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

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ABSTRACT
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.

BACKGROUND
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, Fifth 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 oxtocin, an endogenous hormone involved in sociability and stress regulation (Qi 2016), an early trial investigated oxtocin 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; Karstøl 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.

**OBJECTIVES**

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.

**METHODS**

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, F1h 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 the rating. 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 derived 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 imputational strategies 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 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 asymmetry 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. Uniform 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 of fit).

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 fitting models at drug class level using the WHO's ATC/DDD Index 2019 as 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).

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 deviance), then we will fit node-splitting models (van Valkenhoef 2016), using the Graphical Mixed 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 intensive 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 outcome 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 assess 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 of findings' 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 Reviews 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 categorize the certainty of the evidence as high (further research is not likely to change our confidence 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 cannot 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 outcomes.

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).
References

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Amos 2014

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Aupperle 2012

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Barbee 1993

Beck 1961

Beck 1988

Besnard 2012

Birur 2017

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Breslau 2012

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Cahill 1994

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Sijbrandij 2015

Smith 2005

Smoller 2016

Southwick 1993

Southwick 1997

Southwick 1999

Spielberger 1970

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WHO 1992

WHO 1997

WHO 2017

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WinBUGS 2000

Woon 2011

Yehuda 1995

Yehuda 2002

Yehuda 2009

Yehuda 2009a

Yepes-Nunez 2019

Zatziek 1997

Zieker 2007
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 (Dean et al. 2018). This is consistent with results from twin studies estimating the heritability post-traumatic stress at about 39% (Stein et al. 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 serotonergic systems, in the hypothalamic-pituitary-adrenal (HPA) axis regulation, in the encoding of neurotrophins and in the locus coeruleus-noradrenergic system (Pitman 2012; Smoller 2014). 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; Zilber 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 (Liberman 1999; Southwick 1993), and this can be correlated with the hypervigilance and posttraumatic symptoms. It has also been proposed that an excessive surge of the adrenal response immediately after the trauma may play a role in the formation of the persistent memories associated with the event (Pitman 1983). The serotonergic system plays another role in the modulation of the PTSD risk and in its clinical manifestations. Evidence of that can be gained from the before-mentioned genetic studies, and from pharmacological studies (Murphy 1991; Southwick 1991): the serotonin pathway is highly likely to be implicated in the process underlying the sleep disturbances, stress modulation, mood, aggressivity, and some of the neuroendocrine aspects (Southwick 1999). Additional evidence of the serotoninergic pathway involvement is provided from receptor imaging studies: 5-HT transporter binding is reduced in the amygdala (Tannock 2010), and 5-HT1A receptors are less concentrated in amygdala and anterior cingulate cortex (Kelmander 2016). Both of these areas are of interest in PTSD as confirmed by morphological studies (see further). The cortical axis regulation is altered in PTSD subjects and some findings on 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 mediates some of the systemic response to stress including cytokine signalling, immunological and hormonal functions (Friedman 2001). 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; Gerasioli 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 unregulated feedback effect (Yehuda 1995). Of interest, some of the genes known to be involved in the process of resilience have glucocorticoid response elements (Nis 1998). Moreover, cortisol has become a focus in PTSD for its role in memory formation and consolidation (McInerney 2007). It is 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 pattern (Pitman 2012; Sandi 2013). The immune system itself may play a role, based on only findings of its activation in PTSD (Nestle 2003), supported by later epigenetic studies (Von Elm 10). The gamma-aminobutyric acid-ergic (GABAergic) system is likely to be involved, and has a role in both memory registration and fear memory encoding (Colcora 2001). A receptor binding study found a global overall reduction in the benzodiazepine receptor (Geuze 2006). 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 2004). Cannabinoid receptor 1 is involved in the modulation of aversive memories (Kelmander 2013), and was found more available in individuals with PTSD, while its endogenous agonist was found lowerend (Neumeister 2013). Recently, a growing interest is focusing on oxytocin, which holds prosocial and anxiolytic effects (DIF 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 reported several alterations (Admon 2013; O’Boherty 2015; Pitman 2014). 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; Smth 2008; Woon 2011), and a recent meta-analysis found the reduction to be bigger in the left hippocampus (O’Boherty 2016). On the assumption that diminished volume may underlie 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 (Bremer 2001; Gillett 2002). Functional studies have produced mixed results with some reporting less activation (Bremer 2003), and others more (Shin 2015). There are findings of prefrontal cortex regions of people affected by PTSD to be reduced in volume in the ventromedial prefrontal cortex (Kemal 2008), and in the dorsal anterior cingulate cortex (Kilts et al. 2008; D’Ohohery 2015). Functional studies have 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 (Godd 2011). Findings on the amygdala report a volume reduction when PTSD patients are compared with healthy non-trauma-exposed subjects, with trauma-exposed non PTSD subjects (O’Boherty 2015). Functional studies found amygdala to be more activated in response to trauma-related stimuli (Liberman 1999a), to generic stimuli (Etkin 2007), and in fear acquisition in PTSD patients compared to control subjects (Bremer 2005). The focus on the amygdala is due to its role in the regulation of traumatic and stressful events, related behaviour and emotions, and is fear conditioning and generalisation (O’Boherty 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, obsessive-compulsive/or anxiety, separation/or panic/or exp anti-anxiety agents/or somatoform disorders/or body dysmorphic disorders/or conversion disorders/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 frontal lobe dysfunction, prefrontal/or sexual dysfunctions, psychological/or vaginismus/or Anhedonia/or Affective Symptoms/or Mental Disorders/. [Title/ Author Keywords]:

(eating disorder* or anorexia nervosa or bulimia* or binge eat* or (self adj (injure* 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 manic or manic or cyclothymic* or depression or depressive or dysthymic or neurotic or neurasthenia or adjustment disorder* or antidepression* or anxiety disorder* or agoraphobia or obsessive* or compuls* or orgastic or phobic* or ped or posttraumatic* or posttrauma* or combat or somatoform or somatisation or medical* unexplained or body dysmorphic* or conversion disorder or hypochondriasis* or neurasthenia* or hysteria or munchausen or chronic fatigue* or gambling or trichotillomania or vaginismus or anhedonia or affective symptoms or mental disorders or mental health). [RCT filter]:

(controlled clinical trial or randomized controlled trial or randomized or randomisation or ab.1 or random ab or (random* adj (administ* or allocat* or assign* or class* or control* or determin* or divide or distribute) or expose* or fashion or number or place or recruit or substi* or treat*). ab. or placebo* or drug therapy or. ts. or trial or ab.1 or groups or ab. or (control* adj (trial or study or studies) or (sing* or doubl* or trip* or treb*). adj (blind* or mask* or dummy*). or m. or clinical trial or phase II or (random controlled trial or pragmat clinical trial or (quasi adj (experimental or random*). t. ab. or (qualitat* or wait* list or or treatment as usual or TAU) adj (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 PsychINFO, using relevant subject headings (controlled vocabularies) and search syntax, appropriate to each resource.


In March 2018, CCMD’s Information Specialists (Chris Cooper) ran a search for all PTSD studies (treatment or prevention, RCT, 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
- Corrigenda, 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 crisis (e.g., 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, 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).

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<td>((trauma* or posttrauma* or post-trauma* or victim* or survivor?) and (exposure adj (therapy* or psychotherap* or training or counsel*))),t,ab.</td>
<td>1086</td>
</tr>
<tr>
<td>9</td>
<td>crisis intervention/</td>
<td>3334</td>
</tr>
<tr>
<td>10</td>
<td>(critic* incident* adj (stress or debrif* or de-brief*)),t,ab.</td>
<td>443</td>
</tr>
<tr>
<td>11</td>
<td>(debriefing or de-briefing),t,ab.</td>
<td>2186</td>
</tr>
</tbody>
</table>
12 (crisis intervention) or CIsD Atlab.

13 (stress or group? or psychological or crisis) adj3 (debrief* or de-brief*)Atlab.

14 (trauma* adj3 (event? or remor* or flashback* or nightmare‡))Atlab.

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

16 clinical trials sh.

17 (randomized or randomization or randomising)Atlab.

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‡))Atlab.

19 (control and (trial or study or group) and (placebo or waitlist* or wait†list* or ((treatment or care) adj2 usual†))Atlab.

20 (single or double or triple or treble) adj2 (blind* or mask* or dummy†)Atlab.

21 trial.ti.

22 placebo.ti,ab,sh.

23 treatment outcome.md.

24 treatment effectiveness evaluation.sh.

25 mental health program evaluation.sh.

26 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25

27 15 and 26

28 (2014 or 2015 or 2016 or 2017 or 2018) yd,sc,me.

29 27 and 28

Notes: N/A
File: V01 PsychINFO m14.txt

5.PILOTS: Published International Literature On Traumatic Stress
Host: ProQuest
Data Parameters: 5871 Current (date limits applied, 2014 onwards)
Date Searched: Monday, March 3rd 2014
Search by: Chris Cooper
Hits: 875
Search Strategy
Sett: S1 Searched for: t1((posttrauma* near4 (stress* or disorder* or psych* or symptom†)) OR ab1((posttrauma* near4 (stress* or disorder* or psych* or symptom†)) Results: 16994‡
Sett: S2 Searched for: t1((posttrauma* near4 (stress* or disorder* or psych* or symptom†)) OR ab1((posttrauma* near4 (stress* or disorder* or psych* or symptom†)) Results: 6647‡
Sett: S3 Searched for: t1((posttrauma* near4 (stress* or disorder* or psych* or symptom†)) OR ab1((posttrauma* near4 (stress* or disorder* or psych* or symptom†)) Results: 7214‡
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.
LF: 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.
JLB: 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.