due to the small number of studies.

Meta analytic results for the secondary outcome measures are presented in table 3. There was evidence that i-CBT was more effective than waitlist/ treatment as usual/ minimal attention in the reduction of symptoms of depression and anxiety post-treatment and at follow-up of less than six months. There was also evidence that i-CBT was more effective than waitlist/ treatment as usual/ minimal attention post-treatment in terms of improvement in quality of life.

i-CBT versus i-non-CBT

I-CBT showed no benefit compared to i-non-CBT in the reduction of PTSD symptoms post-treatment (2 studies; N = 82; SMD; CI: -0.08 -0.52 to 0.35), at follow-up of less than six months (2 studies; n=65; SMD 0.08; CI -0.41 to 0.57), or at follow-up of 6-12 months (1 study; n=18; MD -8.83; CI -17.32 to -

0.34). There was no evidence of greater drop-out from i-CBT than i-non-CBT (2 studies; n=132; RR 2.14; CI 0.97 to 4.73). These results should be interpreted with caution since the analyses only included one or two studies. There was insufficient data to conduct any sub-group analyses.

Meta analytic results for the secondary outcome measures are presented in table 3. There was no evidence of a difference between i-CBT and i-non-CBT on measures of depression or anxiety at post-treatment or follow up at less than 6 months. There was evidence from one study of a greater reduction in depression and anxiety at follow-up of over 6 months for the i-CBT group. Again, these results should be interpreted with caution since the analyses included a maximum of two studies.

Dropout

In total, 370 participants were randomised to iCBT conditions and 93 (25%) dropped out. There was evidence of a significant difference in dropout rates from the i-CBT group compared with the wait list/usual care group (8 studies; n = 585; RR 1.39, 95% CI 1.03 to 1.88). In total, 62 participants were randomised to i-non-CBT conditions and 7 (11%) dropped out. There was no significant difference between dropout rates from the i-CBT and i-non-CBT groups (2 studies; n = 132; RR 2.14, 95% CI 0.97 to 4.73).

Heterogeneity

There was considerable heterogeneity across the i-CBT programmes, which varied in content and delivery. Although all studies included an intervention that was based on cognitive–behavioural principles, the exact nature of what was included varied. The extent and method by which the internet-based therapies were guided by a trained professional also varied; as did the duration of treatment. Considerable statistical heterogeneity was evident in many of the pooled comparisons resulting in regular use of a random-effects model (see table 3). There were an insufficient number of studies to formally explore heterogeneity.

Publication bias

There was an insufficient number of studies to investigate publication bias.

Discussion

Main Findings

The review identified only ten studies that met the inclusion criteria and results should therefore be interpreted with caution. I-CBT was more effective than no intervention or treatment as usual post-treatment, showing a similar effect to that found in a Cochrane Review of internet-based therapies for anxiety disorders (15). However, only three studies reported follow-up data and there was no evidence that treatment gains had been maintained at follow-up of less than six months. This contrasts with the robust findings of maintained effects demonstrated by therapist-delivered CBT for PTSD (2). The magnitude of the post-treatment effect was smaller than that observed for therapist-delivered CBT in a review with similar inclusion criteria and methodology (2). In addition, there was no evidence of a significant difference in efficacy between i-CBT and i-non-CBT post-treatment. It may be argued that whilst showing some benefit post-treatment, many of the existing i-CBTs have failed to optimally deliver the evidence-based components of CBT for PTSD. There may have been a failure to deliver a sufficient 'dose' of exposure for the effective treatment of some participants, which is known to limit treatment gains. It is necessary to determine the participants that are likely to respond to lower-dose therapies such as i-CBT. There may be a tendency for those who develop and deliver i-CBT to be overly cautious about exposure work, potentially preventing delivery of the required dose and thereby impeding optimal efficacy (37). It is also worth noting that evidence of greater treatment effect from trauma-focused i-CBT than i-CBT without a trauma-focus, supporting the view that i-CBT interventions benefit from the addition of exposure work. Another argument is that the findings represent a lack of statistical power, and that further studies with larger sample sizes are needed, with a particular need for the reporting of follow-up data.

There was evidence of greater drop-out from i-CBT than the no treatment control group and i-non-CBT. Although there are many reasons for dropout, this may suggest that i-CBT is not optimally acceptable. However, the overall rate of dropout from I-CBT was 25%, which is of a similar magnitude to therapist-delivered CBT (2). There was evidence of greater treatment effect from trauma-focused i-CBT than i-CBT without a trauma-focus, which is consistent with the wider literature on therapist-delivered CBT (1-3). There was also evidence that treatment effect was increased by the provision of guidance, which is consistent with findings for i-CBT in disorders such as depression and anxiety (11, 38).

Strengths and Limitations

The review rigorously followed guidelines set out by the Cochrane Collaboration (26). Two authors independently screened the abstracts identified by the literature search; read all potentially relevant studies; assessed each study against the inclusion criteria; extracted data from the written reports; and rated each study for risk of bias. Any disagreements were discussed with a third author, and unanimous decisions were reached for inclusion and classification. Following these procedures minimised the potential for bias, but some unavoidable issues remained. Firstly, it is important to acknowledge the possible influence of publication bias, since only published papers were included in the review. In addition, this review relied only on English-language studies, which limits generalisability. Sample sizes were small. It can therefore be argued that the absence of significant differences in some comparisons represents a lack of statistical power rather than true equivalence of the approaches. Many of the included studies demonstrated a lack of independent evaluation. All but one of the programmes were evaluated by the programme developers themselves.

In terms of generalisability, participants included in the ten studies were predominantly from the the USA and Western Europe with samples including few participants from minority ethnic backgrounds. A high proportion were employed and they had relatively high levels of education. Therefore, it is not possible to determine whether similar results would have been obtained from participants with more representative demographic characteristics. The majority of studies recruited participants through advertisements rather than via clinical services. Indiciduals who volunteer to be part of a trial may engage more with i-CBT than the broader population with PTSD. They may also have less severe or complex symptoms than those presenting to clinical services. This could have impacted on results and may limit the generalizability of findings. This review focused on studies of participants who met diagnostic criteria for PTSD. This resulted in the exclusion of several studies of traumatised people with subthreshold PTSD symptoms from the review. It may be argued that this further limits the

generalizability of findings. However, it is intuitive that interventions that are effective for people meeting the criteria for a diagnosis will also be effective in reducing traumatic stress symptoms among people with subthreshold symptomology. Therefore, restricting the review to studies with clinical samples takes a conservative approach, and, consistent with the aims of the review, provides an indication of whether i-CBT is effective for the treatment of clinically significant PTSD symptoms.

Clinical Implications

Despite good evidence that therapist-delivered CBT is an effective treatment, data indicate that few patients in the USA and Europe with a psychiatric disorder receive the intervention (39). There is a clear need for improved dissemination of evidence-based treatment. The interventions considered by this review required significantly less therapist time than current first-line treatments for PTSD, creating an opportunity to increase therapeutic capacity and optimise access to evidence-based treatment. I-CBT is also less reliant on the skills and experience of the therapist (12), it could therefore be delivered by less highly trained practitioners, although this has not yet been evaluated. Internet-based interventions also provide scope to overcome many traditional barriers to treatment, including difficulties committing to weekly appointments. Providing treatment options that maximise the number of PTSD sufferers able to quickly access and engage in evidence-based therapy thereby has the potential to mitigate many of the harmful long-term consequences and help tackle the global burden of the disorder. Reducing the interval between the onset of treatment and receipt of evidence-based treatment has numerous likely benefits. If left untreated, PTSD is associated with functional and emotional impairment (40), reduced quality of life (41), an increased likelihood of developing other psychiatric and physical illnesses (42, 43), suicidal ideation (44), greater healthcare utilisation (45), and higher rates of alcohol abuse and dependence (46).

There is currently a lack of evidence to support maintainance of treatment gains at follow-up, which needs to be remedied before i-CBT is more widely implemented. Since the effect of internet-based CBT was not as strong as that found by reviews of face-to-face therapy, it is likely that careful selection of individuals with milder forms of PTSD is the best strategy for future routine clinical use. Although it is premature to make definitive clinical recommendations on the basis of the current evidence, i-CBT may be particularly appropriate as an initial intervention in a stepped or stratified pathway of care. According to such models, additional treatment only becomes available if the patient fails to benefit sufficiently from i-CBT (47). At least a proportion of individuals may respond to i-CBT

and require no further intervention, which fits well with the principles of prudent healthcare. The studies included in the review excluded individuals with comorbidities of substance dependence, psychosis, and severe depression; we are not, therefore, able to draw any conclusions beyond the use of i-CBT for simple presentations of PTSD. We currently know very little in relation to therapist-factors that may impact outcome and uptake beyond clinical trials. I-CBT is a different way of working, which is likely to suit some therapeutic-styles more than others. Studies have found that therapists are less positive about i-CBT than patients (48). Work is needed to engage clinicians and determine ways to optimally embed i-CBT into routine healthcare at a point that we can be more confident about the evidence-base.

Research Implications

Despite the observed efficacy of i-CBT for PTSD in comparison to no intervention post-treatment, there have been no studies drawing comparisons with therapist-administered treatments. Carefully designed non-inferiority trials with nested process evaluation are required in order to establish the efficacy of these novel interventions in comparison to the current first-line interventions (49). Given the lack of evidence for the longer-term effect of i-CBT, there is an urgent need for future trials to collect follow-up data, ideally spanning a longer-term than previous studies. We currently have a poor understanding of the psychological processes associated with i-CBT for PTSD. Dismantling studies are required to establish the active ingredients and to determine whether these mirror the most effective and necessary components of therapist administered treatment. Whilst it may be assumed that the mechanisms of effect are the same as those underlying therapist-administered trauma-focused psychological therapies, the findings of a smaller effect size than reviews of therapist-delivered CBT indicate that the interventions developed to date may not be optimal. A future research goal is to determine the required dose of exposure and to establish ways of safely delivering this component. PTSD is a highly heterogeneous condition (50) and further research is necessary to determine those individuals most likely to benefit from lower dose treatments such as i-CBT. Further comparison of internet-based trauma-focused versus non-trauma focused CBT, with larger sample sizes, is also warranted.

The necessity and optimal level of guidance is another factor that deserves further investigation. Although systematic reviews of self-help interventions for other disorders have reported better outcomes for interventions with greater levels of guidance (11, 38), there have been an insufficient number of studies for this to be fully explored for PTSD. There have been no trials comparing i-CBT

with or without guidance and no attempts to ascertain the optimal level of therapist input. Trials to date have been cautious and the majority have included participants with mild to moderate or sub-threshold symptoms. It may be possible to safely deliver i-CBT to a wider subgroup of PTSD sufferers as part of a stepped care model; as an interim measure to reduce or stabilise PTSD symptoms; or as an adjunct to therapist-administered treatment. It may also be possible to modify existing therapies to treat milder forms of complex PTSD. However, this remains to be established. There is a need to explore predictors of outcome and dropout, such as participant age, trauma type, levels of computer literacy, and symptom severity. This will provide a greater understanding of the best candidates for internet-based CBT and enable interventions to be targeted accordingly to allow a more personalised approach to treatment (51).

Author Contribution: All authors were responsible for the original study design. The search was conducted by the Cochrane Collaboration. CL and AB were responsible for data extraction, risk of bias assessments and data analysis. All authors were responsible for interpretation of the analyses. All authors were involved in writing the report.

References

1. American Psychological Association. Clinical Practice Guideline for the Treatment of Posttraumatic Stress Disorder (PTSD) in Adults. Washington, DC: American Psychological Association; 2017.
2. Bisson J, Roberts N, Andrew M, Cooper R, Lewis C. Psychological therapies for chronic post-traumatic stress disorder (PTSD) in adults (Review). Cochrane Database of Systematic Reviews 2013;12(CD003388).
3. Jonas D, Cusack K, Forneris C, Wilkins T, Sonis J, Middleton J, et al. Psychological and pharmacological treatments for adults with posttraumatic stress disorder (PTSD). Comparative Effectiveness Review No. 92. 2013.
4. National Collaborating Centre for Mental Health. Post-traumatic stress disorder (PTSD): The management of PTSD in adults and children in primary and secondary care - National cost impact report. London: National Institute for Health and Clinical Excellence; 2005.
5. US Department of Veterans Affairs. VA/DOD Clinical Practice Guideline for the Management of posttraumatic stress disorder and acute stress disorder. VA/DOD Web site. June 2017 https://www.healthquality.va.gov/guidelines/MH/ptsd/VADoDPTSDCPGClinicianSummaryFinal.pdf. 2017.
6. Australian Centre for Posttraumatic Mental Health. Australian guidelines for the treatment of adults with acute stress disorder and posttraumatic stress disorder. Melbourne, Victoria: ACPMH; 2007.
7. Lovell K, Richards D. Multiple access points and levels of entry (MAPLE): ensuring choice, accessibility and equity for CBT services. Behavioural and Cognitive Psychotherapy. 2000;28(4):379-91.
8. Cuijpers P, van Straten A, Andersson G. Internet-administered cognitive behavior therapy for health problems: a systematic review. Journal of Behavioral Medicine. 2008;31(2):169-77.
9. Griffiths KM, Christensen H. Internet-based mental health programs: A powerful tool in the rural medical kit. Australian Journal of Rural Health. 2007;15(2):81-7.
10. Amstadter AB, Broman-Fulks J, Zinzow H, Ruggiero KJ, Cercone J. Internet-based interventions for traumatic stress-related mental health problems: a review and suggestion for future research. Clinical Psychology Review. 2009;29(5):410-20.
11. Gratzer D, Khalid-Khan F. Internet-delivered cognitive behavioural therapy in the treatment of psychiatric illness. Canadian Medical Association Journal. 2016;188(4):263-72.
12. Andersson G. Using the Internet to provide cognitive behaviour therapy. Behaviour research and therapy. 2009;47(3):175-80.
13. Cuijpers P, Donker T, van Straten A, Li J, Andersson G. Is guided self-help as effective as face-to-face psychotherapy for depression and anxiety disorders? A systematic review and meta-analysis of comparative outcome studies. Psychological medicine. 2010;40(12):1943-57.
14. Donker T, Blankers M, Hedman E, Ljotsson B, Petrie K, Christensen H. Economic evaluations of Internet interventions for mental health: a systematic review. Psychological medicine. 2015;45(16):3357-76.
15. Olthuis JV, Watt MC, Bailey K, Hayden JA, Stewart SH. Therapist-supported internet cognitive—behavioural therapy for anxiety disorders in adults. BJPsych Advances. 2015;21(5):290-.
16. Karyotaki E, Ebert DD, Donkin L, Riper H, Twisk J, Burger S, et al. Does guided internet-based interventions result in clinically relevant changes for patients with depression? An individual participant data meta-analysis. Clinical Psychology Review. 2018.
17. Kuester A, Niemeyer H, Knaevelsrud C. Internet-based interventions for posttraumatic stress: a meta-analysis of randomized controlled trials. Clinical Psychology Review. 2016;43:1-16.
18. Sijbrandij M, Kunovski I, Cuijpers P. Effectiveness of internet-delivered cognitive behavioral therapy for posttraumatic stress disorder: A systematic review and meta-analysis. Depression and anxiety. 2016;33(9):783-91.

19. Lewis C, Bethell, A., Roberts, N.R. and Bisson, J.I. . Internet-based cognitive and behavioural therapies for post-traumatic stress disorder (PTSD) in adults (protocol). Cochrane Database of Systematic Reviews 2015;10.1002/14651858.CD011710.pubX.
20. Weathers FW, Bovin MJ, Lee DJ, Sloan DM, Schnurr PP, Kaloupek DG, et al. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5): development and initial psychometric evaluation in military veterans. Psychological Assessment. 2017.
21. Beck AT, Steer RA, Brown GK. BDI-II: Beck depression inventory: Pearson; 1996.
22. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. Journal of Consulting and Clinical Psychology. 1988;56(6):893.
23. Frisch MB. Quality of Life Assessment/Intervention and the Quality of Life Inventory TM (QOLI®). 1999.
24. Review Manager (RevMan) [Computer program]. Version 53 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
25. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled clinical trials. 1986;7(3):177-88.
26. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
27. Lewis, Farewell D, Groves V, Kitchiner NJ, Roberts NP, Vick T, et al. Internet-based guided self-help for posttraumatic stress disorder (PTSD): Randomized controlled trial. Depression and anxiety. 2017;34(6):555-65.
28. Miner A, Kuhn E, Hoffman JE, Owen JE, Ruzek JI, Taylor CB. Feasibility, acceptability, and potential efficacy of the PTSD Coach app: A pilot randomized controlled trial with community trauma survivors. Psychological Trauma: Theory, Research, Practice, and Policy. 2016;8(3):384.
29. Littleton H, Grills AE, Kline KD, Schoemann AM, Dodd JC. The From Survivor to Thriver program: RCT of an online therapist-facilitated program for rape-related PTSD. Journal of anxiety disorders. 2016;43:41-51.
30. Krupnick JL, Green BL, Amdur R, Alaoui A, Belouali A, Roberge E, et al. An Internet-based writing intervention for PTSD in veterans: A feasibility and pilot effectiveness trial. Psychological Trauma: Theory, Research, Practice, and Policy. 2017;9(4):461.
31. Knaevelsrud C, Brand J, Lange A, Ruwaard J, Wagner B. Web-based psychotherapy for posttraumatic stress disorder in war-traumatized Arab patients: randomized controlled trial. Journal of medical Internet research. 2015;17(3).
32. Engel CC, Litz B, Magruder KM, Harper E, Gore K, Stein N, et al. Delivery of self training and education for stressful situations (DESTRESS-PC): a randomized trial of nurse assisted online self-management for PTSD in primary care. General hospital psychiatry. 2015;37(4):323-8.
33. Kuhn E, Kanuri N, Hoffman JE, Garvert DW, Ruzek JI, Taylor CB. A randomized controlled trial of a smartphone app for posttraumatic stress disorder symptoms. Journal of consulting and clinical psychology. 2017;85(3):267.
34. Litz BT, Engel CC, Bryant RA, Papa A, Litz BT, Engel CC, et al. A randomized, controlled proof-of-concept trial of an Internet-based, therapist-assisted self-management treatment for posttraumatic stress disorder. American Journal of Psychiatry. 2007;164(11):1676-83.
35. Spence J, Titov, N., Dear, B. F., Johnston, L., Solley, K., Lorian, C. & Schwenke, G. . Randomized controlled trial of Internet-delivered cognitive behavioral therapy for posttraumatic stress disorder. Depression and Anxiety. 2011;28(7):541-50.
36. Ivarsson D, Blom M, Hesser H, Carlbring P, Enderby P, Nordberg R, et al. Guided internet-delivered cognitive behavior therapy for post-traumatic stress disorder: A randomized controlled trial. Internet Interventions. 2014;1(1):33-40.
37. Lewis C, Roberts N, Vick T, Bisson JI. Development of a guided self help (GSH) programme for the treatment of mild to moderate post traumatic stress disorder (PTSD). Depression and Anxiety. 2013;30(11):1121-8.

38. Lewis, Pearce J, Bisson J. Efficacy, cost-effectiveness and acceptability of self-help interventions for anxiety disorders: systematic review. British Journal of Psychiatry. 2012;200(1):15-21.
39. Shafran R, Clark D, Fairburn C, Arntz A, Barlow D, Ehlers A, et al. Mind the gap: Improving the dissemination of CBT. Behaviour research and therapy. 2009;47(11):902-9.
40. Amaya-Jackson L, Davidson JR, Hughes DC, Swartz M, Reynolds V, George LK, et al. Functional impairment and utilization of services associated with posttraumatic stress in the community. Journal of Traumatic Stress. 1999;12(4):709-24.
41. Olatunji BO, Cisler JM, Tolin DF. Quality of life in the anxiety disorders: a meta-analytic review. Clinical Psychology Review. 2007;27(5):572-81.
42. Pacella ML, Hruska B, Delahanty DL. The physical health consequences of PTSD and PTSD symptoms: a meta-analytic review. Journal of Anxiety Disorders. 2013;27(1):33-46.
43. Brady KT, Killeen TK, Brewerton T, Lucerini S. Comorbidity of psychiatric disorders and posttraumatic stress disorder. Journal of Clinical Psychiatry. 2000.
44. Krysinska K, Lester D. Post-traumatic stress disorder and suicide risk: a systematic review. Archives of Suicide Research. 2010;14(1):1-23.
45. Domin Chan P, Cheadle AD, Reiber G, Unützer J, Chaney EF. Health care utilization and its costs for depressed veterans with and without comorbid PTSD symptoms. Psychiatric Services. 2009;60(12):1612-7.
46. Breslau N, Davis GC, Schultz LR. Posttraumatic stress disorder and the incidence of nicotine, alcohol, and other drug disorders in persons who have experienced trauma. Archives of General Psychiatry. 2003;60(3):289-94.
47. Bower P, Gilbody S. Stepped care in psychological therapies: access, effectiveness and efficiency: narrative literature review. The British Journal of Psychiatry. 2005;186(1):11-7.
48. Waller R, Gilbody S. Barriers to the uptake of computerized cognitive behavioural therapy: a systematic review of the quantitative and qualitative evidence. Psychological medicine. 2009;39(5):705-12.
49. Nollett C, Lewis C, Kitchiner N, Roberts N, Addison K, Brookes-Howell L, et al. Pragmatic RAndomised controlled trial of a trauma-focused guided self-help Programme versus InDividual trauma-focused cognitive Behavioural therapy for post-traumatic stress disorder (RAPID): trial protocol. BMC psychiatry. 2018;18(1):77.
50. DiMauro J, Carter S, Folk JB, Kashdan TB. A historical review of trauma-related diagnoses to reconsider the heterogeneity of PTSD. Journal of anxiety disorders. 2014;28(8):774-86.
51. Hamburg MA, Collins FS. The path to personalized medicine. New England Journal of Medicine. 2010;363(4):301-4.

Table 1: Characteristics of included studies

	Country	N	Method of recruitment	Method of diagnosis	Trauma type	Duration of treatment (weeks)	Relevant outcome measures
Engel 2015 (32)	USA	80	Adverts	Clinician rated	Military	6-8	PCL; PHQ-8; PHQ-15
Ivarsson 2014 (36)	Sweden	62	Adverts	Clinician rated	Various	8 weeks	PDS; BDI-II; BAI; QOLI
Knaevelsrud 2015 (31)	Iraq	159	Adverts	Self-reported	War related	5 weeks	PDS; HSCL-25; EUROHIS-QOL
Krupnick 2017 (30)	USA	34	Clinician referral	Self-reported	Military	10 weeks (check – 10 sessions)	PCL-M; PHQ-9
Kuhn 2017 (33)	USA	120	Adverts	Self-reported	Various	3 months	PCL-C; PHQ-8
Lewis 2017 (27)	UK	42	Clinician referral and advertisements	Clinician rated	Various	8 weeks	CAPS-5; BDI; BAI
Littleton 2016 (29)	USA	87	Adverts	Clinician rated	Rape	14 weeks	PSS-I; CES-D; FDAS
Litz 2007 (34)	USA	45	Adverts	Clinician rated	Military	8 weeks	PSS-I; BDI; BAI
Miner 2016 (28)	USA	49	Adverts	Self-reported	Various	4 weeks	PCL

I-CBT for PTSD

Spence 2011 (35)	Australia	42	Adverts	Clinician rated	Various	8 weeks	PCL-C; PHQ-9; GAD-7

Table 2: Characteristics of the included interventions

	Experimental intervention	Summary of treatment protocol	Guidance/facilitation	Control intervention
Engel 2015 (32)	DElivery of Self-TRaining and Education for Stressful Situa-tions (DE-STRESS)	• Variant of non-trauma focused CBT and stress inoculation training approaches. • Included: (1) Educational information about PTSD, stress, and trauma, as well as common co-morbid problems and symptoms (e.g. depression and survivor guilt). (2) Information on strategies to manage anger and promote better sleep hygiene, as well as indepth information on how to perform and practice deep, slow diaphragmatic breathing, and simple progressive muscle relaxation. (3) Cognitive reframing techniques. (4) Hierarchy of difficult and avoided situations that triggered deployment memories or were generally stressful. • Participants were required to complete homework to continue subsequent content. • Each login intended to take 15-30 minutes and homework assignments another 30 minutes.	**Guidance provided by:** nurses who were able to access a private portion of the DESTRESS-PC website where they could monitor compliance and symptom levels **Frequency of guidance:** as necessary **Automated contact:** none **Treatment fidelity:** unclear	**Optimised usual care** (consisted of usual primary care PTSD treatment augmented with low intensity care management, feedback to the primary care provider, and training of the clinic providers in management of PTSD. Designed to approximate the level of PTSD care normally provided in primary care while incorporating the non-specific treatment elements of the DESTRESS intervention).
Ivarsson 2014 (36)	(unnamed)	• Eight text-based modules delivered once a week. • Included: (1) Psychoeducation (2) Anxiety coping skill training (controlled breathing and conditioned relaxation, with skills training to facilitate trauma exposure, and some information on sleep) (3) Imaginal exposure (4) cognitive restructuring • Participants given an opportunity to make a personal commitment for change through a treatment contract. • Final module aimed at relapse prevention and maintenance of progress. • Mostly text and images with a “basic layout.”	**Guidance provided by:** clinical psychology students **Frequency of guidance:** once a week and occasional reminders via website **Automated contact:** none **Treatment fidelity:** weekly supervision with an experienced clinical psychologist	**Minimal attention** (answering weekly questions on wellbeing, stress and sleep (participants not required to answer questions and were told that this would not affect their later treatment. Weekly questions were neutral to minimise spontaneous trauma writing. A Clinician monitored responses for suicidal ideation and answered questions about trial.)

		• All modules accompanied by written homework assignments sent to therapist once a week. • New modules only made available once previous one had been completed.		
Knaevelsrud 2015 (31)	Interapy	• 2 weekly structured writing activities assigned each week over period of 5 weeks. • Incuded 3 treatment phases: (1) Self-confrontation with the traumatic event (2) Cognitive restructuring (3) Social sharing.	**Guidance provided by:** psychotherapists **Frequency of guidance:** Weekly reminder emails and phone contact if no response **Automated contact:** not reported **Treatment fidelity:** weekly supervision sessions, either face-to-face or via Skype	**Waitlist** (participants were on a waitlist for 6 weeks and then received the intervention)
Krupnick 2017 (30)	Warriors Internet Recovery and Education (WIRED) Adapted from Interapy	• 10 writing sessions (adapted from Interapy). • First 4 sessions confronted the trauma. • Next 4 focused on cognitive restructuring of maladaptive thoughts about the experience. • Final 2 sessions emphasised leave-taking and social sharing.	**Guidance provided by:** psychologist **Frequency of guidance:** Short response after each writing exercise and as required **Automated contact:** none **Treatment fidelity:** unclear	**Treatment as usual** (4 participants began and 1 completed a course of cognitive processing therapy; 8 participants received antidepressant medication; 1 participant received 13 sessions of acupuncture.)
Kuhn 2017 (33)	PTSD Coach	• Included four core sections. (1) The 'Learn' section provides PTSD psychoeducation, information about professional support, and material related to PTSD and the family. (2) The 'Track Symptoms' feature, allows users to complete the PTSD Checklist for DSM-5 and receive feedback on their severity scores, with recommendations for treatment if indicated.	None	**Waitlist** (participants received no intervention during the treatment period. After the post-treatment assessment, they were told that the app being studied was PTSD Coach and that it was available to download and use)

		(3) The 'Manage Symptoms' sections offers the user the opportunity to select a symptom-type to be offered appropriate coping tools. (4) The 'Get Support' section contains crisis support resources, including supportive contacts added by the user. • PTSD Coach condition participants were instructed to download the app and use it however they would like in an attempt to mimic real use.		
Lewis 2017 (27)	Spring	• Interactive, online, guided self-help intervention, which included 8 online steps designed for delivery over 8 weeks. • Steps focused on: (1) Psychoeducation (2) Grounding (3) Managing anxiety (4) Behavioural reactivation (5) Imaginal exposure (6) Cognitive techniques (7) In-vivo exposure (8) Relapse prevention	**Guidance provided by:** trauma therapists **Frequency of guidance:** Hour long introductory session followed by fortnightly appointments face to face or by phone **Automated contact:** none **Treatment fidelity:** therapists attended regular supervision meetings to maximise adherence to the manual	**Waitlist** (participants were on a wait list for 14 weeks and then received the intervention)
Littleton 2016 (29)	From Survivor to Thriver	• Nine programme modules to be completed sequentially • The program included 3 phases: (1) The first phase (modules 1-3) was designed to provide psychoeducation about PTSD and the impact of unwanted sex, as well as introduce general distress management strategies (i.e. relaxation, grounding) and healthy coping (e.g. asking others for help, setting an action plan) skills. (2) The second phase (modules 4-5) introduced the cognitive model and taught participants to identify distorted and unhelpful automatic thoughts and utilise the challenging questions technique to respond to these thoughts. (3) The third phase (modules 6-9) focused on using	**Guidance provided by:** clinical psychology students **Frequency of guidance:** Brief check-ins, approximately 5 minutes once every two weeks **Automated contact:** none **Treatment fidelity:** therapist competence was rated by psychologists unaffiliated with the project	**Psychoeducational website:** written informational content of the first 3 modules of the iCBT-based programme. No guidance from a therapist.

		a number of cognitive behavioural techniques (e.g. the challenging questions technique, the pros and cons technique, behavioural experiments) to address specific concerns common among women following sexual assault.		
Litz 2007 (34)	DElivery of Self-TRaining and Education for Stressful Situa-tions (DE-STRESS)	• Included: (1) Self-monitoring of situations that triggered trauma-related distress. (2) Generation of a serial ordering (hierarchy) of these trigger contexts in terms of their degree of threat or avoidance. (3) Stress management strategies. (4) Graduated, self-guided, in vivo exposure to items from the personalised hierarchy (starting with the least threatening or least avoided item in week 3). (5) Seven online trauma writing sessions. (6) A review of progress (charts of daily symptom reports were presented), a series of didactics on relapse prevention, and the generation of a personalised plan for future challenges.	Guidance provided by: Therapists Frequency of guidance: two hour long introductory session (including baseline assessment) followed by phone and email guidance as required. Automated contact: none Treatment fidelity: not reported	Non-CBT based internet intervention Included: (1) Monitoring non-trauma related concerns (2) Psychoeducation (3) Stress management. Guidance provided by: Therapists Frequency of guidance: two hour long introductory session (including baseline assessment) followed by phone and email guidance as required (focused on non-trauma related concerns). Automated contact: none Treatment fidelity: not reported
Miner 2016 (28)	PTSD Coach	• Participants given the app and instructed to use it however they would like for the following month. • No specific training, instructions for use, or suggestions of how PTSD Coach might be helpful were provided in attempt to represent real-world use.	None	Waitlist (no intervention over 1 month. Participants completed the post-condition assessment 1 month later. Upon completion of the post-condition assessment, participants received the PTSD Coach)
Spence 2011 (35)	(unnamed)	•7 step programme • Included: (1) Lesson 1: education about the prevalence, symptoms, and treatment of PTSD, including an explanation of the functional relationship between symptoms. (2) Lesson 2: instructions about controlling physical symptoms including dearousal strategies. (3) Lesson 3: basic principles of cognitive therapy, including strategies for monitoring and challenging thoughts.	Guidance provided by: Clinical psychologists Frequency of guidance: Weekly telephone calls or secure emails Automated contact: reminders and notifications Treatment fidelity: not reported	Waitlist (duration 8 weeks)

		(4) Lesson 4: education and guidelines about practicing graded exposure. (5) Lesson 5: education and guidelines about practicing imaginal exposure, using repeated written exposure, audio-recording, or both, and repeatedly listening to the recording. (6) Lesson 6: education and guidelines about challenging dysfunctional beliefs, including trauma related beliefs. (7) Lesson 7: information about relapse prevention and constructing relapse prevention plans.		

Table 3: Meta-analytic results

Comparison	PTSD symptoms post-treatment	PTSD symptoms follow-up (less than 6 months)	PTSD symptoms follow-up (6 to 12 months)	Depression symptoms post-treatment	Depression symptoms follow-up (less than 6 months)	Depression symptoms follow-up (6 to 12 months)	Anxiety symptoms post-treatment	Anxiety symptoms follow-up (less than 6 months)	Anxie sympt follow (6 to 1 month
Internet-based CBT versus waitlist/minimal attention/usual care	8 studies N = 560 SMD Random (95% CI): -0.60 (-0.97 to -0.24)	3 studies N = 146 SMD Random (95% CI): -0.43 (-1.41 to 0.56)	No data available	5 studies N = 425 SMD Random (95% CI): -0.61 (-1.17 to -0.05)	1 study N = 42 MD Fixed (95% CI): -8.95 (-15.57 to -2.33)	No data available	4 studies N = 305 SMD Random (95% CI): -0.67 (-0.98 to -0.36)	1 study N = 42 MD Fixed (95% CI): -12.59 (-20.74 to -4.44)	No dat availab
Internet-based CBT versus internet-based non-CBT	2 studies N = 82 SMD Fixed (95% CI): -0.08 (-0.52 to 0.35)	2 studies N = 65 SMD Fixed (95% CI): 0.08 (-0.41 to 0.57)	1 study N = 18 MD (95% CI): -8.83 (-17.32 to -0.34)	2 studies N = 84 SMD Fixed (95% CI): -0.08 (-0.53 to 0.37)	2 studies N = 61 SMD Fixed (95% CI): 0.20 (-0.31 to 0.71)	1 study N = 18 MD Fixed (95% CI): -8.34 (-15.83 to -0.85)	2 studies N = 74 SMD Random (95% CI): 0.08 (-0.78 to 0.95)	2 studies N = 60 SMD Fixed (95% CI): -0.16 (-0.67 to 0.35)	1 stud N = 18 MD Fi (95% C 8.05 (- to -0.9

[1] there was no quality of life data available at follow-up.

Figure 1: Flow diagram for study selection

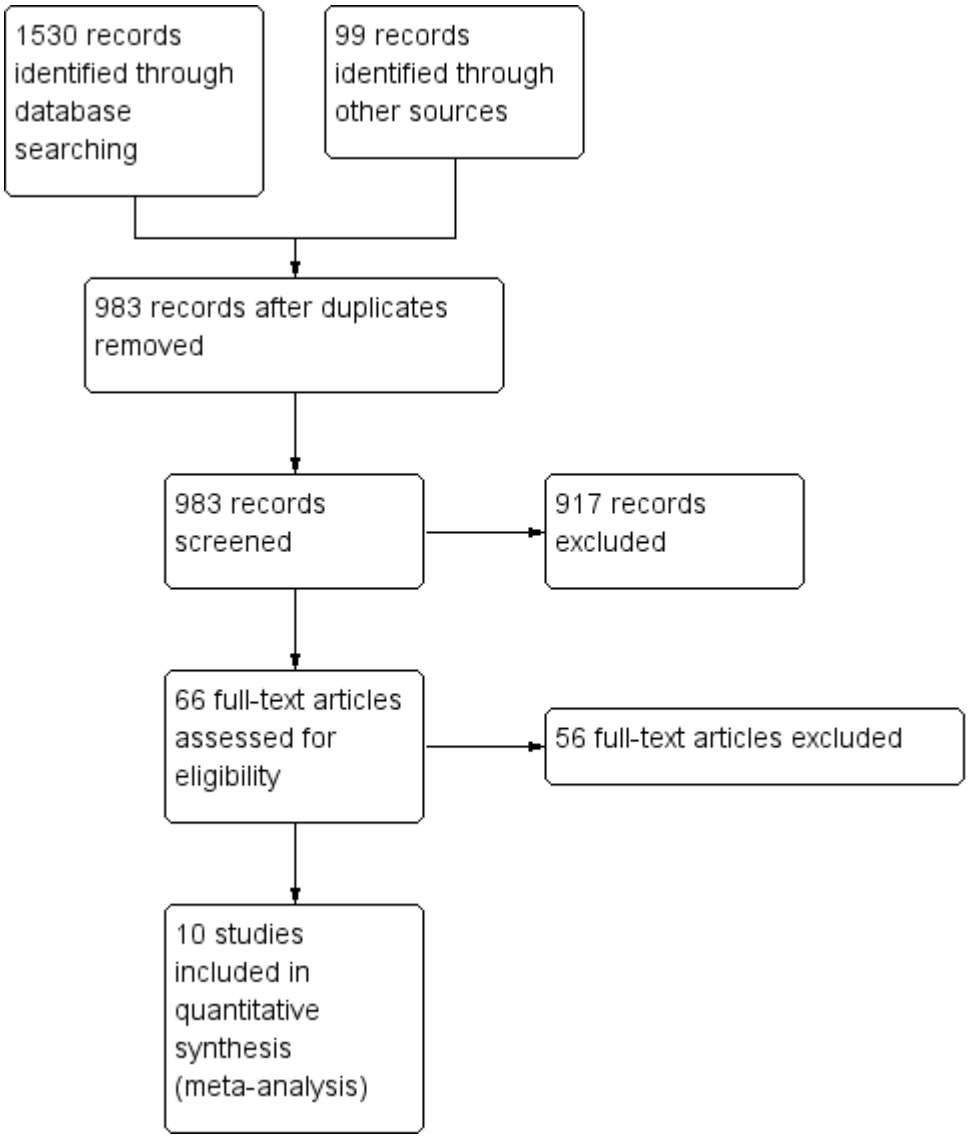
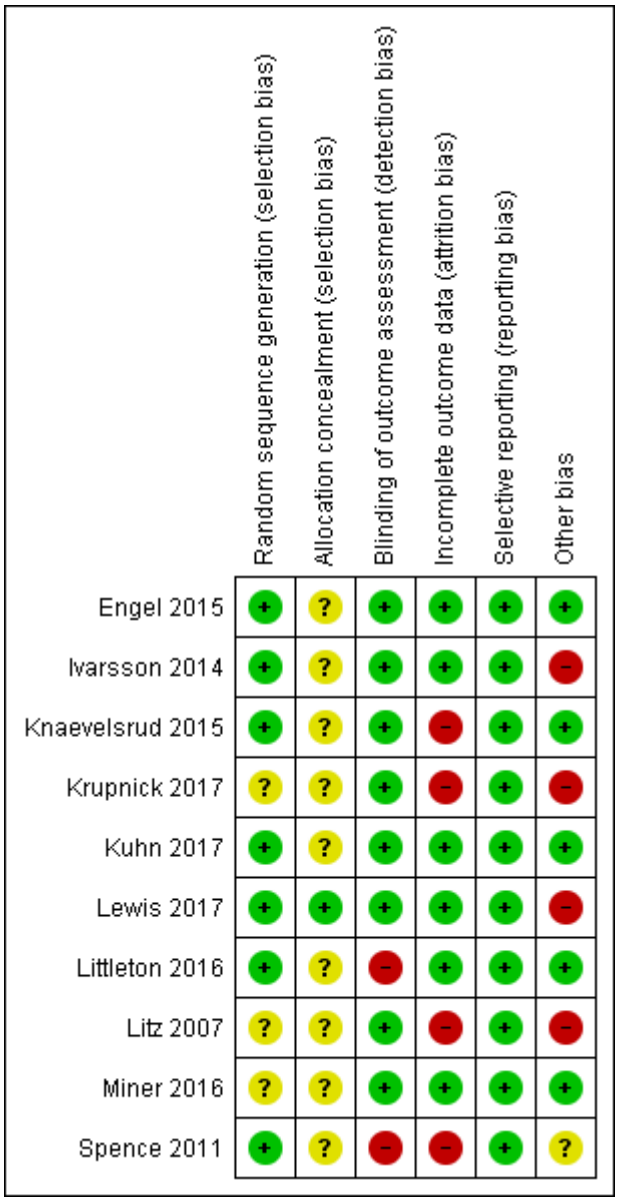
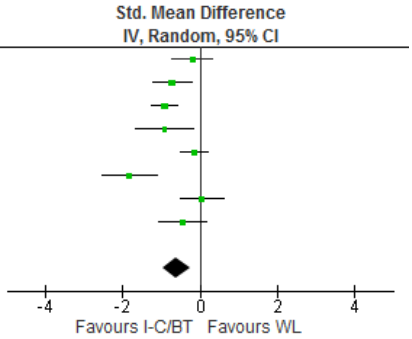


Figure 2: Methodological quality of included studies



Risk of bias judgments for each study (in seven domains: A = random sequence generation; B = allocation concealment;; C = blinding of assessors; D = incomplete data; E = selective reporting; F = other bias) are illustrated to the right of the forest plots (green = low risk; yellow= unclear risk; red = high risk).

Figure 3: i-CBT vs waitlist/usual care/minimal attention

Study or Subgroup	I-C/BT Mean	I-C/BT SD	I-C/BT Total	WL Mean	WL SD	WL Total	Weight	Std. Mean Difference IV, Random, 95% CI
Engel 2015	43.8	18.33	30	47.36	17.45	25	12.7%	-0.20 [-0.73, 0.34]
Ivarsson 2014	17.32	9.86	31	25.04	11.14	31	12.9%	-0.72 [-1.24, -0.21]
Knaevelsrud 2015	20.29	12.45	79	30.17	8.7	80	15.2%	-0.92 [-1.24, -0.59]
Krupnick 2017	3.58	0.3	16	3.91	0.4	15	10.1%	-0.91 [-1.66, -0.17]
Kuhn 2017	51.93	14.04	62	53.9	13.78	58	14.8%	-0.14 [-0.50, 0.22]
Lewis 2017	17.93	12.25	21	36.53	7.1	21	10.3%	-1.82 [-2.55, -1.09]
Miner 2016	56.31	10.51	25	55.77	12.99	24	12.3%	0.05 [-0.52, 0.61]
Spence 2011	44.78	17.29	23	51.79	12.51	19	11.6%	-0.45 [-1.06, 0.17]
Total (95% CI)			**287**			**273**	**100.0%**	**-0.60 [-0.97, -0.24]**

Heterogeneity: Tau² = 0.20; Chi² = 28.96, df = 7 (P = 0.0001); I² = 76%
Test for overall effect: Z = 3.22 (P = 0.001)