Combined pharmacotherapy and psychological therapies for post traumatic stress disorder (PTSD) (Review)

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[Intervention Review]

Combined pharmacotherapy and psychological therapies for post traumatic stress disorder (PTSD)

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ABSTRACT

Background

PTSD is an anxiety disorder related to exposure to a severe psychological trauma. Symptoms include re-experiencing the event, avoidance and arousal as well as distress and impairment resulting from these symptoms.

Guidelines suggest a combination of both psychological therapy and pharmacotherapy may enhance treatment response, especially in those with more severe PTSD or in those who have not responded to either intervention alone.

Objectives

To assess whether the combination of psychological therapy and pharmacotherapy provides a more efficacious treatment for PTSD than either of these interventions delivered separately.

Search methods

Searches were conducted on the trial registers kept by the CCDAN group (CCDANCTR-Studies and CCDANCTR-References) to June 2010. The reference sections of included studies and several conference abstracts were also scanned.

Selection criteria

Patients of any age or gender, with chronic or recent onset PTSD arising from any type of event relevant to the diagnostic criteria were included. A combination of any psychological therapy and pharmacotherapy was included and compared to wait list, placebo, standard treatment or either intervention alone. The primary outcome was change in total PTSD symptom severity. Other outcomes included changes in functioning, depression and anxiety symptoms, suicide attempts, substance use, withdrawal and cost.

Data collection and analysis

Two or three review authors independently selected trials, assessed their 'risk of bias' and extracted trial and outcome data. We used a fixed-effect model for meta-analysis. The relative risk was used to summarise dichotomous outcomes and the mean difference and standardised mean difference were used to summarise continuous measures.

Main results

Four trials were eligible for inclusion, one of these trials (n =24) was on children and adolescents. All used an SSRI and prolonged exposure or a cognitive behavioural intervention. Two trials compared combination treatment with pharmacological treatment and two compared combination treatment with psychological treatment. Only two trials reported a total PTSD symptom score and these data could not be combined. There was no strong evidence to show if there were differences between the group receiving combined interventions compared to the group receiving psychological therapy (mean difference 2.44, 95% CI -2.87, 7.35 one study, n=65) or pharmacotherapy (mean difference -4.70, 95% CI -10.84 to 1.44; one study, n = 25). Trialists reported no significant differences between combination and single intervention groups in the other two studies. There were very little data reported for other outcomes, and in no case were significant differences reported.

Authors' conclusions

There is not enough evidence available to support or refute the effectiveness of combined psychological therapy and pharmacotherapy compared to either of these interventions alone. Further large randomised controlled trials are urgently required.

PLAIN LANGUAGE SUMMARY

Combined pharmacotherapy and psychological therapies for post traumatic stress disorder (PTSD)

PTSD is a potentially debilitating anxiety disorder triggered by exposure to a traumatic experience such as an interpersonal event like physical or sexual assault, exposure to disaster or accidents, combat or witnessing a traumatic event. There are three main clusters of symptoms: firstly, those related to re-experiencing the event; secondly, those related to avoidance and arousal; and thirdly, the distress and impairment caused by the first two symptom clusters.

Both psychological therapy and pharmacotherapy have been used to treat PTSD and guidelines suggest that a combination of both may mean people recover from PTSD more effectively. Four trials including 124 participants were included in this review. One of these trials (n =24) was on children and adolescents. The trials all used SSRIs and prolonged exposure or a cognitive behavioural intervention. Only two trials reported on total PTSD symptoms but the data could not be combined.

In this review, there are too few studies to be able to draw conclusions about whether a combination of psychological therapy and pharmacotherapy result in better outcomes for patients than either of these treatments alone.

BACKGROUND

Description of the condition

PTSD is an anxiety disorder related to exposure to a severe psychological trauma. PTSD was first brought to public attention by combat veterans. It was formally recognised as a clinical disorder in 1980, when its description and diagnostic criteria were specified in the Diagnostic and Statistical Manual of Mental Disorders Version III (DSM-III) (APA 1980). The disorder stands alone in psychiatry in having the requirement of an external stimulus, the traumatic experience, which then results in PTSD symptoms. Re-experience of the event is common to both major diagnostic systems (DSM and ICD) as is avoidance and arousal. In DSM, distress or impairment are also required (Lopez-Ibor 2002). DSM is stricter in its definition of PTSD. It has been argued that these clinical decision rules for diagnosis of PTSD may be too restrictive and fail to recognise morbidity and associated impairment of functioning commonly reported by individuals with sub-threshold symptoms, particularly those who experience these over a long period of time (Mylle 2004). To address this limitation, various modifications have been proposed for DSM, such as Disorders of Extreme Stress, Not Otherwise Specified (DES-NOS), which is described under PTSD 'associated features'. DES-NOS includes symptoms relating to affect dysregulation, attention and consciousness (e.g. dissociation), disturbances in self perception, relations with others, somatization and disturbances in systems of meaning.

Finally, PTSD has been differentiated from Acute Stress Disorder (ASD) (another modification to DSM since the introduction of

PTSD) in which distressing re-experiencing, avoidance and arousal symptoms are reported within two days to four weeks of experiencing a trauma, but persist for no longer than four weeks. For this reason, it is now recommended that treatment for PTSD should not be considered until four weeks after symptoms are first reported (Ballenger 2004).

The estimated life time prevalence of PTSD in community samples ranges between five and ten per cent (ACPMH 2007). It affects women more than men. PTSD in men is more commonly related to combat exposure, and in women it is more commonly related to sexual assault and other forms of interpersonal violence (Kessler 1995). The reasons for higher rates in women are not fully understood but may be related to the type of trauma, younger age of exposure to trauma, stronger perceptions of threat and loss of control and biological reactions to trauma, to name a few (Olff 2007). On the other hand, gender differences have been noted for ICD-10 but not DSM-IV (APA 1994) diagnostic systems, due to the different endorsement of symptoms by males and females, and different configuration of symptoms in each diagnostic system (Peters 2006). There is some evidence of genetic vulnerability for PTSD (Yehuda 1999). The prognosis is often poor, with up to a third of patients not recovering after many years (Kessler 1995).

Description of the intervention

Psychological interventions

Treatments for PTSD were primarily focused on psychological interventions in the years immediately following its formal recognition. Clinicians of this orientation argued that relief of PTSD symptoms achieved with pharmacological interventions was superficial at best, and at worst, could hinder full resolution of the trauma. They also argued that it encouraged patients' early withdrawal from their longer-term psychological treatment (Friedman 1988).

Pharmacological interventions

Initially, pharmacological interventions, such as tricyclic antidepressants (TCAs) and mono-amine oxidase inhibitors (MAOIs), were regarded only as an adjunct to long-term psychotherapy, usually to address the symptoms of comorbid depression experienced by those with PTSD (Boehnlein 1985). By 1992, this position had changed considerably. It was argued that effective treatment of PTSD often required use of pharmacological interventions, although clinicians' awareness of the efficacy of these treatments was generally limited (Davidson 1992). Antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), have been the most commonly used pharmacological intervention (Davidson 1999; Davidson 2000). While few RCTs exist, antipsychotic medication is also used, most often in the case of patients who do not respond adequately to antidepressants and psychotherapy (Hamner 2005).

How the intervention might work

Psychological interventions are primarily based on cognitive processing theories that contend that it is not the nature of the event *per se* that affects subsequent psychological functioning, but the individual's appraisal of the event and the significance they attach to it (e.g., Foa 1989; Creamer 1992). Trauma-focused CBT, including forms of exposure, emerged from cognitive processing theories and is now recommended treatment for the clinical management of PTSD (ACPMH 2007).

Pharmacotherapy may work by correcting imbalances in neurotransmitters thought to play a role in causing and/or maintaining PTSD symptoms (Stein 2000).

The combination of the two interventions may further enhance treatment outcomes, particularly in those with comorbid conditions, with pharmacotherapy making exposure therapy more tolerable (Marshall 2000).

Why it is important to do this review

Clinical expert opinion on the treatment of PTSD has been revised considerably during the past six years.

A consensus statement on PTSD treatment in 2000 recommended psychotherapy (exposure therapy, stress inoculation training and cognitive therapy) for mild PTSD and a combination of psychotherapy and pharmacotherapy for moderate to severe cases of this disorder (Ballenger 2000). Recommendations made in the most recent update of this statement focus on the early use of SSRIs and/or CBT within 3 to 4 weeks of presentation of substantial, persistent PTSD symptomatology. This revised statement advised that treatment for chronic PTSD may be most effective in the longer term when both SSRIs and CBT are included in the treatment plan (Ballenger 2004) .

A number of systematic reviews have been prepared about psychological interventions for preventing and treating PTSD. Neither single session (Rose 2002) nor multiple session (Roberts 2009) interventions were recommended as interventions to prevent PTSD. Bisson 2007, in a Cochrane systematic review, concluded that trauma-focused cognitive behavioural therapy (CBT), as individual or group therapy, eye movement desensitisation and reprocessing (EMDR) and stress management were effective in reducing PTSD symptoms. These reviews are of adults; a Cochrane protocol (Gillies 2007) aims to examine the effectiveness of psychological interventions to prevent and treat PTSD in children and adolescents.

A Cochrane review of pharmacotherapy in adults with PTSD concluded that pharmacotherapy can be effective in treating symp-

toms, and that SSRIs should be first line agents for this disorder (Stein 2006).

While combination treatments for PTSD are recommended by clinical expert opinion as potentially effective, a systematic review of the literature is required to appraise and assemble the evidence for this. This review also adds to the programme of Cochrane reviews on the prevention and treatment of PTSD.

OBJECTIVES

The purpose of this review was to assess:

1. whether the combination of psychological therapy and pharmacotherapy provides a more efficacious treatment for PTSD than either of these interventions delivered separately

2. whether combination treatment is tolerable to patients with diagnosed PTSD.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials were included. Cluster randomised controlled trials and cross over trials would have been included, however, none were identified. Quasi-randomised controlled trials were not included.

Types of participants

Patients of any age or gender with a primary diagnosis of PTSD, diagnosed by a clinician using a structured or semi structured interview based on DSM (APA 1994) or ICD (WHO 1992). Participants with sub-clinical symptoms were also included. Sub-clinical symptoms were defined as at least one symptom in each of the three symptom clusters (re-experiencing, avoidance, arousal) or any acceptable definition adopted by the trialist. Definitions were noted and described in Characteristics of included studies. Trials of interventions for those with ASD were not included.

Chronic (>2 years or as defined by the trialist) and recent onset (<2 years or as defined by the trialist) PTSD with any length of untreated illness, and of any severity (as defined by the trialist usually as a score on a PTSD scale), arising from any type of event relevant to the diagnostic criteria, including and grouped according to: 1. interpersonal events; 2. disaster or accidents; 3. combat; and 4. witnessing an event, were included. Those with psychiatric comorbidity, except psychotic illness, were included. These aspects of the population were recorded, given their potential effect on the treatment outcome.

Types of interventions

Intervention

Combination of any type of pharmacotherapy and any type of psychological therapy were included, including individual and group therapies. Categories of pharmacotherapy include SSRIs, SNRIs, tricyclic antidepressants, anxiolytic medication, mood stabilizers, atypical antipsychotics and other. Categories of psychological therapy comprise cognitive and/or behavioural approaches (including exposure therapy and trauma-focused CBT), eye movement desensitisation and reprocessing (EMDR), interpersonal therapy, supportive counselling and psychodynamic treatments.

Control conditions

1. Waitlist control
2. Pharmacotherapy placebo (which may be used in conjunction with psychological therapy)
3. Standard treatment
4. Pharmacotherapy alone
5. Psychological therapy alone

Trials that combined two pharmacological interventions within a trial or two psychological therapies within a trial were excluded. Trials were also excluded where the combined treatment was usual care and psychological therapy or pharmacological therapy.

Main comparisons

The main comparisons made included:

1. Combination psychological and pharmacological intervention vs waitlist control;
2. Combination psychological and pharmacological intervention vs pharmacotherapy placebo;
3. Combination psychological and pharmacological intervention vs standard treatment;
4. Combination psychological and pharmacological intervention vs pharmacotherapy alone;
5. Combination psychological and pharmacological intervention vs psychological therapy alone

Separate meta-analyses were undertaken for children/adolescents using these comparisons.

In future versions of this review, we anticipate reducing the number of comparisons and outcomes given the large number of analyses these may result in (which increase the chances of spurious findings). In the update we will include the following comparisons only:

- Combination psychological and pharmacological intervention vs pharmacotherapy alone

- Combination psychological and pharmacological intervention vs psychological therapy alone

Types of outcome measures

Primary outcomes

1. Change from baseline to endpoint (or endpoint scores) of PTSD symptom severity using valid and reliable clinician-rated scales (e.g. The Clinician-Administered PTSD Scale, CAPs, Blake 1990; the Short PTSD Rating Interview, SPRINT (Davidson 2001))
2. Number of withdrawals due to adverse events (number of events)

Secondary outcomes

1. Change from baseline to endpoint (or endpoint scores) of PTSD symptom severity using valid and reliable self-rated scales (e.g. The Child PTSD Rating Scale, CPSS, Foa 2001)
2. Change (or endpoint) in Global Functioning scores using valid and reliable scales (e.g. The Global Assessment of Functioning score, GAF APA 1994)
3. Change from baseline to endpoint (or endpoint scores) of comorbid depression/anxiety using valid and reliable (a) clinician-rated and (b) self-rated scales (e.g. the Beck Depression Inventory Beck 1961; The State Trait Anxiety Inventory Spielberger 1970)
4. Change from baseline to endpoint (or endpoint scores) of suicidal ideation using valid and reliable scales (e.g. The Scale for Suicidal Ideation, SSI, Beck 1979)
5. Suicide attempt (reported in number of events)
6. Comorbid substance use (reported in number of events or on valid and reliable scales) (e.g. Penn Alcohol Craving Scale Flannery 1999)
7. Vocational and social functioning (either in number of events e.g. return to full time work or on valid reliable scales e.g. The Work and Social Adjustment Scale, Mundt 2002)
8. Quality of life using valid and reliable scales (e.g. The Quality of Life Scale, Burckhardt 2003)
9. Cost of treatment

While originally listed as a primary outcome in the protocol of this review, Global Functioning scores and self-rated PTSD scores were moved to secondary outcomes in the review. The number of withdrawals due to adverse events was moved to the primary outcomes according to the Cochrane Handbook (Higgins 2008). As with the comparisons, we anticipate that in future updates we will reduce the number of outcomes in order to reduce the likelihood of multiple analyses generating spurious results. Outcomes will be limited to:

1. Change from baseline to endpoint (or endpoint scores) of PTSD symptom severity (clinician-rated standardised, validated, reliable rating scales)
2. Change from baseline to endpoint (or endpoint scores) of PTSD symptom severity (self-rated standardised, validated, reliable rating scales)
3. Change (or endpoint) in Global Functioning scores (standardised, validated, reliable rating scales)
4. Change from baseline to endpoint (or endpoint scores) of comorbid depression/anxiety (standardised, validated, reliable rating scales)
5. Number of withdrawals due to adverse events (number of events)

Search methods for identification of studies

The Cochrane Depression, Anxiety and Neuorosis Group (CCDAN) maintains two clinical trials registers at their editorial base in Bristol, UK, a references register and a studies based register. The CCDANCTR-References Register contains over 24,500 reports of trials in depression, anxiety and neurosis. Approximately 70% of these references have been coded to individual trials. These coded trials are held in the CCDANCTR-Studies Register (which contains over 11,000 records). Records are linked between Registers through the use of unique Study ID tags. Coding of trials is based on the EU-Psi coding manual.

References to trials for inclusion in the Group's registers are collated from routine (weekly) generic searches of MEDLINE, EMBASE and PsycINFO; quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and review specific searches of additional databases (PSYNDEX, LILACS, AMED, CINAHL). Details of CCCDAN's generic search strategies can be found in the 'Specialized Register' section of the Cochrane Depression, Anxiety and Neurosis Group's module text.

Details of trials are also sourced from international trials registers c/o the World Health Organisation's trials portal (http://apps.who.int/trialsearch/), drug companies, the hand-searching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses.

Electronic searches

a) In 2007 and in June 2010, the CCDAN trial registers were searched by Hugh McGuire and (later) Sarah Dawson, CCDAN Trials Search Co-ordinators (TSC) using the following terms:

CCDANCTR-Studies

Diagnosis = Post-Traumatic Stress Disorders

And

Intervention = "Combined Modality"

The TSC screened search results to exclude studies which combine two pharmacological interventions within a trial or two psychological therapies within a trial. Studies were also excluded where the combined treatment was usual care and psychological therapy or pharmacological therapy

CCDANCTR-References

Keyword = “stress disorder*”
Or
Full-text = PTSD or “trauma* stress”
Again, results were screened in a similar way to above and references obviously not relevant were excluded.
Any published or unpublished (including unpublished abstracts and reports) were eligible for inclusion. There were no date or language of publication restrictions applied in the search or selection.

Searching other resources

Reference lists

The reference section of each included trial was searched.

Personal communication

In order to ensure that as many as possible RCTs were identified, the authors of the included trials and other experts in the field were consulted to find out if they knew of any published or unpublished RCTs in the area which had not been identified in the search.

Data collection and analysis

Selection of studies

Two review authors independently selected trials for possible inclusion in the study. Firstly, the titles and abstracts of trials identified from the search were independently reviewed. Secondly, each review author independently examined the full text of all studies that they considered to be of possible relevance. Each review author compiled a list of studies, which they believed met the inclusion criteria. The content of each review author’s list was compared, and any discrepancies discussed. Any disagreement was resolved by discussion and consensus between all of the review authors.

Data extraction and management

Two review authors independently extracted data using specially developed data extraction forms. Information was collected on:

1. Participants: age, gender, ethnicity, incident episode, length of time since episode, length of time since onset of PTSD, severity of PTSD, previous treatment for PTSD or other mental health disorders, type and severity of comorbid substance use disorder(s) and other psychiatric comorbidities and suicide-related behaviours.
2. Interventions and comparisons: description of medication including planned and actual dose, length of treatment and description of psychological intervention including type, whether it is delivered to groups or individuals, whether it was manualised, who delivered it and for how long, and the actual amount of therapy received. Information on other adjunctive interventions was also collected. The number of participants randomised to each group, as well as total drop-outs and drop-outs due to adverse effects, was extracted.
3. Outcome measures: description of measures used, timing of administration, continuous/dichotomous nature, psychometric properties, references.
4. Results: point estimates and measures of variability and frequency counts for dichotomous variables.
One review author compiled all comparisons and entered outcome data into the Review Manager software program for meta-analysis. A second review author performed double-data entry to ensure accuracy of results. We sought to obtain missing data from trial authors wherever possible.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias of the included trials using a descriptive approach as advocated by the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). Potential for bias, including selection, performance, attrition and detection bias, was considered using the following criteria:

Sequence generation

Was the allocation sequence adequately generated?

Allocation concealment

Was the allocation adequately concealed?

Blinding of participants, personnel and outcome assessors

Were the allocated interventions adequately blinded during the study? (participant/care provider)? How did you know that blinding was maintained? (In this review, given psychological treatment is one of the interventions, it was not possible for the participant and provider to be blinded). Were the outcome assessors adequately blinded to the allocated interventions?

Incomplete outcome data

Were dropouts and exclusions adequately addressed? (Were losses to follow-up described?) Were intention-to-treat analyses used?

Selective outcome reporting

Have authors reported on all the outcomes they set out to? To assess reporting bias, we recorded which of the review outcomes were available with usable data from each included trial as well as noting which of the review outcomes were only reported in

terms of whether there were significant differences between groups. Additionally the other outcomes (not collected for the review) reported by the trialists in the paper publication(s) were compiled.

Other sources of bias

Was the study apparently free of other problems that could mean a high risk of bias e.g. early stopping, baseline imbalance, choice of design, evidence of carry over effect, funding?

Each criterion was graded as yes, no or unclear, and scored as adequate (A), unclear (B) or inadequate (C), according to the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). When criteria were scored as unclear, one review author attempted to obtain further information from the authors of the trial. The review authors discussed any disagreement in the assessment of risk of bias to reach a consensus.

Measures of treatment effect

For dichotomous outcomes, such as 'response', results from each trial were expressed as a Risk Ratio (RR) with 95% confidence intervals, and combined in meta-analysis.

Continuous outcomes, such as symptom measures, may be presented in several ways. When absolute values of post-treatment means and standard deviations (SD) were given, using the same rating scale across studies, these were used to calculate the mean difference (MD) and 95% confidence intervals. If different scales were used to measure the same outcomes the standardised mean difference (SMD) was calculated with 95% confidence intervals and then combined for meta-analysis.

Unit of analysis issues

Cross-over trials were eligible for inclusion only when possible to extract data from the first treatment period; or when inclusion of data from both treatment periods is justified by a sufficiently long wash-out period to minimise the effects of 'carry-over'. Data from both periods can only be included when it is possible to determine the correlation between participants' responses to interventions in the different phases (Elbourne 2002).

Had studies that randomise or allocate clusters (professionals or health care organisations) been included that did not account for clustering during analysis they would have been reanalysed using the intraclass correlation coefficient (ICC), noting from where this ICC was obtained.

There were no multiple arm trials included in the current review. Should multiple treatment group trials be included in any update, unit of analysis errors will be avoided by combining all relevant experimental intervention groups of the study into a single group, and combining all relevant control intervention groups into a single control group.

Review authors also checked for and report where skewed data exist (in updates if there is skewed data, these will be reported in additional tables). This was checked by comparing whether the standard deviation for an observed mean was larger than the mean.

Dealing with missing data

Trial authors were contacted for any missing data. Missing data were imputed in order that standard deviations could be obtained. Data from intention-to-treat (ITT) were extracted in the first instance with the type of imputation carried out by trialists noted. If it had been possible, observed case (OC) data (as well as last observation carried forward data) would have been extracted and results compared with ITT data, with results compared in the context of the assumptions inherent in both these types of data.

Assessment of heterogeneity

We ensured clinical homogeneity by only combining studies when participants, interventions and outcome measures were considered to be similar. As such, studies of adults and children/adolescents were considered too different to combine. All studies included SSRIs but in future updates it may be necessary to stratify analyses by medication category as different medications may have differing effects (Categories of pharmacotherapy include SSRIs, SNRIs, tricyclic antidepressants, anxiolytic medication, mood stabilizers, atypical antipsychotics and other). In future studies it may be necessary to stratify analyses by psychotherapy type (Categories of psychological therapy comprise cognitive and/or behavioural approaches (including exposure therapy and trauma-focused CBT), eye movement desensitisation and reprocessing (EMDR), interpersonal therapy, supportive counselling and psychodynamic treatments). For trials that were clinically heterogeneous or presented insufficient information for pooling, a descriptive analysis of main results was performed. Statistical homogeneity was assessed using the I-squared (I^2) statistic (Higgins 2003).

As a rough guide the review authors used the following:

0% to 40%: might not be important;

30% to 60%: may represent moderate heterogeneity;

50% to 90%: may represent substantial heterogeneity;

75% to 100%: considerable heterogeneity.

Additionally, the importance of the observed value of I^2 depends on (i) magnitude and direction of effects and (ii) strength of evidence for heterogeneity (e.g. P value from the chi-squared test, or a confidence interval for I^2) and these factors were taken into consideration. Given the small number of studies, analysis of heterogeneity is limited.

Assessment of reporting biases

We aimed to investigate the potential for publication bias using a funnel plot for the primary outcomes relating to PTSD diagnosis and/or symptoms. However, given so few studies were included in the review, this was not feasible. Publication bias has long been associated with funnel plot asymmetry, however asymmetry may

be due to reasons other than publication bias and is difficult to assess in the case of a small number of trials.
An assessment of the risk of reporting bias was also included as stated above.

Data synthesis

When appropriate, meta-analysis was performed and pooled effect estimates obtained, using the Review Manager statistical software program.
For all meta-analyses a fixed-effect (Mantel 1959) meta-analysis was used in the first instance. Where statistical heterogeneity was found, it was examined by subgroup and sensitivity analyses. Where this did not account for heterogeneity, we used the random-effects models (DerSimonian 1986). When the pooled summary statistic using the random-effects model differed from that using the fixed-effect model, it was reported.

Subgroup analysis and investigation of heterogeneity

If statistical heterogeneity was found, the aim was to examine it by the following subgroup analyses, should there be a sufficient number of studies.
1. Short term (acute) (<2 years) vs chronic PTSD (>2 years)
2. Mild vs severe PTSD (according to established scores on validated symptom severity measures)

3. Comorbid substance use disorders (SUD) vs no comorbid SUD (diagnosed according to DSM or ICD)
There were insufficient studies however to undertake these subgroup analyses.
In future updates of the review, the number of subgroup analyses will be reduced to avoid the large number of analyses these may result in (which increase the chances of spurious findings). The following subgroup analysis will be included:
1. Acute (<2 years) vs chronic PTSD (>2 years)

Sensitivity analysis

The aim was to perform sensitivity analyses to assess the robustness of findings to decisions made about the risk of bias in studies. The following groups were defined:
1. Allocation concealment is rated as yes, no or unclear (and attempts to clarify with authors fail) (A)
2. Blinding of outcome assessment is rated as yes, no or unclear (and attempts to clarify with authors fail) (B)
3. Intention-to-treat analysis is rated as yes, no or unclear (and attempts to clarify with authors fail) (C).
These criteria for assessing the risk of bias have been shown to influence estimates of treatment effect (Juni 2001). The aim was to perform sensitivity analyses in which studies categorised as A, B or C were excluded, however, there were too few studies for this to be meaningful.
In the future sensitivity analysis will be conducted removing those studies where imputation of data was carried out.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.
See also Characteristics of included studies.

Results of the search

Over time, two searches were run on the CCDAN registers by TSCs Hugh McGuire (HM) in 2007 and Sarah Dawson (SD) in 2010. The first set of searches were screened by HM and 11 studies and 3 uncoded references were sent to authors. Separate searches run by authors at the time identified 111 citations from MEDLINE and 9 from PsycINFO. When combined (and excluding duplicates) a total of 123 citations were retrieved; 106 were excluded following scrutiny of the title/abstract and the full paper of 17 possibly included studies were retrieved for closer inspection. Of these, 11 were excluded, 4 (Cohen 2007; Otto 2003; Rothbaum 2006;Simon 2008) were included, some with multiple publications, and one (Pai 2004) was an ongoing trial.
In the 2010 searches conducted by SD, 122 references were identified. Following screening at the editorial base, reports of 10 new studies were sent to authors, of which one was judged irrelevant, five were formally excluded and four placed in the 'Ongoing studies' section of the review.

Included studies

Four trials were completed and published, although data for meta-analysis were not available from all of these trials for all outcomes. The size of the trials varied between 10 (Otto 2003) and 65 (Rothbaum 2006) participants. The trials were undertaken in Cambodia (Otto 2003) and the USA (Cohen 2007; Rothbaum 2006 Simon 2008). Three of the included studies were of adults and one was of children and adolescents (Cohen 2007). This study was of females only, as was one of the adult studies (Otto 2003).

Participants

In all of the adult trials, PTSD was the primary diagnosis. In all trials PTSD was diagnosed using a structured clinical interview for PTSD based on the DSM-IV (Cohen 2007; Otto 2003; Rothbaum 2006) or the Mini International Neuropsychiatric Interview (MINI) (Simon 2008).The index trauma in Otto 2003

was exposure to the Pol Pot regime in Cambodia (including starvation, overwork, execution, threat of death, torture, severe physical deprivation and physical and/or sexual violence); in Simon 2008 and Rothbaum 2006 the predominant type of index trauma was exposure to physical and/or sexual abuse. Comorbid anxiety and depression symptoms were evident in the participants in each of the trials, but other comorbidities, notably substance use and suicidality were not documented.

In the trial of Cambodian refugees (Otto 2003), inclusion was on the basis of previous failure to response to clonazepam. In Simon 2008,participants were included in the trial if they remained symptomatic after eight weekly 90 to 120 minute sessions of prolonged exposure. In no trial was there description of treatments that had been received by participants prior to involvement in the studies.

In the trial of children and adolescents (Cohen 2007), all participants had sexual-abuse related PTSD symptoms (defined as at least 5 symptoms on the Schedule for Affective Disorders and Schizophrenia in School Aged Children, K-SADS-PL) with at least one symptom in each of the three clusters. They were required to have had these symptoms for at least two years. 68.2% met criteria for comorbid diagnoses (72.7% in the combined pharmacotherapy and psychological therapy group; 63.5% in the psychological therapy and placebo group) with all but one experiencing major depressive disorder. Details of other comorbidities were not reported, but it was noted by the trialist that of those with at least one comorbid diagnosis some had a diagnosis of substance abuse not otherwise specified (Cohen 2007).

Interventions

In the smaller trial of Cambodian refugees (Otto 2003), the psychological intervention added to pharmacotherapy was CBT-based and covered the following elements: (1) information on the symptoms and nature of PTSD from a cognitive-behavioural perspective, (2) clarification of the difference between PTSD symptoms and culturally-distinct fears of death or disability associated with somatic symptoms, (3) exposure to somatic sensations associated with PTSD and anxiety, (4) exposure to memories of specific trauma events with rehearsal of emotional acceptance and cognitive coping strategies, (5) progressive muscle relaxation and diaphragmatic breathing skills, and (6) self-care skills and assignment of pleasant events. This treatment was provided in a group setting over 10 sessions. The length of this intervention period is unclear (Otto 2003). Information on training of therapist(s) who provided this treatment is not given. The pharmacotherapy comprised their existing dosage of the benzodiazepine, clonazepam, and a titrated dosage of sertraline (up to 200mg/day) commenced at the beginning of the trial period (trial period unspecified).

In the trial by Rothbaum 2006, prolonged exposure treatment was given and comprised: psychoeducation about common reactions to trauma, breathing retraining, *in vivo* exposure, prolonged imaginal exposure and homework. Prolonged imaginal exposure consisted of reliving the traumatic event in imagination and recounting the memory in the present tense for 45-60 minutes per session. Participants received 10 twice-weekly sessions, each lasting 90-120 minutes (Rothbaum 2006). Therapists at all three sites had at least a master's degree in clinical psychology. All participants that had had a 10 week course of sertraline were randomly assigned to remain on sertraline alone (up to 200mg/day) for a further five weeks or to receive 10 sessions of prolonged exposure therapy in addition to sertraline over this period.

In the third adult trial (Simon 2008), patients were randomised to receive paroxetine CE (mean 45.8mg) or placebo as augmentation to an additional five sessions of prolonged exposure (delivered every second week). Few details are given about the prolonged exposure treatment. It was delivered according to a standard protocol developed by one of the authors. The prolonged exposure treatment was delivered less intensively in the intervention than it had been delivered prior to randomisation to augmentation with paroxetine (every two weeks rather than weekly).

In the trial of children and adolescents (Cohen 2007), participant (all females) were randomly assigned to sertraline (up to 200mg/day) and 12 sessions of trauma-focused CBT or placebo and 12 sessions of trauma-focused CBT. Parents were included in the psychological intervention which included parenting skills, psychoeducation, relaxation, affect modulation, cognitive processing, trauma narrative, in vivo mastery of trauma reminders, conjoint child-parent session, and enhancing safety, healthy sexuality, and future development. Therapists were master's degree level social workers.

Outcomes

A range of outcome measures were used in the included trials. In the study of Cambodian refugees (Otto 2003), a total PTSD score was not given, but rather subscale scores from the Clinician Administered PTSD Scale (CAPS) including re-experiencing, avoidance and arousal were used. Rothbaum 2006 used the Structured Interview for PTSD (SIP) which yields a total severity score. Simon 2008 used the clinician rated Short PTSD Rating Interview (SPRINT). Simon 2008 also provided data from the Clinical Global Impression-Severity of Illness scale (CGI-S). Otto 2003 measured depression and anxiety on the Hopkins Symptom Checklist-90. Rothbaum 2006 measured depression using the Beck Depression Inventory and anxiety using the State-Trait Anxiety Inventory with the state anxiety scale being used. Both of these trials provided appropriate data for depression and anxiety symptoms for meta-analysis. None of the adult studies provided data on functioning.

In the trial of children and adolescents the K-SADS-PL - PTSD section and the Children's PTSD Symptoms Scale (CPSS) was used. A total PTSD symptom score for the K-SADS-PL was not provided for each of the intervention and comparison groups, nor were scores provided for the CPSS. Cohen 2007 measured de-

pression using the Beck Depression Inventory and the Mood and Feeling Questionnaire and measured anxiety with the Screen for Children's Anxiety Related Disorders (SCARED); however no usable data was provided. Cohen 2007 did provide data on functioning, using the CGAS. All of the above instruments are well-documented with good psychometric properties.

Excluded studies

See also table of Excluded studies.

In two of the excluded studies, interventions comprised only psychological treatments with no regulation of medications used during the study period (Kessler 2003; Wright 2003). In one study, participants were allocated to three groups: psychological treatment alone, psychological treatment plus medication, or medication alone. The use of medication was not regulated and could have included anxiolytics and/or tricyclic antidepressants (Drozdek 1997). Two studies by Hinton (Hinton 2004; Hinton 2005) were also excluded, both on the basis that the psychological treatment (CBT) was used as an add-on to existing medication treatment that was not regulated over the period of the intervention. One study was not an RCT (Oflaz 2008). One study examined the effects of pharmacological treatments for sleep in addition to other treatments for PTSD (Abramowitz 2008); another was a dose-finding trial (Bouso 2008). Several studies featured non-pharmacological treatments that could not be described as 'psychological' in nature e.g. 'script driven traumatic imagery' (Brunet 2008); 'collaborative care' (Chan 2008), 'rTMS' (Osuch 2009) and 'biofeedback' (Zucker 2009) did not meet criteria for psychological therapy for this review. The final studies did not include a group receiving combined medication and psychological intervention (Clark 2008; Cottraux 2008; Resnick 2008; van der Kolk 2007).

Ongoing Studies

Five studies appear in this review's list of currently ongoing studies which may or may not meet final inclusion for updates of this review. See also table of Characteristics of ongoing studies.

One ongoing study (Pai 2004) was identified that examines the effectiveness of several interventions for adults with comorbid PTSD and alcohol dependence. The study uses a 2 (naltrexone vs. placebo) X 2 (CBT: prolonged exposure vs. no-prolonged exposure) design to assess the efficacy of naltrexone (NAL), prolonged exposure (PE), and their combination (NAL + PE), vs. pill placebo (PBO). One study (Gamito 2005) appears to involve a three-way comparison between virtual reality exposure (VRE), drug treatment; and VRE + drug treatment. A third involves the administration of an antibiotic d-cycloserine in addition to CBT (Guay 2007); a fourth, the addition of fluoxetine to veterans already receiving psychological treatment (Hicks 2009) and the final study (McAllister 2009) appears to involve venlaflaxine in addition to CBT, although the number of arms in this trial is not clear.

Risk of bias in included studies

Allocation

Only one trial gave details of the randomisation generation, stating that a computer generated random number sequence was generated (Cohen 2007). No details were provided in the other trials. There were no details given about the concealment of allocation in any of the published reports; however Simon 2008 did provide additional information confirming allocation was concealed.

Blinding

It was not possible to blind care providers or participants to the interventions in two of the adult trials, but in the Simon 2008 study where paroxetine CR was added, providers and participants were blinded due to use of a placebo pill. In the trial of children and adolescents, the use of a placebo pill also allowed blinding. Outcome assessors were blind to treatment allocation in Cohen 2007, Rothbaum 2006 and Simon 2008 but not in the small trial conducted in Cambodia (Otto 2003).

Incomplete outcome data

Rothbaum 2006 described drop outs and reported using intention-to-treat analysis; Simon 2008 described drop-outs and reported use of intention-to-treat analysis for 23 of the initial 25 randomised participants, but the remaining studies (Cohen 2007; Otto 2003) did not provide detail.

Selective reporting

It is difficult to assess reporting bias given limited access to trial protocols to assess *a priori* outcomes.

It should be noted that there were very little usable data for PTSD symptom outcomes. In two trials, PTSD total scores were not reported for each group (Cohen 2007; Otto 2003) and Cohen 2007 did not report all measures stated as being used.

Simon 2008 reports data obtained from one centre only of a larger four-centre trial. Data from the other three centres have not yet been published. We also noted that in Simon 2008 the SPRINT is the only *a priori* outcome mentioned in the methods, but the CGI-S outcomes are reported, raising the possibility that other outcomes were measured and not reported.

Other potential sources of bias

The studies were generally small (ranging from 10 to 65 participants). In the trial by Cohen 2007 participants were not formally diagnosed with PTSD but were entered into the trial if they had PTSD symptoms (defined as at least 5 symptoms on the Schedule for Affective Disorders and Schizophrenia in School Aged Children, K-SADS-PL).

Effects of interventions

Few data from any included trial could be used in meta-analysis. Data pooling for the PTSD outcome was impossible. Despite attempts to contact all authors, we were only able to secure additional data for one included trial (Rothbaum 2006), and one ongoing trial (Pai 2004) (although no outcome data were provided given this study is yet to be completed).

Three trials included sertraline alone (Cohen 2007; Otto 2003; Rothbaum 2006) and compared it to sertraline plus individual prolonged exposure (Rothbaum 2006) or sertraline plus group CBT (Otto 2003) or sertraline plus trauma focused CBT (Cohen 2007). The fourth trial examined prolonged exposure and compared it to prolonged exposure plus paroxetine CR (Simon 2008). There were only trials available for two comparisons (with results for adults and children/adolescents reported separately; hence, three comparisons in total).

- Combination psychological and pharmacological intervention vs pharmacotherapy alone
- Combination psychological and pharmacological intervention vs psychological therapy alone

1) Combination psychological and pharmacological intervention vs pharmacotherapy alone

PTSD symptom severity (clinician rated)

Two studies (Otto 2003 and Rothbaum 2006) compared psychological and pharmacological intervention versus pharmacotherapy alone.

One study (Rothbaum 2006, n = 65) reported a total PTSD symptom score. In Rothbaum 2006 there were no statistically significant differences between the group receiving both an SSRI and psychotherapy and those receiving an SSRI alone (mean difference -4.70, 95% CI -10.84 to 1.44) based on final scores on the Structured Interview for PTSD (SIP).

Otto 2003 (n = 10) did not report on the significance of findings, but reported "effect sizes indicative of consistent advantages" of combined treatment compared to sertraline alone. However, in this case, the numbers were very small and standard deviations were noted to be much larger than the means reported, suggesting the data were skewed and not appropriate for analysis.

Withdrawals

Withdrawals due to adverse effects were not reported but authors extracted data on drop outs as a surrogate. One of the two included trials within this comparison, with a total of 65 participants (Rothbaum 2006), provided data on dropouts and showed no statistically significant differences between the groups (RR 5.47, 95% CI 0.70 to 42.93).

PTSD symptom severity (self-rated)

Neither study reported data for this outcome.

Global Functioning

Neither study reported data for this outcome.

Depression

Both studies in this comparison (Otto 2003; Rothbaum 2006) reported depression severity scores. There were no statistically significant differences between the groups (SMD -0.40, 95% CI -0.86 to 0.07) (Analysis 1.3).

Anxiety

Both studies in this comparison (Otto 2003; Rothbaum 2006) reported anxiety severity scores. There were no statistically significant differences between the groups (SMD -0.39, 95% CI -0.85 to 0.07) (Analysis 1.4).

Suicidal ideation

Neither study reported data for this outcome.

Suicide attempt

Neither study reported data for this outcome.

Substance use

Neither study reported data for this outcome.

Vocational and social functioning

Neither study reported data for this outcome.

Quality of life

Neither study reported data for this outcome.

Cost of treatment

Neither study reported data for this outcome.

3) Combination psychological and pharmacological intervention vs psychological therapy alone

One trial including 25 participants (Simon 2008) compared psychological and pharmacological intervention vs psychological therapy alone.

PTSD symptom severity

In Simon 2008 there were no statistically significant differences between the group receiving both prolonged exposure and paroxetine CR and those receiving prolonged exposure alone (mean difference 2.44, 95% CI -2.87, 7.35) on a total PTSD symptom score.

Withdrawals

Withdrawals due to adverse effects were not reported but authors extracted data on drop outs as a surrogate.
In Simon 2008 (N=25) there were no statistically significant differences between groups (RR 1.91 95% CI 0.38 to 9.51).

PTSD symptom severity (self-rated)

The single included study (Simon 2008) did not report data for this outcome.

Global Functioning

In this study (Simon 2008), the authors also report no significant differences between groups on CGI-S or Clinical Global Impressions-Improvement scale (CGI-I) and low rates of remission in both groups, with no differences between the groups in rates of remission.

Depression

No data were reported for this outcome.

Anxiety

No data were reported for this outcome.

Suicidal ideation

No data for were reported for this outcome.

Suicide attempt

No data were reported for this outcome.

Substance use

No data were reported for this outcome.

Vocational and social functioning

No data were reported for this outcome.

Quality of life

No data were reported for this outcome.

Cost of treatment

No data were reported for this outcome.

2) Combined SSRI plus TFCBT versus TFCBT alone (children/adolescents)

One trial including 24 participants who were either children or adolescents (Cohen 2007) compared psychological and pharmacological intervention vs psychological therapy alone.

PTSD symptom severity (clinician rated)

While no usable data were reported, Cohen 2007 stated there were no significant differences in PTSD symptoms between groups at the end of treatment on the K-SADS-PL-PTSD and no differences in the numbers in each group who moved into a 'no PTSD diagnosis' category.

Withdrawals

In the study of children and adolescents (Cohen 2007; N=24) there were no statistically significant differences between groups (RR 0.50 95% CI 0.05 to 4.81) (both were due to residential relocation).

PTSD symptom severity (self-rated)

The single included study (Cohen 2007) did not report data for this outcome.

Global Functioning Scores

Data for this outcome related to functioning were provided using the Children's Global Assessment Scale (CGAS). There were no statistically significant differences between the groups (mean difference 7.09, 95% CI -1.19 to 15.37).

Depression

No data were reported in a form suitable for RevMan 5 (i.e. means and SDs). Trialists reported that "on the MFQ, nine participants scored in the nonclinical range (score < 27) at prettreatment (three TF-CBT + sertraline; six TF-CBT + placebo); at posttreatment 13 additional participants had improved into the nonclinical range (eight TF-CBT + sertraline and five in the TF-CBT plus placebo)."

Anxiety

No data were reported in a form suitable for RevMan 5 (i.e. means and SDs). Trialists reported that "on the SCARED, four participants (two in each group) scored in the nonclinical range (score < 25) at prettreatment; at posttreatment 13 additional participants had improved into the nonclinical range (eight TF-CBT + sertraline and five in the TF-CBT plus placebo)."

Suicidal ideation

Trialists reported "at pre-treatment, 5 participants responded 'True' to the question 'I thought about killing myself' (four in the TF-CBT + sertraline and one in the TF-CBT plus placebo). At post-treatment, no participants responded 'True' to this question."

Suicide attempt

No data were reported for this outcome.

Substance use

No data were reported for this outcome.

Vocational and social functioning

No data were reported for this outcome.

Quality of life

No data were reported for this outcome.

Cost of treatment

No data were reported for this outcome.

DISCUSSION

Summary of main results

There were four trials included in the review, one of which included children and adolescents (N=24) and three involving adults participants (N=100).

As there were few trials, and very little data included in the review, definitive conclusions are difficult to draw. Overall there is insufficient evidence to assess whether or not a combination of pharmacotherapy and psychotherapy is more effective in treating PTSD than either of these interventions alone. In terms of the severity of PTSD symptoms as an outcome measure, no pooling of data was possible, although each trial alone appeared to suggest that there was no benefit of combination therapy. Some pooling was possible for depression and anxiety outcomes, but again there was no benefit of combination therapy. No trial reported on adverse outcomes, and while three of the four included trials reported on drop outs, the results were heterogeneous, with drop outs varying according to intervention type across each study (for example, there were fewer drop outs in the combined treatment arm in Cohen 2007, in the SSRI alone treatment arm in Rothbaum 2006, and in the psychological treatment only group in Simon 2008).

In the absence of evidence, it is not clear whether combination treatments provide any advantage over a single modality alone. One clinically appropriate approach for all age groups might be to begin treatment with a single modality, before more intense approaches are trialled. In light of the controversy surrounding the use of SSRIs in children and adolescents (Hammad 2006), beginning treatment with a psychological treatment may be the preferred approach. The addition of medication should be cautious and well monitored for this age group (Bridge 2007).

Overall completeness and applicability of evidence

With so few trials and data available for the review, there is a paucity of information available about the effectiveness of combination interventions for PTSD. A major weakness in the included trials was the lack of measurement and/or reporting of total PTSD symptom outcome scores. PTSD symptoms were only measured using clinician-rated tools, and functional outcomes were not reported in any case. Adverse events were not measured, including suicide-related behaviours, nor was comorbid substance use, which is considered an important and common comorbid condition in PTSD.

Variants of CBT and exposure therapy were used in all the included trials, with sertraline and paroxetine the only medications studied. The study populations varied in each trial, although sexual and physical violence were the most common precipitating traumatic events. There were no trials with a focus on combat related trauma, accidents or disasters. The included trials focused predominantly on participants with chronic PTSD symptoms. Only one trial included participants who were eligible for inclusion due to having PTSD symptoms, although trialists considered this to be equivalent to diagnosis. No trial that described participants as having sub-clinical symptoms were located for inclusion in the review.

There were no data on long-term outcomes.

Quality of the evidence

There were few included trials, and the trials ranged in size between 10 and 65 participants. The quality of included trials was difficult to evaluate given inadequate description of the methodological details, which hampered the assessment of their internal validity. Of note is the lack of reporting of outcomes in sufficient detail or in a usable format for meta-analysis. Of the data that were available, there was evidence of skew. Meta-analytic techniques frequently

face the problem of managing non-parametric data. While there is not a clear consensus regarding the resolution of this statistical issue, we note the limitations of our analysis in accounting for skewed data. The consistency of results cannot be evaluated here given the small number of trials and the lack of usable data.

Potential biases in the review process

Many of the aims of the review could not be addressed due to the limited number of included trials and the lack of usable data. The review team made all efforts to locate all published and unpublished trials by writing to the trial authors of included as well as ongoing studies, and in every case attempted to obtain additional data, both relating to the conduct of the trials and to the outcomes. As we are aware of several ongoing trials for which we could not yet obtain outcome data, the review will be updated to include these subsequently published trials.

Agreements and disagreements with other studies or reviews

In an earlier review, Marshall 2000 advocated the use of combined approaches for the clinical management of PTSD, given that ongoing residual symptoms were frequently observed in trials utilising single modality treatments. However, no data about the efficacy of combined approaches were provided in Marshall's review, given the relative novelty at that time of this field of enquiry. In contrast, a more recent review (Davis 2006) has highlighted potential risks of combination treatment, citing evidence that pharmacotherapy can lessen the efficacy of psychotherapy. Davis points to the possible efficacy of newer pharmacological agents that may improve the effect of psychotherapy because of their impact on learning.

AUTHORS' CONCLUSIONS

Implications for practice

There is currently insufficient evidence regarding the potential benefits and risks of combined pharmacotherapy and psychotherapy for PTSD compared with either modality alone. The findings are far from robust, are based on a small number of trials and are largely unrepresentative of the many differing presentations of PTSD seen in clinical practice. There is not enough evidence to be able to determine if there is any advantage of combined treatment over a single modality alone in patients with long-standing PTSD symptoms.

Although this review could not determine the benefit of combined interventions in children and adolescents specifically, given the controversy about the use of antidepressants in this age group making judicious use of such medications is crucial and psychotherapy may be preferred as the first line treatment. It may also be that those who present for treatment in the early stages of illness, or those with symptoms that do not yet meet the full threshold for a diagnosis of PTSD, would benefit from a trial of psychotherapy in the first instance, given the results of the Cochrane Systematic review. The trials included in this review mostly pertain to the treatment of chronic populations with no detail about intervention strategies that had already been trialled. It is possible however that if effective (even if more simple) interventions were delivered earlier in the course of illness, the outcomes may be more positive (McGorry 2006).

Implications for research

Further research into the clinical management of PTSD is required, including larger trials that use (i) reliable and clinically meaningful outcome measurements, such as remission of PTSD, (ii) consistent measures of PTSD symptom reduction and (iii) functional outcomes, including those related to social and occupational functioning. The impact of, and outcomes related to, substance use and suicidal ideation should be subject to more evaluation.

There is also a need for trials within homogenous patient populations, such as those exposed to combat-related trauma and disaster-related trauma, in addition to larger studies of those with interpersonal-related violence and trauma. Trials in specific populations such as children and adolescents are also required, and trials of participants with sub-threshold PTSD or sub-clinical symptoms would be valuable.

A consistent approach to stepped care models should be tested, for example with medication introduced subsequent to the trial of a psychological intervention. A range of commonly used and newer psychotherapies and pharmacotherapies should also be trialled.

Finally, greater attention to the methodological and reporting requirements for RCTs, as specified in the CONSORT statement (Moher 2001) is warranted in all future research in this field.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cohen 2007

Methods	**RCT**
Participants	**Setting:** *Unclear* **Recruitment strategy:** *Consecutively referred* **Country:** USA **N:** Number randomised 24 (12 to each treatment) **Exclusion criteria:** *non-English speaking; schizophrenia or other active psychotic disorder; mental retardation or pervasive developmental disorder (all due to the requirement to receive TF-CBT, a cognitive-oriented psychotherapy); or taking current psychotropic medications. Current substance dependence.* **Primary diagnosis?** *PTSD* **How was PTSD measured?** A*t least five PTSD symptoms on the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version [K-SADS-PL] with at least one symptom in each of the three PTSD clusters and clinically significant impairment* **Index trauma?** contact sexual abuse that was confirmed by Child Protective Services **Time since incident episode:** *Total only provided - mean months since most recent abuse 22.9(SD 35.6)* **Previous treatment for PTSD***: Not stated* **Previous treatment for other mental disorders?** *Not stated* **Age** *Total Range only provided 5 x 10-11yrs; 10 x 12-14yrs; 7 x 15-17yrs* **Sex:** *100% Female* **Ethnicity:** *total only - 17 white; 5 African American* **Comorbid substance use:** *Not stated* **Suicidality:** *Not stated* **Comorbidity:** *68.2% met criteria for comorbid diagnoses (TF-CBT+Sert =72.7%; TF-CBT+Placebo = 63.5%). All but one had MDD; other diagnoses included general anxiety disorder, substance abuse not otherwise specified, oppositional defiant disorder, panic disorder, and anorexia nervosa.*
Interventions	**Comparison Group 1** **Type**: *Pharmacotherapy and Psychotherapy combined* **Pharmacotherapy:** *Sertraline: started at 25mg and titrated to 50mg - 200mg day as clinically indicated* **Length of pharmacotherapy:** *12 weeks* **Other treatments being used**: *None* **Psychotherapy:** *Trauma focused CBT - (TF-CBT)* **Individual/group:** *Individual* **Manualised:** *There are two published books and a web-based learning course* **Delivered by:** *One of two randomly assigned clinicians who were licensed masters level social workers* **Length of sessions:** *Unclear.* **Number of sessions:** *12* **Length of intervention***: 12 weeks*

	How many sessions actually delivered: *Unclear* **Was it intended as intervention or control:** *As intervention condition with Sertraline/ placebo control condition* **Comparison Group** 2 **Type:** *Psychotherapy and placebo* **Pharmacotherapy:** *Placebo pill* **Psychotherapy:** *As above*
Outcomes	***PTSD symptoms*** *(K-SADS-PL and CPSS)* ***Global impairment*** *(CGAS)* ***Depression*** *(MQF)* ***Anxiety symptoms*** *(SCARED)* ***Suicidal ideation*** ***Child-abuse related attributions and perceptions*** (*The Childrens Attributions and Perceptions Scale)* ***Childrens' behaviour and symptoms*** *(CBCL)* ***Parental depression*** *(BDI)* ***Parental emotional distress*** *(The Parent's Emotional Reaction Questionnaire)* ***Parental support*** *(the Parental Support Questionnaire)* ***Sertraline side effects*** *(SEF-CA)*
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	..."randomised according to a computerized random number sequence" (p. 814)
Allocation concealment?	Unclear	No statement
Blinding? Outcome assessor	Yes	..."double-blind procedure whereby no one directly involved in the study (i.e., parents, children, independent evaluator, therapists, or child and adolescent psychiatrist) knew which condition the children were assigned to throughout the course of treatment" (p. 814)
Incomplete outcome data addressed? All outcomes	Unclear	Number dropped out: *1 TF-CBT + Sertraline; 1 TF-CBT + Placebo* ITT analysis not undertaken, unclear description of reason for drop-outs
Free of selective reporting?	No	All a-prior outcomes described in methods were reported on but not in a usable format for meta-analysis; e.g. total PTSD symptoms were not reported on for the sertraline and placebo groups separately

Cohen 2007 (*Continued*)

Free of other bias?	No	Low recruitment rate; large number refused due to medication concerns

Otto 2003

Methods	**RCT**
Participants	**Setting:** *Unclear* **Recruitment strategy:** *Unclear* **Country:** *USA (but participants are Cambodian refugees)* **N:** *Randomised 10* **Exclusion criteria:** *Not stated* **Primary diagnosis?** *Current PTSD, failure to respond to clonazepam* **How was PTSD measured?** *Structured interview for PTSD ? DSM-IV* **Severity:** *CAPS re-experiencing:* *Intervention: 21.4 (6.3); Control: 15.2 (6.2)* *CAPS avoidance/numbing* *Intervention: 24.4(12.1); Control:21.4(14.7)* *CAPS hyperarousal:* *Intervention: 18.8(10.1); Control:20.6 (9.8)* **Index trauma:** *Pol Pot regime with exposure to starvation, overwork, illness, or execution. In addition many survivors were subjected to the constant threat of death, torture, severe physical deprivation, physical and sexual violence, and physical displacement* **Time since incident episode:** *Total only provided : Approx 21-25 years ago* **Previous treatment for PTSD:** *Total only provided: Pharmacotherapy: Clonazapam, SSRI (not Sertraline)* **Previous treatment for other mental disorders?** *Not stated* **Age:** *Total only provided 47.2 years* **Sex**: *100% female* **Ethnicity:** *All Cambodian* **Comorbid substance use:** *Not stated* **Suicidality:** *Not stated* **Comorbid anxiety:** *HSCL-90 anxiety:* *Intervention: 29.2 (8.5);Control: 31.4 (6.2)* *Anxiety sensitivity index (ASI)* *Intervention:38.8 (11.0);Control 37.6 (15.2)* *ASI-Khmer items:* *Intervention: 37.6 (15.2);Control: 51.4 (7.8)* **Comorbid depression** *HSCL-90 depression:* *Intervention: 34.4 (7.6);Control: 38.2 (9.2)* *HSCL-90 somatisation:* *Intervention: 36.2 (9.4);Control: 26.2 (6.1)*
Interventions	**COMPARISON GROUP 1** **Type:** *Pharmacotherapy alone* **Pharmacotherapy**: *Sertraline: 25mg/d for Week 1; 50mg/d for Week 2; with titration up*

	by 50mg/d to a maximum of 200 mg/d. Length of pharmacotherapy: *Unclear* Other treatments being used: *Unclear; however, 'clonazepam treatment was held constant 0.5-1mg, BID; adjunctive treatment with benzodiazepam also use.* **COMPARISON GROUP 2** **Type:** *Pharmacotherapy and Psychotherapy combined* **Pharmacotherapy:** *As above* **Psychotherapy:** *CBT - culture specific* **Individual/group:** *Group* **Manualised:** *Unclear* **Delivered by:** *Unclear* **Length of sessions**: *Unclear.* **Number of sessions:** *10* **Length of intervention:** *Unclear* **How many sessions actually delivered:** *Unclear* **Was it intended as intervention or control:** *As intervention added on to Sertraline (control condition)*
Outcomes	***PTSD symptoms*** *(CAPS re-experiencing, avoidance/numbing and hyperarousal symptoms)* ***Measures of comorbid anxiety*** *(HSCL-90 anxiety, ASI, ASI-Khmer)* ***Measures of comorbid depression*** *(HSCL-90 depression; HSCL-90 somatisation)*
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No statement
Allocation concealment?	Unclear	No statement
Blinding? Outcome assessor	Unclear	No statement
Incomplete outcome data addressed? All outcomes	Unclear	No statement
Free of selective reporting?	No	Total PTSD symptom scores not reported by group
Free of other bias?	Unclear	Small trial; some baseline imbalance in symptom severity

Rothbaum 2006

Methods	**RCT**
Participants	**Setting:** *Outpatient* **Recruitment strategy:** *Advertisements, referrals from professionals* **Country:** *USA* **N** = *Number randomised = 65 for phase 2* **Exclusion criteria:** *History of psychotic, bipolar disorder; prior failure with Sertraline, medical contraindications to taking sertraline*; *current administration of psychiatric medication* **Primary diagnosis?** *Primary psychiatric diagnosis of PTSD, duration >=3 months* **How was PTSD measured?** *Structured clinical interview for DSM-IV* Severity: *Intervention: Wk 10 Mean (SD) SIP 16.16 (10.64)* *Control: Wk 10 Mean (SD) SIP 14.5 (11.65)* **Index trauma?** *The most common index traumas were sexual assault, including childhood sexual abuse (37%); nonsexual assault, including childhood physical abuse (25%); and the death (not combat-related) of another person (22%), usually someone of significance to the participant (i.e., child, parent, sibling, spouse or romantic partner).Another 9% reported being in a motor-vehicle accident as the index trauma.* *The remaining traumas coded as other were one case each of the following: combat exposure, house fire, airplane crash, discovering a parent after a nonfatal overdose, and a police officer who felt he came very close to shooting an unarmed suspect.* **Time since incident episode:** *Total only provided (n=43) 8.1 years (11.77SD)* **Previous treatment for PTSD:** *not stated* **Previous treatment for other mental disorders?** *open label treatment with sertraline for 10 weeks as part of protocol (called Phase 1)* **Age:** *Total only provided* mean (SD) = 39.3 (10.69) **Sex:** *Total only provided* 35.4% male; 64.6% female **Ethnicity:** *Total only provided* 80% White; 18.5% Afr-Am; 1.5% Other **Comorbidity:** *63% had current major depression, dysthymia or both; 52% had one or more anxiety disorder* **Comorbid substance use:** *not stated* **Suicidality:** *not stated* **Comorbid anxiety:** *STAI-S Mean (SD) Wk 10* *Intervention:43.0(13.21); Control:39.2(13.90)* **Comorbid depression** *BDI Mean (SD) Wk 10* *Intervention: 11.2(8.94);Control: 9.5 (7.57)*
Interventions	**COMPARISON GROUP 1** **Type:** *Pharmacotherapy alone* Pharmacotherapy: 10 *weeks of open-label Sertraline, 200mg/day or maximum tolerated dose; followed 5 weeks of Ssertraline, started at 25 mg/day increased to 200mg or maximum tolerated dose per day. The average dose was 173.1 mg/day at the beginning of week 10 and 173.5mg/day at week 15.* **COMPARISON GROUP 2** **Type:** *Pharmacotherapy and psychotherapy combined* **Pharmacotherapy:** *As above* **Psychotherapy:** *Prolonged exposure (PE) therapy* **Individual/group:** *Individual* **Manualised:** *Yes*

	Delivered by: *Therapists trained in the use of PE* **Length of sessions:** *90-120 minutes.* **Number of sessions**: *10* **Length of intervention:** *5 weeks* **How many sessions actually delivered:** *Unclear; 10 for completers unknown for non-completers.* **Was it intended as intervention or control**: *As intervention added on to sertraline (control condition)*
Outcomes	***Reduction in PTSD symptoms*** *(SIP)* ***Reduction in comorbid anxiety*** *(STAI)* ***Reduction in comorbid depression*** *(BDI)*
Notes	For depression and anxiety scores, the SD has been imputed for each group from the combined SD of the change score. Mean change scores for each group were calculated from endpoint scores in Table 2

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No statement
Allocation concealment?	Unclear	No statement
Blinding? Outcome assessor	Yes	"independent evaluators" p 630; "The independent evaluators were not otherwise involved in participants' treatment and were kept blind to the treatment condition of those participants who entered Phase II" p 631 Additional information from the author: "the only person who was kept blind to treatment condition was the IE, and of course, the IE was only blind to whether the person got PE or not during phase II. The IE was not blind to the fact that the person was on sertraline. We instructed the patient not to discuss therapy with the IE and we took steps to prevent the IE from seeing the patient accompanied by a study therapist (e.g., having IE behind office doors when the patient was in for a therapy visit, taking the "back route" to a therapist's office to avoid the waiting room, changing the IE if the blind was blown, excluding the IE from supervision of study cases)"
Incomplete outcome data addressed? All outcomes	Yes	Drop outs described and ITT analysis undertaken; uneven drop outs across groups (number dropped out: Intervention: 6 Phase 2 ; Control: 1 Phase 2)
Free of selective reporting?	Unclear	Usable data not fully reported
Free of other bias?	No	

Simon 2008

Methods	**RCT**
Participants	**Setting:** *Outpatient* **Recruitment strategy:** *Advertisements and clinical referral* **Country:** *USA* **N:** *Intervention: 9; Control: 14* **Exclusion criteria:** *Serious medical illness; pregnant or lactating women; concurrent use of other psychotropic medication; lifetime diagnosis of schizophrenia or psychotic disorder; mental retardation; organic mental disorders or bipolar disorder; OCD exhibited in last six months; eating disorders; cutting or self-injurious behaviour or alcohol or substance abuse disorders within the last 6 months; current primary diagnosis of MDD, dysthymia, social anxiety disorder or GAD; history of hypersensitivity or poor response to paroxetine; Current compensation of legal action related to effects of trauma, those with ongoing relationship with assailant.* **Primary diagnosis?** *PTSD with participants still symptomatic (greater than or equal to 6 on SPRINT and CGI-S greater than or equal to 3) after 8 sessions of prolonged exposure* **How was PTSD measured?** *Mini International Neuropsychiatric Interview (MINI) for DSM-IV* **Severity:** *all participants remained symptomatic after 8 sessions of PE* *SPRINT total score:* *Intervention: 16.11 ; Control 17.00* *CGI-S:* *Intervention: 4.11 ; Control 4.00* **Index trauma?** *Physcial and/or sexual abuse: intervention 89%; control 57%* *Exposure to war: intervention 0%; control 14%* *Physical accident and/or medical trauma: intervention 11%; control 29%* **Time since incident episode:** *Unclear* **Previous treatment for PTSD:** *8 sessions of Prolonged Exposure therapy as part of protocol* **Previous treatment for other mental disorders?** *Unclear* **Age** *Intervention mean 47.8; Control mean 44.2* **Sex** *Intervention F=4 (44%) M=5 (56%); Control F=9 (64%) M=5(36%)* **Ethnicity** *Intervention 71% white; Control 78% white* **Comorbid substance use:** *unclear* **Suicidality** *Those with cutting or self-injurious behaviour were excluded but no other detail about baseline suicidality given* **Comorbid anxiety/depression** *Number with at least 1 mood or anxiety disorder:* *Intervention:* 8 (89%); *Control: 11(79%)* *Number with MDD:* *Intervention: 3 (33%); Control: 9 (64%)*
Interventions	**COMPARISON GROUP 1** **Type:** *Pharmacotherapy and Psychotherapy combined* **Pharmacotherapy:** *Paroxetine-CR initiated at 12.5mg/day and flexibly titrated based on efficacy and tolerability from 12.5mg/day to a maximum of 62.5mg/day for 10 weeks. Included management by a study psychiatrist during 10-20 minute sessions weekly for first two weeks and then once every two weeks.* *Mean dose 45.8 (SD16.5)* **Psychotherapy:** *Prolonged exposure (PE) therapy*

	Individual/group: *Individual* **Manualised:** *Yes* **Delivered by:** *Trained therapists who received certification in PE* **Length of sessions:** *90-120 minutes* **Number of sessions:** 5 once every two weeks **Length of intervention:** *10 weeks* **How many sessions actually delivered:** *not reported* **Was it intended as intervention or control:** *as intervention added on to PE (control condition)* **COMPARISON GROUP 2** **Type:** *Psychotherapy and placebo* **Pharmacotherapy**: *placebo (mean dose 44.8 (SD15.5)* **Psychotherapy:** *As above*
Outcomes	***Level of impairment (CGI-S)*** ***PTSD symptoms (SPRINT)***
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No description except that random assignment was blocked by CGI-S score
Allocation concealment?	Yes	Additional information from author: "Study was double blind with the study staff giving the patient a randomization number that only the research pharmacy supplying the medication knew was placebo or active medication"
Blinding? Outcome assessor	Yes	Additional information from author: "Study was double blind". Paper describes a "rater blind to treatment assignment" pg 401
Incomplete outcome data addressed? All outcomes	Yes	5 drop outs; two before starting medication and not included in ITT analysis, 1 additional from medication group due to inpatient admission for suicidal ideation; 2 from placebo group due to dizziness/nausea (1) and noncompliance (1)
Free of selective reporting?	Unclear	No information about outcome measurement planned a-priori.
Free of other bias?	No	small study; some imbalance - more females in placebo group; more participants in placebo group had MDD; more participants in medication group had index trauma of sexual abuse

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abramowitz 2008	The study treatments are hypnotherapy and zolpidem aimed at the sleep difficulties being suffered by participants with PTSD who are already medicated with an SSRI and receiving psychotherapy
Bouso 2008	Dose-finding (rather than effectiveness) trial
Brunet 2008	'Script driven traumatic imagery' did not meet criteria for psychological therapy for this review
Chan 2008	Intervention 'collaborative care'; does not meet inclusion criteria
Clark 2008	Participants not randomised to a combined intervention
Cottraux 2008	Participants not randomised to a combined intervention
Drozdek 1997	Medication not controlled and not clear whether groups are randomised
Hinton 2004	Participants not randomised to a combined intervention
Hinton 2005	Participants not randomised to a combined intervention
Kessler 2003	No random assignment to combined treatment (no mention of pharmacotherapy); unlikely that participants have a primary diagnosis of PTSD
Oflaz 2008	Not an RCT
Osuch 2009	The pharmacological component of the trial was delivered in combination with repetitive transcranial magnetic stimulation (rTMS) and not a psychological therapy
Resnick 2008	Participants not randomised to a combined intervention
van der Kolk 2007	No combined intervention group
Wright 2003	No random assignment to combined treatment; 90% of participants already on prescribed medication; the intervention targeted major depressive disorder
Zucker 2009	Biofeedback not an eligible psychological intervention

Characteristics of ongoing studies *[ordered by study ID]*

Gamito 2005

Trial name or title	Virtual war PTSD
Methods	3 armed RCT
Participants	Males with the diagnostic of War PTSD according to DSM-IV-TR who looked for treatment at Hospital Julio de Matos in Lisbon, Portugal
Interventions	Virtual reality exposure (VRE); Drug treatment; VRE + Drug Treatment. The adequate therapeutic dosage of Sertraline (Zoloft, Pfeizer) will be administrated during 16 weeks to the Drug Treatment groups. VRE groups will use a Head Mounted Device that enables fully immersive experience in the following war virtual scenarios: mine deflagration, mine deflagration + ambush, ambush and assisting casualties and waiting for a rescue helicopter
Outcomes	CAPS, BDI, STAI, SCL-90, MCM-II for psychometric measures and TAS, DES, PQ, SUDS, heart rate and blood pressure, ECG, EEG and ACTH for physiological measures are the evaluation procedures selected for assessing the results
Starting date	
Contact information	
Notes	

Guay 2007

Trial name or title	Comparative Study of the Efficacy of a Cognitive-Behavioral Therapy for Post-Traumatic Stress Disorder With or Without D-Cycloserine
Methods	RCT
Participants	Either gender, aged 18 to 65, clinical diagnosis of PTSD
Interventions	CBT with and without D-Cycloserine
Outcomes	Primary Outcome Measures: Clinician-administered measures collected at initial assessment, post-treatment and six-months follow-up: CAPS: PTSD symptoms SCID: AXIS I disorders Secondary Outcome Measures: Patient self-report forms collected at initial assessment, post-treatment and six-months follow-up: BDI: depression symptoms BAI: anxiety symptoms WHOQL-Bref: quality of life
Starting date	February 2007

Guay 2007 (*Continued*)

Contact information	Sarah Jane Parent: sparent.hlhl@ssss.gouv.qc.ca
Notes	Authors will have to consider their inclusion criteria as d-cycloserine

Hicks 2009

Trial name or title	Predictors of Treatment Response to Fluoxetine in PTSD Following a Recent History of War Zone Stress Exposure
Methods	Double blind placebo controlled prospective 12 week trial of fluoxetine in veterans already receiving usual psychological treatment
Participants	Operation Enduring Freedom and Operation Iraqi Freedom (OEF/OIF) veterans
Interventions	Double-blind, placebo-controlled prospective 12-week trial of fluoxetine in OEF/OIF campaign veterans. All participants will (also) receive usual psychological treatment by mental health services of the Carl R. Darnall Army Medical Center
Outcomes	PTSD symptom severity and related functional impairment, comorbid depression, anxiety symptoms, and alcohol intake
Starting date	Enrolling from 2009
Contact information	Paul Hicks, Central Texas Veterans Health Care System, USA
Notes	

McAllister 2009

Trial name or title	Venlafaxine and CBT for Psychological Distress After TBI: A Randomized Controlled Trial
Methods	12 week RCT
Participants	Veterans and service members who have mild to severe TBI and PTSD or MDD
Interventions	Venlafaxine XR (VFN), Cognitive Behavioral Therapy (CBT), and a placebo and psycho-educational control (CTL)
Outcomes	Primary outcomes: PTSD and depression symptoms; secondary aims include comparing response, remission, and relapse rates; determining if treatment is associated with greater improvement in neuropsychological functioning, functional status, and post-concussive symptoms; examining tolerability and cost-effectiveness of VFN and CBT for the treatment of PTSD and MDD; and exploring predictors of treatment response
Starting date	Enrolling in 2009
Contact information	Thomas W McAllister, Dartmouth Medical School, Dartmouth, New Hampshire, USA

Notes	

Pai 2004

Trial name or title	Treating co-morbid PTSD and alcohol dependence
Methods	RCT
Participants	Setting: Community-Outpatient Recruitment strategy: *Newspaper advertisement, Veterans Administration* Country: *USA* Exclusion criteria: *Current DSM diagnosis of substance dependence other than alcohol, nicotine, cannabis; 2) opiate use in past 30 days; 3) significant risk of violence/ history of serious violent behaviour in past 4 years; 4) report assault as index trauma combined with continuing relation ship with perpetrator; 5) current treatment for psychotropic medications(excl short-term use of benzodiazepines for detoxification); 6 unstable or serious medical illness; 7) current severe psychiatric symptoms; 8) mental retardation or other pervasive developmental disorder; 9) investigational medication in past 30 days; 10) for women, pregnant, nursing or non-use of reliable contraception* Primary diagnosis? *PTSD and Alcohol dependence*
Interventions	COMPARISON GROUP 1 Type: *Pharmacotherapy and Psychotherapy combined* Pharmacotherapy: *Naltrexone 50mg/morning for 3 days then 100mg/morning* Length of pharmacotherapy: *24 weeks* Psychotherapy: *CBT ? prolonged exposure therapy* Individual/group: *Individual* Manualised: *Yes* Delivered by: *Psychologists and a registered nurse* Number of sessions: *18 - 1/week for 12* weeks, *then 1/fortnight for 12 weeks.* Length of intervention*: 24 weeks* How many sessions actually delivered: *ongoing study* Was it intended as intervention or control: *As control condition with Naltrexone/placebo intervention condition* COMPARISON GROUP 2 Type: *Psychotherapy and placebo* Pharmacotherapy: *Placebo* Length of pharmacotherapy: *24 weeks* Psychotherapy: *CBT ? prolonged exposure therapy* Individual/group: *Individual* Manualised: *Yes* Delivered by: *Psychologists and a registered nurse* Number of sessions: *18 - 1/week for 12 weeks, then 1/fortnight for 12 weeks.* Length of intervention: *24 weeks* COMPARISON GROUP 3 Type: *Placebo medication alone* Type of pharmacotherapy*: Placebo pill*
Outcomes	*Alcohol consumption (Days drinking; drinks per drinking day; alcohol craving using Timeline Follow-Back Interview and Penn Alcohol Craving Scale)* *PTSD symptoms*

Pai 2004 (*Continued*)

	(*PTSD Symptom Scale, PSS-I)*
Starting date	
Contact information	*Professor E Foa Director,* Director of the Center for the Treatment and Study of Anxiety University of Pennsylvania 3535 Market Street, 6th Floor Philadelphia, PA 19104, USA
Notes	

DATA AND ANALYSES

Comparison 1. Combined SSRI plus CBT versus SSRI alone (adults)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PTSD symptom severity (clinician rated) post intervention (final scores SIP)	1	65	Mean Difference (IV, Fixed, 95% CI)	-4.70 [-10.84, 1.44]
2 Drop outs	1	65	Risk Ratio (M-H, Fixed, 95% CI)	5.47 [0.70, 42.93]
3 Depression severity (self rated) post intervention (change scores)	2	74	Std. Mean Difference (IV, Fixed, 95% CI)	-0.40 [-0.86, 0.07]
4 Anxiety severity (self rated) post intervention (change scores)	2	74	Std. Mean Difference (IV, Fixed, 95% CI)	-0.39 [-0.85, 0.07]

Comparison 2. Combined SSRI plus CBT versus PE alone (adults)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PTSD symptom severity (clinician rated) post intervention (change scores SPRINT)	1	23	Mean Difference (IV, Fixed, 95% CI)	2.24 [-2.87, 7.35]
2 Drop outs	1	25	Risk Ratio (M-H, Fixed, 95% CI)	1.91 [0.38, 9.51]

Comparison 3. Combined SSRI plus TFCBT versus TFCBT alone (children/adolescents)

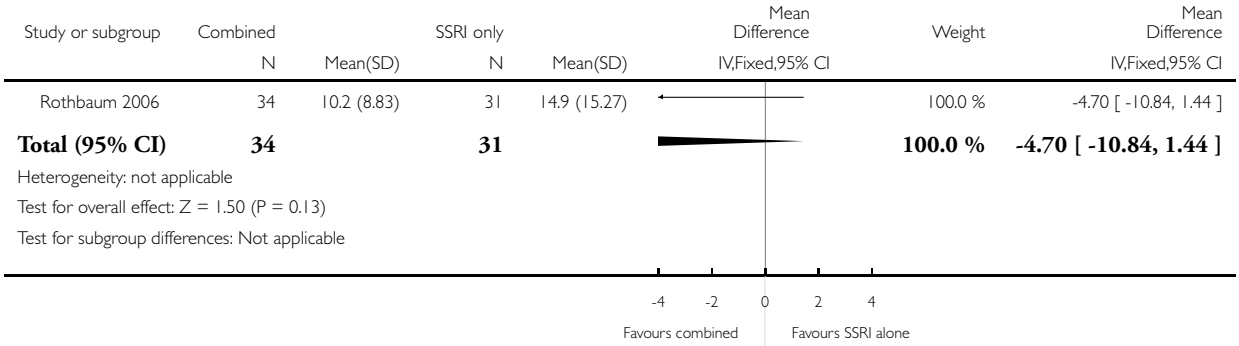
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Drop outs	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 4.81]
2 Functioning CGAS	1	22	Mean Difference (IV, Fixed, 95% CI)	7.09 [-1.19, 15.37]

Analysis 1.1. Comparison 1 Combined SSRI plus CBT versus SSRI alone (adults), Outcome 1 PTSD symptom severity (clinician rated) post intervention (final scores SIP).

Review: Combined pharmacotherapy and psychological therapies for post traumatic stress disorder (PTSD)

Comparison: 1 Combined SSRI plus CBT versus SSRI alone (adults)

Outcome: 1 PTSD symptom severity (clinician rated) post intervention (final scores SIP)

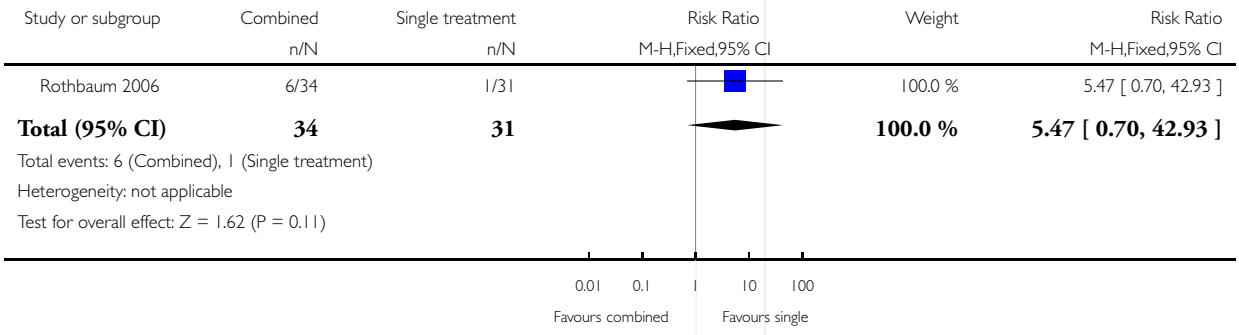


Analysis 1.2. Comparison 1 Combined SSRI plus CBT versus SSRI alone (adults), Outcome 2 Drop outs.

Review: Combined pharmacotherapy and psychological therapies for post traumatic stress disorder (PTSD)

Comparison: 1 Combined SSRI plus CBT versus SSRI alone (adults)

Outcome: 2 Drop outs



Analysis 1.3. Comparison 1 Combined SSRI plus CBT versus SSRI alone (adults), Outcome 3 Depression severity (self rated) post intervention (change scores).

Review: Combined pharmacotherapy and psychological therapies for post traumatic stress disorder (PTSD)

Comparison: 1 Combined SSRI plus CBT versus SSRI alone (adults)

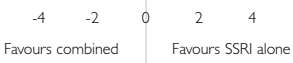
Outcome: 3 Depression severity (self rated) post intervention (change scores)

Study or subgroup	Combined N	Mean(SD)	SSRI alone N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Otto 2003	5	-8.6 (7.2)	5	-8.6 (6)		13.9 %	0.0 [-1.24, 1.24]
Rothbaum 2006	34	-3.2 (7.52)	30	0.3 (7.52)		86.1 %	-0.46 [-0.96, 0.04]
Total (95% CI)	**39**		**35**			**100.0 %**	**-0.40 [-0.86, 0.07]**

Heterogeneity: Chi² = 0.46, df = 1 (P = 0.50); I² =0.0%

Test for overall effect: Z = 1.68 (P = 0.093)

Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1 Combined SSRI plus CBT versus SSRI alone (adults), Outcome 4 Anxiety severity (self rated) post intervention (change scores).

Review: Combined pharmacotherapy and psychological therapies for post traumatic stress disorder (PTSD)

Comparison: 1 Combined SSRI plus CBT versus SSRI alone (adults)

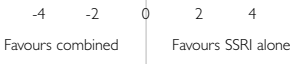
Outcome: 4 Anxiety severity (self rated) post intervention (change scores)

Study or subgroup	Combined N	Mean(SD)	SSRI alone N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Otto 2003	5	-8.4 (5.6)	5	-5.2 (5.3)		13.1 %	-0.53 [-1.81, 0.74]
Rothbaum 2006	34	-3.9 (10.4)	30	0 (10.4)		86.9 %	-0.37 [-0.87, 0.12]
Total (95% CI)	**39**		**35**			**100.0 %**	**-0.39 [-0.85, 0.07]**

Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² =0.0%

Test for overall effect: Z = 1.66 (P = 0.097)

Test for subgroup differences: Not applicable



Analysis 2.1. Comparison 2 Combined SSRI plus CBT versus PE alone (adults), Outcome 1 PTSD symptom severity (clinician rated) post intervention (change scores SPRINT).

Review: Combined pharmacotherapy and psychological therapies for post traumatic stress disorder (PTSD)

Comparison: 2 Combined SSRI plus CBT versus PE alone (adults)

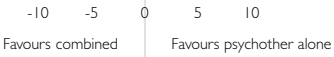
Outcome: 1 PTSD symptom severity (clinician rated) post intervention (change scores SPRINT)

Study or subgroup	Combined N	Mean(SD)	Psychotherapy only N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Simon 2008	9	-2.33 (5.24)	14	-4.57 (7.24)		100.0 %	2.24 [-2.87, 7.35]
Total (95% CI)	**9**		**14**			**100.0 %**	**2.24 [-2.87, 7.35]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.86 (P = 0.39)

Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2 Combined SSRI plus CBT versus PE alone (adults), Outcome 2 Drop outs.

Review: Combined pharmacotherapy and psychological therapies for post traumatic stress disorder (PTSD)

Comparison: 2 Combined SSRI plus CBT versus PE alone (adults)

Outcome: 2 Drop outs

Study or subgroup	Combined n/N	Single treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Simon 2008	3/11	2/14		100.0 %	1.91 [0.38, 9.51]
Total (95% CI)	**11**	**14**		**100.0 %**	**1.91 [0.38, 9.51]**
Total events: 3 (Combined), 2 (Single treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.79 (P = 0.43)					

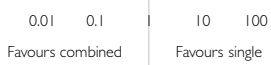
Analysis 3.1. Comparison 3 Combined SSRI plus TFCBT versus TFCBT alone (children/adolescents), Outcome 1 Drop outs.

Review: Combined pharmacotherapy and psychological therapies for post traumatic stress disorder (PTSD)

Comparison: 3 Combined SSRI plus TFCBT versus TFCBT alone (children/adolescents)

Outcome: 1 Drop outs

Study or subgroup	Combined n/N	Single treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cohen 2007	1/12	2/12		100.0 %	0.50 [0.05, 4.81]
Total (95% CI)	**12**	**12**		**100.0 %**	**0.50 [0.05, 4.81]**
Total events: 1 (Combined), 2 (Single treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.60 (P = 0.55)					

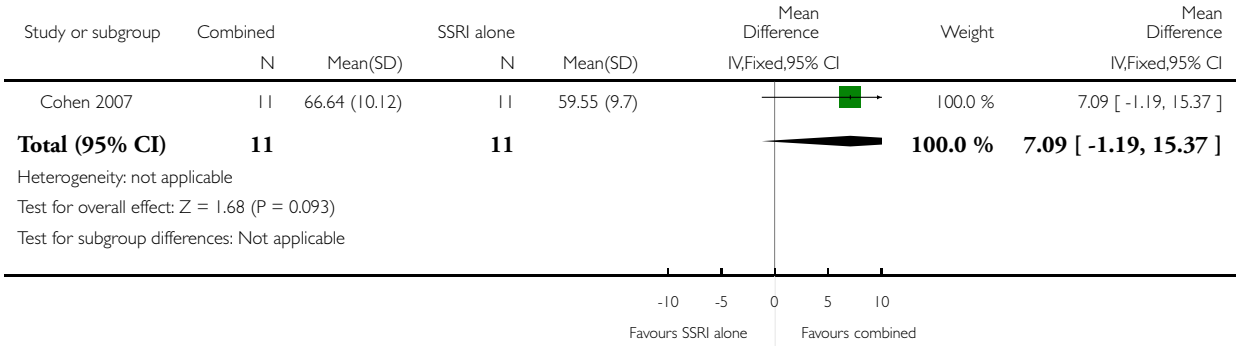


Analysis 3.2. Comparison 3 Combined SSRI plus TFCBT versus TFCBT alone (children/adolescents), Outcome 2 Functioning CGAS.

Review: Combined pharmacotherapy and psychological therapies for post traumatic stress disorder (PTSD)

Comparison: 3 Combined SSRI plus TFCBT versus TFCBT alone (children/adolescents)

Outcome: 2 Functioning CGAS



HISTORY

Protocol first published: Issue 3, 2008

Review first published: Issue 7, 2010

Date	Event	Description
14 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Ruth Parslow conceived the review. Ruth Parslow co-ordinated the development of the protocol with all authors contributing equally to the design and development of the protocol. All authors were involved in the inclusion and exclusion of trials, data extraction, entry and quality appraisal. BG compiled all of the information about the trials in the Tables. SH drafted the text of the review and responded to editorial comments, with all authors providing comment and feedback.

DECLARATIONS OF INTEREST

No declarations of interest.

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- ORYGEN Research Centre, University of Melbourne, Australia.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

Child Abuse, Sexual [psychology]; Clonazepam [therapeutic use]; Cognitive Therapy [*methods]; Combined Modality Therapy [methods]; Paroxetine [therapeutic use]; Randomized Controlled Trials as Topic; Refugees [psychology]; Serotonin Uptake Inhibitors [*therapeutic use]; Sertraline [therapeutic use]; Stress Disorders, Post-Traumatic [drug therapy; *therapy]

MeSH check words

Adolescent; Adult; Child; Female; Humans; Male