Early pharmacological interventions for preventing post-traumatic stress disorder (PTSD): a network meta-analysis

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AB S T R A C T

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:
To assess the efficacy and acceptability of pharmacological interventions for preventing post-traumatic stress disorder (PTSD) in adults exposed to a traumatic event and to generate a clinically useful ranking of pharmacological interventions according to their efficacy and acceptability by performing a network meta-analysis.

B A C K G R O U N D

Description of the condition

Post-traumatic stress disorder (PTSD) is a severe and debilitating disorder which may develop in people exposed to traumatic events. Up to 80% of the adult population in the USA have been exposed to a traumatic event eligible for diagnosis of PTSD (Breslau 2012), and estimates are similar for Europe (de Vries 2009). The lifetime prevalence of PTSD is estimated at 6.8% (Kessler 2005), and the 12-month prevalence at 3.5% (Kessler 2005a). General prevalence rates are higher in displaced populations (Bogic 2015; Turrini 2017), and populations exposed to conflict (Steel 2009).

According to the Diagnostic and Statistical Manual of Mental Disorders, FiJh Edition (DSM-5), traumatic events eligible for the diagnosis "include, but are not limited to, exposure to war as a combatant or civilian, threatened or actual physical assault, threatened or actual sexual violence, being kidnapped, being taken hostage, terrorist attack, torture, incarceration as a prisoner of war, natural or human-made disasters, and severe motor vehicle accidents" (APA 2013). As stated by the DSM, this list is not comprehensive and many different traumatic events have proved capable of triggering PTSD. For instance, in recent years there has been an increase in reports of PTSD in survivors of critical illness, with an estimated prevalence of 25% among this population (Wade 2013). With some limitations regarding the nature of the traumatic incident, witnessing a trauma, learning that a relative or close friend was exposed to trauma, or being exposed to aversive details about a trauma (as in the course of professional duties) may also precipitate PTSD (APA 2013).

Not all individuals exposed to traumatic experiences will develop PTSD. The likelihood of developing PTSD is associated with a number of pre-, peri-, and post-traumatic factors (Bisson 2007; Qi 2016), such as history of a psychiatric disorder, gender (females are more vulnerable than males), low socioeconomic status, belonging to a minority, history of previous trauma, genetic endowment and epigenetic regulation, impaired executive functioning and higher emotional reactivity (Aupperle 2012; Guthrie 2005), the severity of the trauma itself, the perceived threat to life, whether the event was intentional or unintentional, peritraumatic emotions and dissociation (Ozer 2003), and the perceived lack of social support and subsequent life stress (e.g. inability to work as a result of the event) (Brewin 2000).

Individuals who develop PTSD following a trauma may experience a wide range of symptoms, which are presented in four categories in the DSM-5 (APA 2013).

• **Re-experiencing**, e.g. recurrent unwanted intrusive memories, distressing dreams, flashbacks, distress at re-exposure.
• **Avoidance of stimuli associated with the trauma behaviours**, e.g. the avoidance of distressing memories associated with the traumatic event or avoidance of external reminders.
• **Negative alteration in cognitions and mood associated with the traumatic event**, e.g. impairment in recalling important aspects of the trauma, negative thoughts and assumptions about oneself or the world, negative beliefs about the causes or consequences of the traumatic event, diminished interest or participation in significant activities, feeling of detachment from others, inability to experience positive emotions.
• **Arousal symptoms**, e.g. hypervigilance, insomnia, irritability, reckless or self-destructive behaviour, problems concentrating. The development and maintenance of PTSD is most likely the product of an interaction of different factors. Although, current evidence alone cannot explain the complexity underlying PTSD, it is clear that multiple and interconnected systems are involved (Kelmendi 2016; Koch 2014; Lee 2016; Pitman 2012), and although psychological mechanisms are involved, the disorder has a distinct biological profile (Besnard 2012; Nickerson 2013). Appendix 1 presents a summary of the main evidence related to the biological profile of PTSD.

Description of the intervention
Interventions for preventing the development of PTSD can be divided into two main categories: psychosocial and pharmacological. Although this review focuses on the latter, several other publications have examined and reviewed the former (Bryant 2007; Forneris 2013; Kearns 2012; Qi 2016; Roberts 2010; Rose 2002).

With respect to pharmacological interventions, drugs belonging to different classes have been examined by means of randomised clinical trials, and some reviews have already been published (Amos 2014; Sijbrandij 2015). It should be noted that the mechanisms underlying the onset of the disorder are likely to be different from the ones maintaining it, and therefore some of the interventions proposed to prevent the onset of the disorder differ from the interventions for treatment.

Glucocorticoids are synthetic analogues of hormones involved in immunity and stress response. They can be administered in several ways including oral, intravenous and intramuscular. Depending on the purpose, a treatment course can last from a single shot to several days. The trials testing steroids for PTSD prevention have used either single dose administration or a course of a few days in individuals with severe physical conditions (Delahanty 2013; Schelling 2001; Weis 2006). Hydrocortisone, along with some other steroids, is also included in the World Health Organization (WHO) Model List of Essential Medicines (WHO 2017), and therefore expected to be commonly available in several global contexts. Propranolol is a beta blocker, primarily used for long-term treatment in cardiology. Some trials have tested it on a three-week time span for PTSD prevention (Hoge 2012; Pitman 2002; Stein 2007). Propranolol is also included in the WHO Model List of Essential Medicines (WHO 2017). A small trial has investigated a short course of temazepam, which belongs to the class of benzodiazepines (common anxiolytic drugs), but found an increase of PTSD onset rather than a decrease (Mellman 2002). Recently, there is growing interest in oxytocin, an endogenous hormone involved in sociability and stress regulation (Qi 2016), an early trial investigated oxytocin administered in a single intranasal dose (van Zuiden 2017). Escitalopram is a selective serotonin reuptake inhibitor (SSRI) antidepressant, and although this class has yielded good results in PTSD treatment, there is uncertainty whether SSRIs are effective in reducing the incidence of PTSD (Shalev 2012). Gabapentin, an anticonvulsant with anxiolytic properties and a benign side effect profile, has been included in trials of PTSD prevention (Stein 2007). Opioids have been proposed too, for example a large retrospective study on USA soldiers with combat injury, found an association between morphine administration and lower PTSD incidence (Holbrook 2010).

How the intervention might work
The biological features of PTSD provide several possible targets for the pharmacological prevention of PTSD. Different rationales can explain the efficacy of the investigated drugs.

Glucocorticoids
Glucocorticoids are involved in both hormonal stress response and memory formation. The hypothalamic-pituitary-adrenal (HPA) axis has long been a focus in PTSD investigations, and a role for hydrocortisone in facilitating extinction learning has been hypothesised (Hruska 2014). In a rodent model a negative association has been found between a high dose of steroids and prevalence of PTSD-like behaviour in rats exposed to predator scent stress (Cohen 2008), and coherent results were found in a morphological study (Zohar 2011). There is also epidemiologic evidence that lower urinary cortisol

levels in the immediate aftermath of the trauma are associated with future PTSD symptoms (Delahanty 2000; McFarlane 1997).

Beta blockers

A role for adrenaline in the formation of traumatic memories has long been postulated (Pitman 1989). It has been argued that a surge in adrenaline concentration in conjunction with trauma, results in a strong emotional memory and fear conditioning that could prime PTSD. Later human studies supported a role for the beta adrenergic system in memory storing and in the enhanced memories associated with emotional arousal (Cahill 1994; Southwick 1999), and for propranolol to limit this process (Reist 2001).

Benzodiazepines

Benzodiazepines are known for reducing arousal and decreasing distress. They have amnesic properties as well, mostly inhibiting memory consolidation by impairing long-term episodic storage (Barbee 1993). Despite this, no clinical research has found a positive effect for benzodiazepines in the management of traumatic stress symptoms (Howlett 2016).

Opioids

Studies on rodents have found retrograde amnesia properties for morphine, and a possible mechanism for that has been proposed via decreasing cyclic adenosine monophosphate or activating Nmethyl- D-aspartate (NMDA) receptors in the hippocampus (McNally 2003). Human observational studies support a protective effect for morphine (Bryant 2009; Mouthaan 2015).

Oxytocin

A possible role for oxytocin in the prevention of PTSD is quite a recent approach, which has been proposed on a dual assumption theory: a reduction in the amygdala activation and an increase in the activation of the social reward brain areas (OIC 2010). Behavioural data on rodents seem to confirm a plausible role for oxytocin (Cohen 2010).

SSRIs

SSRI antidepressants are generally considered the first-line pharmacological treatment for PTSD (ISTSS 2018; NICE 2018), and might thereby have a putative role in the prevention of the disorder.

Mood stabilisers/anticonvulsants

As for SSRIs, mood stabilisers/anticonvulsants might have a putative role in PTSD prevention, considering their employment as adjuvant/ second-line treatment for anxiety disorders (Van Ameringen 2004). A trial of gabapentin has been reported in a previous metaanalysis (Stein 2007).

Omega-3 fatty acid compounds

Considering their ability to promote neurogenesis in the hippocampus, a key area in memory consolidation and fear maintenance, a role has been proposed for omega-3 fatty acids in PTSD prevention (Matsuoka 2011).

Why it is important to do this review

PTSD represents a heavy burden for the people affected, those around them, health systems and society. Findings from the National Vietnam Veterans Longitudinal Study showed that, even after decades, an important share of male war veterans have PTSD (4.5%, 95% confidence interval (CI) 1.7 to 7.3) or subthreshold PTSD symptoms (6.4%, 95% CI 3.0 to 9.7) (Marmar 2015). Moreover, PTSD is associated with poor general health status and unemployment (Zatzick 1997). Most of the evidence regards psychosocial intervention, among which trauma-focused and exposure-based therapies are the most promising ones, but many of the studies are restricted by small sample sizes and methodological limits (Birur 2017). Despite the abundance of putative biological and clinical risk factors for PTSD and various predictive strategies being tested, e.g. supervised machine learning (Galatzer-Levy 2014; KarstoJ 2015; Kessler 2014), there is currently no effective way to predict who will develop PTSD after a traumatic experience. The biological features of PTSD provide several possible targets for the prevention of PTSD, and encouraging results were found in previous meta-analyses (Amos 2014; Sijbrandij 2015). Although it would be valuable to have effective interventions for prevention of PTSD, the risk-to-benefit ratio needs to be carefully assessed, as drugs will entail possible side effects for all of those receiving them, and not all of the individuals exposed to a trauma will develop PTSD.

It should be noted that very different kinds of pharmacological interventions have been proposed to prevent PTSD onset, but there is a lack of head-to-head trials between them. It is therefore difficult to make an overall comparison and establish a hierarchy, both in terms of efficacy, tolerability and acceptability. It therefore appears of important value to assess pharmacological interventions to prevent the onset of the condition, applying a methodology that allows indirect comparisons.

O B J E C T I V E S

To assess the efficacy and acceptability of pharmacological interventions for preventing post-traumatic stress disorder (PTSD) in adults exposed to a traumatic event and to generate a clinically useful ranking of pharmacological interventions according to their efficacy and acceptability by performing a network meta-analysis.

M E T H O D S

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) comparing one medication with placebo or one medication with another. We will consider trials for inclusion irrespective of language or publication status. For cross-over trials, we will consider the data from the first randomised phase only.

Types of participants

Individuals

We will include trials on individuals with all of the following characteristics.

- History of any traumatic event
- Aged 18 and older

We will exclude studies targeting symptomatic patients at baseline, as these studies will be included in a second parallel review on early interventions, while the present review is on prevention.

Setting

We will consider trials performed in any type of setting.

Subset data

We will include trials in which only a portion of the sample meets the above criteria, provided that the relevant data can be gained from the study report or by contacting the authors, and that the effect of randomisation is not affected by doing so.

Types of interventions

The Diagnostic and Statistical Manual of Mental Disorders, FiJh Edition (DSM-5) regards the three months from the trauma as a relevant timeframe for symptoms' evolution (APA 2013). We will then consider any pharmacological intervention administered with the intention to prevent the onset of post-traumatic stress disorder (PTSD) or PTSD symptoms within such a timeframe. We will set no restriction regarding dose, duration, administration route of the intervention,
nor on the presence of any co-medication not related to PTSD prevention. We will not consider trials where the experimental medication was used as an augmentation agent to ongoing psychotherapy (e.g. cognitive enhancers).

Based on our knowledge of the literature, we expect drugs from the following pharmacological groups to be found.

- Glucocorticoids
- Beta-blockers
- Benzodiazepines
- Opioids
- Other hormones (oxytocin)
- Selective serotonin reuptake inhibitors (SSRIs)
- Mood stabilisers/anticonvulsants
- Omega-3 fatty acid compounds

We assume that any individual that meets the inclusion criteria is, in principle, equally likely to be randomised to any of the eligible interventions.

We will include any other pharmacological interventions we might find during the review process and clearly report them. We will consider them eligible for the network meta-analysis after assessing their comparability with the before mentioned prespecified set of competing interventions, in order to preserve the assumption of 'jointly randomisable' treatments.

Types of comparison
We will include studies using both placebo and any active pharmacological comparison. We will not consider studies comparing pharmacological interventions with only psychosocial interventions (i.e. with no other pharmacological or placebo arm).

We will include studies that meet the above criteria, irrespective of whether they report any of our outcomes of interest.

Types of outcome measures
Primary outcomes
• **PTSD severity (continuous):** we will use the mean score on the Clinician-Administered PTSD Scale (CAPS) (Blake 1995), or the Comprehensive International Diagnostic Interview (CIDI) (WHO 1997), or any other validated rating scale to assess symptom severity.
• **Dropouts due to adverse events (dichotomous):** we will consider the number of participants who leave the assigned arm
early due to side effects, out of the number of randomised individuals.
Secondary outcomes
• **PTSD rate (dichotomous):** we will consider PTSD rates, as measured by a DSM or International Classification of Diseases (ICD) (WHO 1992) diagnosis made with a clinician-administered measure.
• **Depression severity (continuous)**: we will consider the severity of depressive symptoms, using the score on the Hamilton Depression Rating Scale (Hamilton 1960), or the Beck Depression Inventory (Beck 1961), or any other validated scale.
• **Anxiety severity (continuous)**: we will consider the severity of the anxiety symptoms using the score on the Covi Anxiety Scale (CAS) (Covi 1984), or the Beck Anxiety Inventory (Beck 1988), or the Spielberger State-Trait Anxiety Inventory (Spielberger 1970), or any other validated scale.
• **Functional disability (continuous):** we will consider the Sheehan Disability Scale (Sheehan 1996), or any other validated
scale.
• **Quality of life (continuous):** we will use the Medical Outcomes Study (MOS) 36-Item Short-Form Health Survey (SF-36) (Ware 1992), or any other validated scale to assess quality of life.
• **Dropout for any reason (dichotomous):** we will consider the number of participants who leave the assigned arm early for any reason, out of the number of randomised individuals.

Hierarchy of outcome measures
The hierarchy of outcome measure scales will follow the order above. As we expect that clinician-administered scales to have been more frequently employed, in case of trials employing validated scales different from the before mentioned, for homogeneity reasons we will give priority to clinician-administered scales over self-reported ones.

Timing of outcome measures
We will synthesise data at three months follow-up (i.e. 3 months after experiencing trauma), operationalised as the time point closest to three months of follow-up (from 2 to 4 months of follow-up). In addition, we will include data at study endpoint as a secondary time point.

Search methods for identification of studies Specialised register: the Cochrane Common Mental Disorders Controlled Trials Register (CCMDCTR)
Cochrane Common Mental Disorders (CCMD) maintained a specialised register of randomised controlled trials (RCTs), the CCMDCTR, to June 2016. This register contains over 40,000 reference records (reports of RCTs) for anxiety and depressive disorders, bipolar disorder, eating disorders, self-harm and other mental disorders within

the scope of CCMD. The CCMDCTR is a partially studies- based register with > 50% of the reference records tagged to 12,600 individually participant, intervention, comparison, outcome (PICO)-coded study records. Reports of trials for inclusion
in the register were collated from (weekly) generic searches of MEDLINE (1950-), Embase (1974-) and PsycINFO (1967-), quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and review-specific searches of additional databases. Reports of trials were also sourced from international trial registries, drug companies, handsearching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and metaanalyses. Details of CCMD's core search strategies (used to identify RCTs) can be found on CCMD's website, with an example of the MEDLINE search displayed in Appendix 2. The register fell out-of date with the relocation of the group from the University of Bristol to York University in June 2016.

Electronic searches

CCMDCTR-studies and references register

We will cross-search the CCMDCTR studies and references register for condition alone, using the following terms:
(*PTSD or posttrauma* or post-trauma* or "post trauma*" or "combat disorder*" or "stress disorder*"*) (all years to June 2016). We will screen the search results for any pharmacological intervention (active intervention versus placebo or active intervention versus active intervention trials) to prevent the onset of PTSD.

Biomedical database search

We will search Ovid MEDLINE, Embase and PsycINFO, Ebsco Published International Literature On Traumatic Stress (PILOTS) and the Cochrane Central Register of Controlled Trials (CENTRAL) from 2014 onwards. This is to account for the period when the CCMDCTR fell out-of-date. A search has already been conducted by the CCMD editorial base (3 March 2018) (Appendix 3). We will screen the results of this search for all relevant pharmacological RCTs to prevent the onset of PTSD.

International trials registers

We will search for unpublished studies in international trials registers via the World Health Organization's trials portal (ICTRP), and the National Institute of Health's trials website (clinicaltrials.gov). See Appendix 4 for search strategies on these sources. We will not apply any publication status or language restrictions. We will re-run all searches close to publication if the initial search date is greater than 12 months.

Searching other resources

We will check the reference list of all included studies and relevant systematic reviews.

Data collection and analysis

Selection of studies

We will import all records obtained via the electronic search, plus the handsearch, into Endnote software (EndNote) in order to remove all duplicates. Two review authors (FB and LR) will work in duplicate and independently. They will screen all potential papers' titles and abstracts and code them as 'retrieve' or 'not retrieve', obtain the full-text publication of the records coded as 'retrieve', and assess inclusion and exclusion criteria. Disagreement will be resolved by discussion or, if necessary, by involving a third review author (NM). We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

Two review authors (FB and LR) working independently and in duplicate will extract data from the included trials. We will use a data extraction sheet developed in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* section 7.5 (Higgins 2011). We will collect the following data.

• First author, year of publication, journal, source of funding, notable conflict of interest of authors, total duration of study, number of centres and location.

• Methodological characteristics of the trial: randomisation, blinding, allocation concealment, number of arms, follow-up
time points.

• Sample characteristics: study setting, type of trauma, criteria for enrolling, age, gender, number of participants randomised to each arm, history of previous trauma.

• Intervention details: time from the traumatic event to treatment, medication employed, period over which it has been administered, dosage range, mean dosage prescribed.

• Outcomes: time points of outcome assessment, instrument used to assess PTSD symptoms, instrument used to assess PTSD rate, instrument used to assess depression symptoms, instrument used to assess anxiety, instrument used to assess functional disability, outcome measure employed by original trial (primary and secondary), data of continuous (means and standard deviation or standard error if standard deviation is not

provided) and dichotomous variables of interest, number of total dropouts, number of dropouts due to pharmacological side effect, whether the data reflect an intention-to-treat (ITT) model, methods of estimating the outcome for participants who dropped out (last observation carried forward (LOCF) or completer/observed case (OC) approach, or other).

Assessment of risk of bias in included studies

Two review authors (FB and LR) working independently and in duplicate will assess risk of bias for each study according to the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Disagreement will be resolved by discussion, or if necessary by involving a third review author (NM). We will assess the risk of bias according to the following domains.

1. Random sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personal (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective reporting (reporting bias)
7. Other bias

We will assess performance, detection and attrition bias on a per outcome basis rather than per study. We will rate each source of bias as high, low or unclear. We will provide reasons to justify therating. We will present all data regarding risk of bias both graphically and in the text.

Measures of treatment effect

Dichotomous data

For dichotomous data, we will calculate risk ratio (RR) estimates and their 95% confidence interval (CI). RRs are more easily interpreted than odds ratios (ORs) (Boissel 1999), and as clinicians may risk interpreting ORs as RRs (Deeks 2002), this may lead to an over-estimation of the effect. We will calculate the number needed to treat to benefit (NNTB).

Continuous data

For continuous data, we will calculate the mean differences (MDs)and the 95% CI, where data are measured on the same scale. If the studies employed different scales, we will use standardised mean differences (SMDs). The trials may report the results either as end point means or using change in mean values from baseline assessment. Preference will be given to endpoint measures, given the nature of the review (prevention) and that endpoint data are easier to interpret from a clinical point of view. Where sufficient data are reported, we will convert change scores into endpoint data using standard formulas reported in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We will interpret SMDs according to the following guidelines: 0.2 represents a small effect,0.5 a moderate effect, and 0.8 a large effect (Cohen 1988).

Unit of analysis issues

Crossover trials

We will consider only the first phase from cross-over trials as the carry over effect cannot be excluded on a prevention measure, regardless of appropriate washout times.

Cluster randomised trials

If cluster-RCTs are included, but have not appropriately adjusted for the correlation between participants within clusters, we will contact trial authors to obtain an estimate of the intra cluster correlation (ICC), or impute using estimates from the other included trials or from similar external trials. If imputation of ICCs is required, we will conduct sensitivity analyses to examine the impact on estimates.

Multiple treatment group studies

For the pair-wise meta-analysis, we will compare each arm with placebo separately and include each pair-wise comparison separately. We plan the following means to prevent 'double-counting', in accordance with the Cochrane Handbook for Systematic Reviews of Interventions, section 16.5.4 (Higgins 2011): in the case of dichotomous variables, we will split the comparison group evenly among the intervention groups, in the case of continuous variables, we will only divide the total number of participants and leave the mean and SDs unchanged.

For the network meta-analyses, we will adjust for correlations inherent in multiple-arm trials using standard methods (e.g. Dias2013a).

Dose-ranging studies

If a study has multiple arms with the same medication administered at different doses or administered for a different time length, we will pool these intervention groups into a single one, as recommended by the Cochrane Handbook for Systematic Reviews of Interventions, section 16.5.4 (Higgins 2011).

Dealing with missing data

As a first measure, we will contact study investigators to obtain missing data. Should this not be effective, we will employ the following approaches.

Dichotomous data

Where reported, we will use ITT data analysed on a 'once randomised, always randomised' basis. In case of trials conducting different imputational strategies, we will give preference to data de-rived from multiple imputation or mixed-effects models. For studies that did not perform an ITT analysis, we will assume a negative outcome (i.e. onset of PTSD) for individuals lost at follow-up.

Continuous data

As above, we will use ITT data where reported, and favour multiple imputation or mixed-effects models where different imputationals trategies have been used. In the context of prevention, last observation carried forward (LOCF) provides the least conservative option and therefore observed case (OC) data will be preferred. For studies not reporting ITT analyses, we will not impute missing data for continuous outcomes, as this usually requires access to individual participant data.

We will report, in the relevant section of the results, if the data employed were based on an imputational method and if so, which one.

Missing statistics

Where possible, we will calculate SDs when only P values, CIs, standard errors etc. are reported. If this is not be possible, we will calculate an arithmetic mean of the SDs of studies using the same scale of the one with missing SD, as in Furukawa 2006.

Assessment of heterogeneity

We will assess heterogeneity by means of:

•visual inspection on the overlap of the CIs for individual studies in the forest plot;

•Chi2 test, with a P value set at 0.10 (we presume the number of studies to be small);

•I2 statistic: in accordance with the suggestion in the Cochrane Handbook for Systematic Reviews of Interventions section 9.5.2(Higgins 2011), we will follow a rough guide to interpretation as follows: 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. We will also take into account magnitude and direction of effects.

Assessment of reporting biases

If more then 10 studies are included per primary outcome, we will:

•visually inspect the relative funnel plots, test them for asymme-try and investigate possible reasons for funnel plot asymmetry;

•employ Egger's regression test (Egger 1997).

Data synthesis

Methods for pair-wise meta-analysis

We will perform standard pair-wise meta-analysis with a random-effects model for every comparison with at least two studies, using Review Manager 5 (Review Manager 2014). Given the nature of the data, and the likely heterogeneity, we think a random-effects model makes more plausible assumptions. We will perform the pair-wise comparison at individual medicine level (e.g. propranolol versus placebo), but if this is not feasible due to the number of studies, we will shift to drug class level (e.g. Beta blocking agents versus placebo), using the WHO's Anatomical Therapeutic Chemical (ATC) / Defined Daily Dose (DDD) Index 2019 as a reference (WHO2018). We will not perform a pair-wise meta-analysis in the case of comparisons with less than two contributing trials.

Methods for network meta-analysis

For primary outcomes, at both time points (3 months from trauma and at study endpoint), we will assess if there are sufficient data to perform a network meta-analysis. If there are sufficient data, we will perform a network meta-analysis using Markov Chain MonteCarlo methods. We will fit random-effects models in a Bayesian framework using WinBUGS/OpenBUGS (WinBUGS 2000), with standard code (Dias 2013a).

The binomial likelihood will be used for dichotomous data and the normal likelihood for continuous data.

We will assume a common between study heterogeneity variance for the relative treatment effects. Normal non-informative priors (0,100) will be used for trials baselines and treatment effects. Uni-form non-informative priors (0,5) for between trial SDs.

We will assess convergence of three chains (using different initial values) based on visual inspection of history, Brooks-Gelman Rubin, and autocorrelation plots. If chains are judged to have converged, the preceding iterations will be discarded, and a further 50,000 iterations will be run. Estimates will be based on the latter iterations.
We will report posterior medians with 95% credible intervals for all treatment effects, between-study standard deviations (to assess heterogeneity), and total residual deviance (to assess goodness off it).
We will calculate the mean rank and probability of being most effective for each treatment (both with 95% credible intervals).

We plan to perform the network meta-analysis at individual medicine level, but should this not be feasible we will also consider fit-ting models at drug class level using the WHO's ATC/DDD Index 2019as a reference (WHO 2018), or including both individual medicine and drug class levels.

We will assess the transitivity assumption (i.e. that effect modifiers are equally distributed across the comparisons) in several steps. First, we will assess the distribution of potential effect modifiers across treatment comparisons for the following study characteristics: year of publication, study setting, type of trauma, criteria for enrolling, age, gender, history of previous trauma of participants, time from traumatic event to treatment, period over which the treatment has been administered. Second, we will use standard methods to conduct a global assessment of inconsistency using WinBUGS/OpenBUGS (Dias 2013b;WinBUGS 2000).

We will compare the goodness of fit of an inconsistency model with the network meta-analysis model used in the main analyses which assumes consistency between direct and indirect evidence. We will assess the impact on between-study SD (i.e. heterogeneity) and goodness of fit statistics (residual deviance and deviance information criterion (DIC)).

Third, if there is sufficient evidence of potential inconsistency (e.g. improved fit of the inconsistency model of 5 or more on the DIC, substantial reduction in between-study deviation), then we will fit node-splitting models (van Valkenhoef 2016), using the GraphicalMixed Treatments Comparisons (GeMTC) package in R (R 2017).

Subgroup analysis and investigation of heterogeneity
For both pairwise and network meta-analyses we will perform meta-regression analyses on primary outcomes only, to avoid the risk of identifying false positive findings through multiple testing. We plan to assess the impact on effectiveness of the following co-variates.
•Setting (e.g. acute and emergency departments, surgery or in-tensive care survivors).
•Interventions starting within 12 hours from trauma and interventions starting after 12 hours from trauma

Sensitivity analysis
We plan to investigate the impact of excluding studies at high risk of bias, defined by unclear allocation concealment or unblinded out-come assessment or uncertain unblinding of outcome assessment; the impact of using ITT data versus completer outcomes; and the impact of excluding cluster RCTs.

To estimate the influence of small study effects on the network meta-analyses we will examine the association between effect estimates and their variance (small studies tend to have larger variances) for the primary outcomes (Dias 2010). We will asses the magnitude of the bias parameter along with its 95% credible intervals as well as the impact on relative effects estimates and between-trial standard deviation

Summary of findings
Direct treatment comparisons
We will present the results of the meta-analysis using a 'Summary of findings' table for the pair-wise comparisons. The 'Summary offindings' table will include the following outcomes.
•PTSD severity
•Dropouts due to adverse events

•PTSD rate
•Functional disability
•Quality of life

We will use the five GRADE 'certainty assessment' domains (study design, risk of bias, inconsistency, indirectness, imprecision) to assess the certainty of the evidence in consideration of the studies that provided data for the specific outcome. We will use the GRADE-pro software (GRADEpro GDT 2015), and apply the methods and recommendations from the Cochrane Handbook for Systematic Re-views of Interventions, section 11.5 (Higgins 2011). Grading will be assigned by at least two different review authors, disagreement will be resolved through discussion or if required by consulting a third review author (NM). We will use footnotes to justify the downgrading and upgrading of the evidence. We will note comments to aid the reader, when suitable. We will categorise the certainty of the evidence as high (further research is not likely to change our confience in the estimate of effect), moderate (further research is likely to have an important impact on the estimate of effect and may change it), low (further research is very likely to have an important impact on the estimate of effect and is likely to change it), or very low (estimate of effect is very uncertain).

If we find that additional information regarding the outcome can-not be incorporated in the meta-analysis, we will report this in the comments and state whether this information supports or contradicts the meta-analysis results.

Indirect and mixed comparisons

We will create a ‘Summary of findings' table for the primary out-comes.

We will use the five GRADE domains (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of the evidence from the network meta-analysis, using the standard methods (Section 8.5 and Chapter 12 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011)),but with modifications to reflect specific issues in network meta-analysis. As proposed by Salanti 2014, we will:

•evaluate each piece of direct evidence in the network and classify it as either at low, moderate or high risk of bias, according to the usual GRADE guidelines;
•for each pair-wise network estimate, we will consider the contribution of all direct estimates feeding into it, using the contributions matrix;
•illustrate the ‘Risk of bias' assessments according to the contributions of each source of direct evidence to each network meta-analysis effect estimate. We will display this in a bar chart using green, yellow and red to represent low, moderate and high risk of bias, respectively;
•for each pair-wise comparison, we will integrate the ‘Risk of bias' judgements and the respective contributions into a single judgement about study limitations and consider whether to down grade the quality of the evidence. We will assign numerical scores to each risk of bias judgement (e.g. 0 for low, −1 for moderate, and −2 for high risk of bias), and take a weighted average of these using the contribution of each direct estimate to the network estimates from the contributions matrix.

We will use GRADEpro GDT and CINeMA software to generate data for the 'Summary of findings' tables (CINeMA 2007; GRADEpro GDT2015), which will be presented according to Yepes-Nunez 2019, using placebo as comparator. We will justify all decisions to down-grade or upgrade the quality of the evidence using footnotes and make comments to aid the reader's understanding of the review, where necessary (Salanti 2014).

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APPENDICES

Appendix 1. PTSD biological profile

A recent large genome-wide association study on post-traumatic stress disorder (PTSD) reports a molecular genetics-based heritability for European-American females of 29%, with an estimate not distinguishable from zero for males (Duncan 2018). This is consistent with results from twin studies estimating the heritability post-trauma at about 30% (Stein 2002; True 1993), with female heritability two to three times higher than in males (Sartor 2011). The loci identified so far are involved in the dopaminergic and serotoninergic systems, in the hypothalamic-pituitary-adrenal (HPA) axis regulation, in the encoding of neurotrophins and in the locus coeruleus-noradrenergic system (Pitman 2012; Smoller 2016). There are findings to support an epigenetic contribution as well, mainly on the expression of genes related to immune functions, signal transduction, neuronal signalling and HPA axis activity (Yehuda 2009; Zieker 2007). As a whole, however, the genetic role in PTSD remains mainly uncharted (Smoller 2016). The sympathetic nervous system appears to be upregulated (Southwick 1999), and hyper-reactive in individuals affected by PTSD (Liberzon 1999; Southwick 1993), and this can be correlated with the hypervigilance-hyperarousal-insomnia symptoms and to the cluster of 're-experience' symptoms. It has also been proposed that an excessive surge in the adrenal response immediately after the trauma may play a role in the formation of the persistent memories associated with the event (Pitman 1989). The serotoninergic system plays another role in both the modulation of the PTSD risk and in its clinical manifestations. Evidence of that can be gathered from the before mentioned genetic studies, and from neuropharmacological studies (Murphy 1991; Southwick 1997): the serotonin pathway is highly likely to be implicated in the process undergoing the sleep disturbances, stress modulation, mood, aggressivity, and some of the neuroendocrine aspects (Southwick 1999). Additional evidence of the serotoninergic pathway involvement are provided from receptor imaging studies: 5-HT transporter binding is reduced in the amygdala (Murrough 2011), and 5-HT_{1B} receptors are less concentrated in amygdala and anterior cingulate cortex (Kelmendi 2016); both of these areas are of interest in PTSD as confirmed by morphological studies (see further). The cortisol axis regulation is altered in PTSD subjects and some findings do suggest that an altered HPA axis could be present before the trauma (Yehuda 2009a). The corticotrophin release hormone is known as an anxiogenic agent and modulates some of the systemic response to stress including cytokine signalling, immunological and hormonal functions (Friedman 2000). It is generally found increased in serum samples of patients, but has yielded mixed results regarding the dynamics of its concentration in the cerebrospinal fluid (Baker 2005; Geracioti 2008), and more evidence is required to determine its role on the central nervous system during stress. Contrary to what one could expect, the cortisol levels are reduced in PTSD patients (Yehuda 2002), perhaps reflecting an excessively upregulated feedback effect (Yehuda 1995). Of interest, some of the genes known to be involved in the process of resilience have glucocorticoid response elements (Hou 1998). Moreover, cortisol has become a focus in PTSD for its role in memory formation and consolidation (McIntyre 2007). In light of the different findings on this relationship on memory formation in PTSD (Schelling 2004), it can be hypothesised that the relationship follows an inverted U tendency (Pitman 2012; Sandi 2011). The immune system itself may play a role, based on early findings of its activation in PTSD (Newport 2000), supported by later epigenetic studies (Uddin 2010). The gamma-aminobutyric acid-ergic (GABAergic) system is likely to be involved, and has a role in both memory registration and fear memory encoding (Corcoran 2001). A receptor binding study found a global overall reduction in the benzodiazepine receptor (Geuze 2008). PTSD patients compared to trauma-exposed non-PTSD people also have lower GABA levels in the mesial temporal lobe and in the parieto-occipital cortex (Meyerhoff 2014). Cannabinoid receptor 1 is involved in the modulation of aversive memories (Kelmendi 2016), and was found more available in individuals with PTSD, while its endogenous agonist was found lowered (Neumeister 2013). Recently, a growing interest is focusing on oxytocin, which holds prosocial and anxiolytic effects (Olff 2014). A disruption in the oxytocin system has been proposed in the development of PTSD (Feldman 2014), and intranasal oxytocin administration has proven to be able to reduce amygdala reactivity in response to threat (Koch 2016).

Morphological and functional studies of the central nervous system in people with PTSD have scoped several alterations (Admon 2013; O'Doherty 2015; Pitman 2012). Some of the abnormalities might be predisposing risk factors (in particular amygdala and dorsal anterior cingulate), while others may become evident only after the onset of the disorder, i.e. the structural/functional connectivity between hippocampus and ventromedial prefrontal cortex (Admon 2013). Meta-analyses have confirmed an hippocampal reduction (Karl 2006; Smith 2005; Woon 2011), and a recent meta-analysis found the reduction to be bigger in the left hippocampus (O'Doherty 2015). On the assumption that diminished volume may underline a diminished function, these findings support the theory that the hippocampus fails to signal a safe environment via contextual cues. It is still a matter of debate whether hippocampal alterations are consequent of PTSD or rather a risk factor (Bremner 2001; Gilbertson 2002). Functional studies have produced mixed results with some reporting less activation (Bremner 2003), and others more (Shin 2010). There are findings of prefrontal cortex regions of people affected by PTSD to be reduced in volume in the ventromedial prefrontal cortex (Kasai 2008), and in the dorsal anterior cingulate cortex (Kitayama 2006; O'Doherty 2015). Functional studies found areas in the ventromedial prefrontal cortex to be less active during tasks involving trauma-related stimuli (Shin 1999). Some reports found similar results for non-trauma-related stimuli as well (Gold 2011). Findings on the amygdala, report a volume reduction when PTSD patients are compared with healthy non-trauma-exposed subjects, but no significant reduction was found when compared with trauma-exposed non-PTSD subjects (O'Doherty 2015). Functional studies found amygdala to be more activated in response to trauma-related stimuli (Liberzon 1999a), to generic stimuli (Etkin 2007), and in fear acquisition in PTSD patients compared to control subjects (Bremner 2005). The focus on the amygdala is due to its role in the regulation of traumatic and stressful events, related behaviour and emotions, and in fear conditioning and generalisation (O'Doherty 2015).

Appendix 2. CCMDCTR (core MEDLINE search)

Core search strategy used to inform specialised register: OVID MEDLINE (1946 to June 2016)

A weekly search alert based on condition + RCT filter only

1. [MeSH Headings]:

eating disorders/ or anorexia nervosa/ or binge-eating disorder/ or bulimia nervosa/ or female athlete triad syndrome/ or pica/ or hyperphagia/ or bulimia/ or self-injurious behavior/ or self mutilation/ or suicide/ or suicidal ideation/ or suicide, attempted/ or mood disorders/ or affective disorders, psychotic/ or bipolar disorder/ or cyclothymic disorder/ or depressive disorder/ or depression, postpartum/ or depressive disorder, major/ or depressive disorder, treatment-resistant/ or dysthymic disorder/ or seasonal affective disorder/ or neurotic disorders/ or depression/ or adjustment disorders/ or exp antidepressive agents/ or anxiety disorders/ or agoraphobia/ or neurocirculatory asthenia/ or obsessive-compulsive disorder/ or obsessive hoarding/ or panic disorder/ or phobic disorders/ or stress disorders, traumatic/ or combat disorders/ or stress disorders, post-traumatic/ or stress disorders, traumatic, acute/ or anxiety/ or anxiety, castration/ or koro/ or anxiety, separation/ or panic/ or exp anti-anxiety agents/ or somatoform disorders/ or body dysmorphic disorders/ or conversion disorder/ or hypochondriasis/ or neurasthenia/ or hysteria/ or munchausen syndrome by proxy/ or munchausen syndrome/ or fatigue syndrome, chronic/ or obsessive behavior/ or compulsive behavior/ or behavior, addictive/ or impulse control disorders/ or firesetting behavior/ or gambling/ or trichotillomania/ or stress, psychological/ or burnout, professional/ or sexual dysfunctions, psychological/ or vaginismus/ or Anhedonia/ or Affective Symptoms/ or *Mental Disorders/2. [Title/ Author Keywords]:

(eating disorder* or anorexia nervosa or bulimi* or binge eat* or (self adj (injur* or mutilat*)) or suicide* or suicidal or parasuicid* or mood disorder* or affective disorder* or bipolar i or bipolar ii or (bipolar and (affective or disorder*)) or mania or manic or cyclothymic* or depression or depressive or dysthymi* or neurotic or neurosis or adjustment disorder* or antidepress* or anxiety disorder* or agoraphobia or obsess* or compulsi* or panic or phobi* or ptsd or posttrauma* or post trauma* or combat or somatoform or somati#ation or medical* unexplained or body dysmorphi* or conversion disorder or hypochondria* or neurastheni* or hysteria or munchausen or chronic fatigue* or gambling or trichotillomania or vaginismus or anhedoni* or affective symptoms or mental disorder* or mental health).ti,kf.3. [RCT filter]:

(controlled clinical trial.pt. or randomized controlled trial.pt. or (randomi#ed or randomi#ation).ab,ti. or randomly.ab. or (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion or number* or place* or recruit* or subsitut* or treat*)).ab. or placebo*.ab,ti. or drug therapy.fs. or trial.ab,ti. or groups.ab. or (control* adj3 (trial* or study or studies)).ab,ti. or ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dummy*)).mp. or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or randomized controlled trial/ or pragmatic clinical trial/ or (quasi adj (experimental or random*)).ti,ab. or ((waitlist* or wait* list* or treatment as usual or TAU) adj3 (control or group)).ab.)4. (1 and 2 and 3)Records are screened for reports of RCTs within the scope of the Cochrane Common Mental Disorders Group. Secondary reports of RCTs are tagged to the appropriate study record.

Similar weekly search alerts are also conducted on OVID Embase and PsycINFO, using relevant subject headings (controlled vocabularies) and search syntax, appropriate to each resource.

Appendix 3. CCMD Editorial Base search strategy (2014-2018)

In March 2018, CCMD's Information Specialist (Chris Cooper) ran a search for all PTSD studies (treatment or prevention, RCTs, condition only) on the main biomedical databases listed below. This was to account for the period when the CCMDCTR was out-of-date and to cover all PTSD reviews within the scope of CCMD.

Search results were deduplicated and screened in Covidence, each record was screened by at least two members of the CCMD editorial base staff.

Inclusion criteria:

- any RCT for the treatment of PTSD (irrespective of intervention, age group or comorbidity)
- any RCT which might be seen as a PTSD prevention study
- any RCT for critical incident stress debriefing (CISD) (simulated crises not included)
- Any RCT for debriefing after psychological trauma or any stress resilience studies
- Any CCT where the treatment allocation is ambiguous
- Corrigendums, errors, retractions or substantial comments relating to the above.

Exclusion criteria:

- all systematic reviews and meta-analyses
- healthy populations
- simulated crises (e.g. for staff training in accident and emergency)
- RCTs which fall outside the scope of CCMD, e.g. serious mental illness (schizophrenia), borderline personality disorder, alcohol use disorder e.g. brief alcohol intervention in accident and emergency department, smoking cessation, traumatic brain injury, fibromyalgia (unless the comorbidity clearly fell within the scope of the search and was an outcome of the trial).

- healthy populations
- simulated crises (e.g. for staff training in accident and emergency)
- RCTs which fall outside the scope of CCMD, e.g. serious mental illness (schizophrenia), borderline personality disorder, alcohol use disorder e.g. brief alcohol intervention in accident and emergency department, smoking cessation, traumatic brain injury, fibromyalgia (unless the comorbidity clearly fell within the scope of the search and was an outcome of the trial).

Databases	Hits
MEDLINE	1742
Embase	3319
CENTRAL	2028
PsycINFO	1449
PILOTS	879
Total	9417
-duplicates	-4635
Studies to screen	4782
Date of Search	3/3/18

1. Cochrane Central Register of Controlled Trials (CENTRAL)
Host: Wiley interface
Data Parameters: Cochrane Central Register of Controlled Trials : Issue 2 of 12, February 2018
Date Searched: Monday, March 3rd 2018
Searched by: Chris Cooper
Hits: 2028
ID Search Hits
#1 MeSH descriptor: [Stress Disorders, Post-Traumatic] this term only 1492
#2 (PTSD or ((posttrauma* or post-trauma* or post trauma*) near/3 (stress* or disorder* or psych* or symptom*)) or acute stress disorder* or combat disorder* or war neuros*) 5065
#3 (((acute or traumatic) near/1 stress*) and (expos* or psyc*)) 1525
#4 (traumatised near/1 (victim* or survivor*)) 2
#5 (traumatized near/1 (victim* or survivor*)) 4
#6 (trauma* near/2 (event* or memor* or flashback* or nightmare*)) 553
#7 ((trauma* or posttrauma* or post-trauma* or victim* or survivor*) and (exposure near/3 (therap* or psychotherap* or training or counsel*))) 417
#8 MeSH descriptor: [Crisis Intervention] this term only 166
#9 (critical incident near/1 (stress or debrief* or de-brief*)) 24
#10 (debriefing or de-briefing) 328
#11 (crisis intervention* or CISD) 1003
#12 ((stress or group* or psychological or crisis) near/3 (debrief* or de-brief*)) 107
#13 (trauma* near/2 (event* or memor* or flashback* or nightmare*)) 553
#14 (EMDR or (eye movement desensitization and reprocessing)) 225
#15 (EMDR or (eye movement desensitisation and reprocessing)) 197
#16 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or
#15 Publication Year from 2014 to 2018 2893
Notes: N/A
File: V01 CENTRAL n2028.txt

2. Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Host: OVID
Data Parameters: 1946-Current (date limits applied, 2014 onwards)
Date Searched: Monday, March 3rd 2018
Searched by: Chris Cooper
Hits: 1742

#	Searches	Results
1	Stress Disorders, Post-Traumatic/	27503
2	(PTSD or ((posttrauma* or post-trauma* or post trauma*) adj3 (stress* or disorder* or psych* or symptom?)) or acute stress disorder* or combat disorder* or war neuros*).ti,ab,kf,kw,id.	31111
3	(([acute or traumatic) adj stress*) and (expos* or psyc*)).ti,ab,kf,kw,id.	10567
4	(traumatized adj (victim? or survivor?)).ti,ab,kf,kw,id.	34
5	(trauma* adj2 (event? or memor* or flashback* or nightmare?)).ti,ab,kf,kw,id.	8174
6	((trauma* or posttrauma* or post-trauma* or victim* or survivor?) and (exposure adj3 (therap* or psychotherap* or training or counsel*))).ti,ab,kf,kw,id,hw.	901
7	Crisis Intervention/	5457
8	(critical incident adj (stress or debrief* or de-brief*)).ti,ab,kf,kw,id.	223
9	(debriefing or de-briefing).ti,kf,kw,id.	577
10	(crisis intervention? or CISD).ti,ab,kf,kw,id.	1744
11	((stress or group? or psychological or crisis) adj3 (debrief* or de-brief*)).ti,ab,kf,kw,id.	406
12	(trauma* adj2 (event? or memor* or flashback* or nightmare?)).ti,kf,kw,id.	1150
13	(EMDR or (eye movement desensitization and reprocessing)).ti,ab,kf,kw,id,sh.	510
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	52168
15	randomized controlled trial.pt.	454849
16	controlled clinical trial.pt.	92204
17	randomized.ab.	404382
18	placebo.ab.	186843
19	clinical trials as topic.sh.	182777
20	randomly.ab.	285994
21	trial.ti.	178689
22	15 or 16 or 17 or 18 or 19 or 20 or 21	1136215

(Continued)

23	14 and 22	4000
24	(2014* or 2015* or 2016* or 2017* or 2018*).yr,dt,ed,ep.	5444042
25	23 and 24	1742

Notes: N/A
File: VO1 MEDLINE n1742.txt

3. Embase
Host: OVID
Data Parameters: 1974 to 2018 March 02 (date limits applied, 2014 onwards)
Date Searched: Monday, March 3rd 2018
Searched by: Chris
Hits: 3319
Search Strategy:

#	Searches	Results
1	posttraumatic stress disorder/	48854
2	"trauma and stressor related disorders"/	34962
3	combat disorders/	26663
4	psychological trauma/	5351
5	stress disorders, post-traumatic/	16743
6	stress disorders, traumatic, acute/	751
7	(PTSD or ((posttrauma* or post-trauma* or post trauma*) adj3 (stress* or disorder* or psych* or symptom?)) or acute stress disorder* or combat disorder* or war neuros*).ti,ab,kw.	39945
8	((acute or traumatic) adj stress*) and (expos* or psyc*)).ti,ab,kw.	15122
9	(traumatized adj (victim? or survivor?)).ti,ab,kw.	51
10	(trauma* adj2 (event? or memor* or flashback* or nightmare?)).ti,ab,kw.	10514
11	(EMDR or (eye movement desensitization and reprocessing)).ti,kw.	527
12	((trauma* or posttrauma* or post-trauma* or victim* or survivor?) and (exposure adj3 (therap* or psychotherap* or training or counsel*))).ti,ab,kw.	1096
13	(critical incident adj (stress or debrief* or de-brief*)).ti,ab,kw.	275
14	(debriefing or de-briefing).ti,ab,kw.	4133
15	(crisis intervention? or CISD).ti,ab,kw.	2273
16	((stress or group? or psychological or crisis) adj3 (debrief* or de-brief*)).ti,ab,kw.	602

17	(trauma* adj2 (event? or memor* or flashback* or nightmare?)).ti,ab,kw.	10514
18	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	74063
19	crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/ or (random* or factorial* or crossover* or cross over* or placebo* or (doubl* adj blind*) or (singl* adj blind*) or assign* or allocat* or volunteer*).tw.	1970074
20	18 and 19	7601
21	(2014* or 2015* or 2016* or 2017* or 2018*).yr,dc.	7084132
22	20 and 21	3319

Notes: N/A
File: V01 Embase n3319.txt

4. **PsycINFO**
Host: OVID
Data Parameters: 1806 to February Week 4 2018 (date limits applied, 2014 onwards)
Date Searched: Monday, March 3rd 2018
Searched by: Chris Cooper
Hits: 1449
Search Strategy:

#	Searches	Results
1	posttraumatic stress disorder/ or complex ptsd/ or desnos/ or acute stress disorder/ or combat experience/ or "debriefing (psychological)"/ or emotional trauma/ or post-traumatic stress/ or exp stress reactions/ or traumatic neurosis/	50806
2	exp disasters/	8186
3	(PTSD or ((posttrauma* or post-trauma* or post trauma*) adj3 (stress* or disorder* or psych* or symptom?)) or acute stress disorder* or combat disorder* or war neuros*).ti,ab.	38985
4	(((acute or traumatic) adj stress*) and (expos* or psyc*)).ti,ab.	16755
5	(traumati#ed adj (victim? or survivor?)).ti,ab.	68
6	(trauma* adj2 (event? or memor* or flashback* or nightmare?)).ti,ab.	11819
7	(EMDR or (eye movement desensiti#ation and reprocessing)).ti,ab.	1640
8	((trauma* or posttrauma* or post-trauma* or victim* or survivor?) and (exposure adj3 (therap* or psychotherap* or training or counsel*))).ti,ab.	1086
9	crisis intervention/	3314
10	(critical incident adj (stress or debrief* or de-brief*)).ti,ab.	443
11	(debriefing or de-briefing).ti,ab.	2186

12	(crisis intervention? or CISD).ti,ab.	3505
13	((stress or group? or psychological or crisis) adj3 (debrief* or de-brief*)).ti,ab.	596
14	(trauma* adj2 (event? or memor* or flashback* or nightmare?)).ti,ab.	11819
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	80813
16	clinical trials.sh.	10820
17	(randomized or randomization or randomizing).ti,ab,id.	72509
18	(RCT or at random or (random* adj3 (assign* or allocat* or control* or crossover or cross-over or design* or divide* or division or number))).ti,ab,id.	82020
19	(control* and (trial or study or group) and (placebo or waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,id,hw.	25590
20	((single or double or triple or treble) adj2 (blind* or mask* or dummy)).ti,ab,id.	24054
21	trial.ti.	25583
22	placebo.ti,ab,id,hw.	37267
23	treatment outcome.md.	18762
24	treatment effectiveness evaluation.sh.	21858
25	mental health program evaluation.sh.	2028
26	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	169119
27	15 and 26	4124
28	(2014* or 2015* or 2016* or 2017* or 2018*).yr,dc,mo.	782907
29	27 and 28	1449

Notes: N/A
File: VO1 PsycINFO n1449.txt

5.**PILOTS: Published International Literature On Traumatic Stress**
Host: Pro Quest
Data Parameters: 1871-Current (date limits applied, 2014 onwards)
Date Searched: Monday, March 3rd 2018
Searched by: Chris Cooper
Hits: 879
Search Strategy

Set#: S1 Searched for: ti((posttrauma* near/4 (stress* or disorder* or psych* or symptom*))) OR ab((posttrauma* near/4 (stress* or disorder* or psych* or symptom*))) Results: 16999*
Set#: S2 Searched for: ti((post-trauma* near/4 (stress* or disorder* or psych* or symptom*))) OR ab((post-trauma* near/4 (stress* or disorder* or psych* or symptom*))) Results: 6647*
Set#: S3 Searched for: ti((post trauma* near/4 (stress* or disorder* or psych* or symptom*))) OR ab((post trauma* near/4 (stress* or disorder* or psych* or symptom*))) Results: 7214*

Set#: S4 Searched for: ti((PTSD or acute stress disorder* or combat disorder* or war neuros*)) OR ab((PTSD or acute stress disorder* or combat disorder* or war neuros*)) Results: 30435*
Set#: S5 Searched for: ti((((acute or traumatic) near/2 stress*) and (expos* or psyc*))) OR ab((((acute or traumatic) near/2 stress*) and (expos* or psyc*))) Results: 2341°
Set#: S6 Searched for: ti((traumatised near/2 (victim* or survivor*))) OR ab((traumatised near/2 (victim* or survivor*))) Results: 84°
Set#: S7 Searched for: ti((trauma* near/3 (event* or memor* or flashback* or nightmare*))) OR ab((trauma* near/3 (event* or memor* or flashback* or nightmare*))) Results: 6974°
Set#: S8 Searched for: ti(((trauma* or posttrauma* or post-trauma* or victim* or survivor*) and (exposure near/4 (therap* or psychotherap* or training or counsel*)))) OR ab(((trauma* or posttrauma* or post-trauma* or victim* or survivor*) and (exposure near/4 (therap* or psychotherap* or training or counsel*)))) Results: 787°
Set#: S9 Searched for: ti((critical incident near/2 (stress or debrief* or de-brief*))) OR ab((critical incident near/2 (stress or debrief* or de-brief*))) Results: 385°
Set#: S10 Searched for: ti((debriefing or de-briefing)) OR ab((debriefing or de-briefing)) Results: 685°
Set#: S11 Searched for: ti((crisis intervention* or CISD)) OR ab((crisis intervention* or CISD)) Results: 784°
Set#: S12 Searched for: ti(((stress or group* or psychological or crisis) near/4 (debrief* or de-brief*))) OR ab(((stress or group* or psychological or crisis) near/4 (debrief* or de-brief*))) Results: 464°
Set#: S13 Searched for: ti((trauma* near/3 (event* or memor* or flashback* or nightmare*))) OR ab((trauma* near/3 (event* or memor* or flashback* or nightmare*))) Results: 6974°
Set#: S14 Searched for: ti((EMDR or (eye movement desensitisation and reprocessing)) OR ab((EMDR or (eye movement desensitisation and reprocessing)) Results: 888°
Set#: S15 Searched for: ti((EMDR or (eye movement desensitiZation and reprocessing)) OR ab((EMDR or (eye movement desensitiZation and reprocessing)) Results: 888°
Set#: S16 Searched for: (s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14 or s15) Results: 36840*
Set#: S17 Searched for: MAINSUBJECT.EXACT("Randomized Clinical Trial") Results: 1210°
Set#: S18 Searched for: ab((randomized or randomised or placebo or randomly)) Results: 2931°
Set#: S19 Searched for: ti(trial) Results: 784°
Set#: S20 Searched for: (S17 or S18 or S19) Results: 3226°
Set#: S21 Searched for: S16 and s20 Results: 2654°
Set#: S22 Searched for: (S16 and s20) AND pd(20140101-20180301) Results: 879°

* Duplicates are removed from your search, but included in your result count.
° Duplicates are removed from your search and from your result count.

Notes: N/A
File: VO1 PILOTS n879.txt

Appendix 4. ICTRP and clinicaltrials.gov search strategies

ClinicalTrials.gov

1. PTSD
2. posttrauma
3. post-trauma
4. "post trauma"
5. (combat and disorder)

ICTRP: (PTSD or posttrauma* or post-trauma* or "post trauma*" or (combat and disorder*))

CONTRIBUTIONS OF AUTHORS

FB: lead author of the protocol, wrote the protocol, developed the selection criteria and the methodology.

LR: contributed to the background and commented on the methodology of the protocol.

GO: contributed to the background and commented on the methodology of the protocol.

NM: contributed to the background of the protocol and developed the methodology.

JIB: contributed to the background of the protocol, developed the selection criteria and commented on the methodology of the protocol.

RC: contributed to the background and commented on the methodology of the protocol.

CB: contributed to the background and commented on the methodology of the protocol.