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Pharmacological interventions for preventing post-traumatic stress disorder (PTSD) (Review)

Amos T, Stein DJ, Ipser JC

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[Intervention Review]

Pharmacological interventions for preventing post-traumatic stress disorder (PTSD)

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ABSTRACT

Background

Post-traumatic stress disorder (PTSD) is a debilitating disorder which, after a sufficient delay, may be diagnosed amongst individuals who respond with intense fear, helplessness or horror to traumatic events. There is some evidence that the use of pharmacological interventions immediately after exposure to trauma may reduce the risk of developing of PTSD.

Objectives

To assess the effects of pharmacological interventions for the prevention of PTSD in adults following exposure to a traumatic event.

Search methods

We searched the Cochrane Depression, Anxiety and Neurosis Controlled Trials Register (CCDANCTR-Studies and CCDANCTR-References) (to 14 February 2014). This register contains relevant reports of randomised controlled trials from the following bibliographic databases: CENTRAL (all years); EMBASE (1974 to date); MEDLINE (1950 to date) and PsycINFO (1967 to date). We identified unpublished trials by searching the National Institute of Health (NIH) Reporter, the metaRegister of Controlled Trials database (mRCT) and the WHO International Clinical Trials Registry Platform (to December 2013). We scanned the reference lists of articles for additional studies. We placed no constraints on language and setting.

Selection criteria

We restricted studies to randomised controlled trials (RCTs) of pharmacological interventions compared with placebo for the prevention of PTSD in adults.

Data collection and analysis

Two authors (TA and JI) independently assessed trials for eligibility and inclusion based on the review selection criteria. We independently extracted sample, methodological, outcome and 'Risk of bias' data, as well as the number of side effects, from each trial and entered these into a customised data extraction form. We contacted investigators for missing information. We calculated summary statistics for continuous and dichotomous variables (if provided). We did not undertake subgroup analyses due to the small number of included studies.

Main results

We included nine short-term RCTs (duration 12 weeks or less) in the analysis (345 participants; age range 18 to 76 years). Participants were exposed to a variety of traumas, ranging from assault, traffic accidents and work accidents to cardiac surgery and septic shock. Seven studies were conducted at single centres. The seven RCTs included four hydrocortisone studies, three propranolol studies (of which one study had a third arm investigating gabapentin), and single trials of escitalopram and temazepam. Outcome assessment measures

included the Clinician-Administered PTSD Scale (CAPS), the 36-Item Short-Form Health Survey (SF-36) and the Center for Epidemiological Studies – Depression Scale (CES-D).

In four trials with 165 participants there was moderate quality evidence for the efficacy of hydrocortisone in preventing the onset of PTSD (risk ratio (RR) 0.17; 95% confidence interval (CI) 0.05 to 0.56; P value = 0.004), indicating that between seven and 13 patients would need to be treated with this agent in order to prevent the onset of PTSD in one patient. There was low quality evidence for preventing the onset of PTSD in three trials with 118 participants treated with propranolol (RR 0.62; 95% CI 0.24 to 1.59; P value = 0.32). Drop-outs due to treatment-emergent side effects, where reported, were low for all of the agents tested. Three of the four RCTs of hydrocortisone reported that medication was more effective than placebo in reducing PTSD symptoms after a median of 4.5 months after the event. None of the single trials of escitalopram, temazepam and gabapentin demonstrated evidence that medication was superior to placebo in preventing the onset of PTSD.

Seven of the included RCTs were at a high risk of bias. Differential drop-outs between groups undermined the results of three studies, while one study failed to describe how the allocation of medication was concealed. Other forms of bias that might have influenced study results included possible confounding through group differences in concurrent medication and termination of the study based on treatment response.

Authors' conclusions

There is moderate quality evidence for the efficacy of hydrocortisone for the prevention of PTSD development in adults. We found no evidence to support the efficacy of propranolol, escitalopram, temazepam and gabapentin in preventing PTSD onset. The findings, however, are based on a few small studies with multiple limitations. Further research is necessary in order to determine the efficacy of pharmacotherapy in preventing PTSD and to identify potential moderators of treatment effect.

PLAIN LANGUAGE SUMMARY

Medications to prevent post-traumatic stress disorder (PTSD): a review of the evidence

Who may be interested in this review?

- People affected by PTSD and their families.
- Professionals working in adult mental health services.
- General practitioners.
- Charities that support victims of trauma or members of the armed forces.

Why is this review important?

PTSD is a condition experienced by some people after traumatic experiences such as warfare or domestic violence. People with PTSD experience symptoms of intense fear, helplessness and horror. Research suggests that changes in stress hormones in the brain may contribute to PTSD. Giving people medications which work in the brain soon after traumatic events may be able to prevent PTSD from developing.

Previous reviews have shown that talking therapy (cognitive behavioural therapy - CBT) is effective in preventing PTSD. This is the first review of medication as a preventative treatment for PTSD.

What questions does this review aim to answer?

- Is medication an effective preventative treatment for PTSD compared to placebo (dummy pills)?
- Is medication an acceptable treatment (do people stop medication due to side effects)?

Which studies were included in the review?

We searched databases to find all studies comparing medication with placebo for the prevention of PTSD, published up until February 2014. To be included in the review, studies had to be randomised controlled trials. Studies were included if they had adult participants aged over 18 who had experienced traumatic events but did not have a diagnosis of PTSD at the time of starting medication.

We included nine studies with a total of 345 participants in the review. Seven out of the nine studies had a high risk of bias due to problems with the research design.

What does the evidence from the review tell us?

There was moderate quality evidence that hydrocortisone (a steroid medication) prevented PTSD.

There was moderate quality evidence that hydrocortisone reduced the severity of PTSD symptoms.

There was no evidence that propranolol (a beta-blocker), escitalopram (a type of antidepressant), temazepam (a tranquillizer) or gabapentin (an anticonvulsant) prevented PTSD.

All medications were acceptable, with low numbers of people dropping out due to side effects; however not all studies provided information on this.

What should happen next?

The review authors do not feel there is sufficient evidence yet to recommend any medication as a preventative treatment for PTSD. The review authors recommend that future high quality research is needed to provide stronger evidence for the effectiveness of medications in preventing PTSD.

Summary of findings for the main comparison. Propranolol compared to placebo for preventing post-traumatic stress disorder (PTSD)

Propranolol compared to placebo for preventing post-traumatic stress disorder (PTSD)

Patient or population: adult participants (18 years and older) who have been exposed to any traumatic events, but who did not meet the diagnostic criteria for PTSD at study recruitment

Settings: in- and outpatients
Intervention: propranolol
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk[1]	Corresponding risk				
	Placebo	Propranolol				
Treatment efficacy CAPS, CIDI Follow-up: median 3 months	**Study population**		**RR 0.62** (0.24 to 1.59)	118 (3 studies)	⊕⊕⊝⊝ **low** [2]	
	100 per 1000	**62 per 1000** (24 to 159)				
	Moderate					
	200 per 1000	**124 per 1000** (48 to 318)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CAPS: Clinician-Administered PTSD Scale; **CI**: confidence interval; **CIDI**: Comprehensive International Diagnostic Interview; **RR**: risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]The assumed risk in the control group is based on an estimated event rate of 10% and 20%, as per Norris 2007.
[2]Approximately five times as many drop-outs prior to the follow-up assessment were observed in the propranolol than in the placebo groups in one study (29.4% versus 5.9% of the respective samples). Another study provided little information on how allocation was concealed and whether/how blinding of the outcome was performed.

Summary of findings 2. Hydrocortisone compared to placebo for preventing post-traumatic stress disorder (PTSD)

Hydrocortisone compared to placebo for preventing post-traumatic stress disorder (PTSD)

Patient or population: adult participants (18 years and older) who have been exposed to any traumatic events, but who did not meet the diagnostic criteria for PTSD at study recruitment
Settings: in- and outpatients
Intervention: hydrocortisone
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk[1]	Corresponding risk				
	Placebo	Hydrocortisone				
Treatment efficacy CAPS, SCID-IV, PTSS-10Q-I Follow-up: median 4.5 months	**Study population**		**RR 0.17** (0.05 to 0.56)	165 (4 studies)	⊕⊕⊕⊖ **moderate** [123]	
	100 per 1000	**17 per 1000** (5 to 56)				
	Moderate					
	200 per 1000	**34 per 1000** (10 to 112)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CAPS: Clinician-Administered PTSD Scale; **CI**: confidence interval;**PTSS-10Q-I**: Post-Traumatic Stress Syndrome 10-Questions Inventory; **RR**: risk ratio; **SCID-IV**: Structured Clinical Interview for DSM-IV

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]The assumed risk in the control group is based on an estimated event rate of 10% and 20%, as per Norris 2007.
[2]Half of the trials reported administering higher levels of norepinephrine to patients on placebo than medication, which may have confounded the evidence of a treatment effect. In a third trial, the differential proportion of drop-outs between interventions suggests possible attrition bias.
[3]Few participants and few events and thus wide confidence intervals.

BACKGROUND

Description of the condition

Post-traumatic stress disorder (PTSD) is a widespread condition that has been recognised in the fourth edition of the Diagnostic and Statistical Manual (DSM-IV) as a pathological response to severe trauma (APA 1994). To fulfil the DSM-IV criteria for PTSD, an individual must have been exposed to a traumatic event; have at least one re-experiencing, three avoidance and two hyperarousal phenomena; and have had the symptoms for at least one month, with the symptoms causing clinically important distress or reduced day-to-day functioning. PTSD is labelled as acute for the first three months and chronic if it lasts beyond three months (Bisson 2010).

There is evidence that PTSD is associated with substantial reductions in quality of life, a high co-morbidity of psychiatric and medical disorders, marked functional impairment and high economic costs (Erbes 2007; Schnurr 2009; Solomon 1997). A nationally representative mental health survey, the National Comorbidity Survey, discovered that between 50% and 60% of people in the United States are exposed to trauma during their lifetimes, with a lifetime incidence of PTSD of 10.4% for women and 5% for men (Kessler 1995). A more recent replication of this survey discovered that as many as 3.5% of those interviewed had developed PTSD within the previous 12 months (Kessler 2005). Higher prevalence rates have been found in African countries, with a reported PTSD lifetime prevalence in four post-conflict settings of 37.4% in Algeria, 28.4% in Cambodia, 15.8% in Ethiopia and 17.8% in Gaza (de Jong 2001).

Reviews of retrospective and prospective studies have been conducted to identify predictive factors distinguishing between people who subsequently develop PTSD and those who do not (Brewin 2000; Ozer 2003). The general finding is that proximal factors, such as social support and trauma intensity, are more strongly implicated in the subsequent development of PTSD than more distal factors (such as history of family psychopathology). While peri-traumatic stress dissociation may predict development of PTSD (Ozer 2003), more than half of individuals who go on to develop PTSD are not diagnosed with acute stress disorder (ASD) (Bryant 2003).

A range of mechanisms have been proposed to account for the development of PTSD. These include hypotheses focusing on: cognitive attributions about the treatment event (Massad 2006; Nickerson 2013); re-consolidation of negative memories (Besnard 2012; Pitman 1989); abnormalities associated with exposure to trauma in neurotransmitter (Krystal 2009); neuroendocrine (van Zuiden 2013; Yehuda 2006) and neurobiological factors (e.g. glucocorticoid-associated hippocampal atrophy systems (Bremner 2004; Sapolsky 2000), and epigenetic mechanisms in which gene-environment factors place certain individuals at greater risk of developing PTSD (Heinzelmann 2013). A number of sophisticated models have been developed in order to integrate cognitive-affective and neurobiological factors (Shalev 2006), which may constitute a focus for prevention interventions or management of PTSD.

Description of the intervention

There are many approaches to PTSD prevention, the most common of which is psychotherapy. Controlled clinical trials suggest that cognitive behavioural therapy (CBT) is likely to be beneficial for the prevention of PTSD development in adults and children (Bisson 2010; Gillies 2012; Mueser 2008; Van Emmerik 2008), with other psychological interventions being less well supported (Mayou 2000; Rose 2002; Ruzek 2001; Turpin 2005). The relatively large body of evidence for the short- and long-term efficacy of medication treatment for PTSD indicates that medication may be effective in preventing PTSD; the most evidence of efficacy currently existing for the selective serotonin reuptake inhibitors (SSRIs), with promising initial findings for the selective noradrenergic reuptake inhibitor venlafaxine and the atypical antipsychotic risperidone (Ipser 2011). Nevertheless, a recent multi-arm randomised controlled trial (RCT) of the SSRI escitalopram failed to observe a reduction in the onset of PTSD relative to placebo at five or nine months post-trauma exposure (Shalev 2012). A similar lack of evidence of efficacy was observed for the antidepressants imipramine and fluoxetine in reducing ASD symptoms in paediatric burn victims (Robert 2008), despite initial promising findings in this population in a RCT of imipramine (Robert 1999).

Several additional classes of medication may be useful in the prevention of PTSD. Findings from controlled trials of the beta-adrenergic antagonists, such as propranolol (Brunet 2008), and glucocorticoids such as hydrocortisone (Delahanty 2012; Schelling 2001), are promising and support suggestions that cortisol administration after trauma may be a useful approach in preventing PTSD (Schelling 1999; Schelling 2001). While benzodiazepines are widely used in acute trauma settings, the rationale for their use in treating trauma has been undermined by the negative findings of a non-randomised controlled trial of clonazepam or alprazolam (Gelpin 1996). Early administration of temazepam following life-threatening incidents actually resulted in a larger proportion of participants developing PTSD in a small randomised, placebo-controlled trial (Mellman 2002). A randomised controlled trial of gabapentin did not provide evidence for the efficacy of anxiolytic anticonvulsants in preventing PTSD (Stein 2007).

How the intervention might work

Abnormal cortical secretion resulting from disruptions in HPA axis functioning in PTSD has been widely documented (Meewisse 2007), with reports of lower urinary and plasma cortisol in PTSD suggesting that administering cortical steroids to individuals at risk of PTSD might prove beneficial in preventing the onset of the disorder (Yehuda 1990; Yehuda 2008). Although the precise mechanism through which glucocorticoids might prevent PTSD is not clear, animal and human studies have identified complex effects of cortisol administration on memory for emotionally arousing events (de Quervain 2009). Specifically, high levels of glucocorticoids appear to improve the initial consolidation of memory for traumatic events, but have detrimental effects on the subsequent recall of these events. Additionally, a substantial body of evidence reviewed by de Quervain 2009 indicates that the effects of glucocorticoids on traumatic memory are modulated by noradrenergic release in response to stress (Nicholson 2013), particularly in the basolateral amygdala (BLA). The reduced incidence of PTSD in a case-control (Schelling 1999) and a randomised controlled trial (Schelling 2001) of hydrocortisone in patients being treated for septic shock has accordingly been explained in terms of the steroid redressing the low levels of cortisol

in combination with elevated levels of noradrenaline typically found in this patient population.

According to Pitman's translational model of PTSD pathogenesis (Pitman 1989; Pitman 2005), agents that block the effect of stress hormones in the brain might be expected not only to reduce the emotional salience of aversive events, but also to disrupt the resulting over-consolidation of traumatic memories and reinforcement of those memory traces through rehearsal of the events. This is consistent with the finding in a controlled pilot study that administration of propranolol, an agent that acts to block post-synaptic beta-adrenergic receptors in the BLA, reduced psychophysiological reactivity to mental imagery (Pitman 2002), as well as PTSD rate and symptom severity in a non-randomised trial in motor vehicle accident or assault victims (Vaiva 2003). Questions remain, however, regarding the relevance of the adrenalin consolidation hypothesis for indirect trauma (Ozer 2003), as well as the possible harmful effects of beta-blockers such as propranolol in reducing the intensity of memory for traumatic events in the reconsolidation of traumatic memories (McCleery 2004).

While the GABAergic system may also be involved in PTSD development, early work has not supported the use of benzodiazepines such as clonazepam, alprazolam and temazepam for PTSD prevention (Gelpin 1996; Mellman 2002). The anteretrograde amnesia induced by benzodiazepines and evidence from animal studies of their possible potentiation of the acquisition of fear responses (Hebert 1996; Lumley 2000) could explain the increased rates of PTSD observed following early use of benzodiazepines in controlled trials (Gelpin 1996; Mellman 2002). The risk of dependency associated with these medications might also make them a less suitable option.

Why it is important to do this review

Despite the vast body of evidence on the treatment of PTSD, little is known about the use of pharmacological interventions for the prevention of PTSD. A number of Cochrane systematic reviews have been published in this area, but these have been restricted to psychological debriefing interventions (Rose 2002), multiple session early psychological interventions (Roberts 2010), and psychosocial interventions (De Silva 2009; Peñalba 2009). A systematic review of randomised controlled clinical trials of medication for the prevention of PTSD would therefore help to characterise the extent to which pharmacotherapy can be considered as a viable alternative to psychotherapy as a secondary prevention strategy in the treatment of PTSD.

OBJECTIVES

To assess the effects of pharmacological interventions for the prevention of PTSD in adults following exposure to a traumatic event.

METHODS

Criteria for considering studies for this review

Types of studies

We considered all randomised controlled trials (RCTs) for inclusion irrespective of publication status or language.

We also included cluster-randomised control trials and studies with multiple treatment groups in the analysis.

Types of participants

Participant characteristics

We included in the review adult participants (18 years and older) who have been exposed to any traumatic events, but who did not meet the diagnostic criteria for post-traumatic stress disorder at study recruitment.

Co-morbidities

These individuals may or may not have been diagnosed with acute stress disorder, or with comorbid psychopathological disorders.

Setting

We placed no restrictions on setting.

Subsets of participants

We also included trials that included a subset of participants that met the review inclusion criteria in the analysis, provided data for this subset could be extracted from the study report.

Types of interventions

We considered any pharmacological interventions, administered with the express intent to prevent the onset of PTSD, compared with a placebo.

Experimental interventions

We grouped specific pharmacological interventions according to medication class. These included the following:

- Antipsychotics
- Benzodiazepines
- Beta-blockers
- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin and norepinephrine reuptake inhibitors (SNRIs)
- Tricyclic antidepressants (TCAs)
- Mono-amine oxidase inhibitors (MAOIs)
- Other medications

Comparator interventions

- Placebo

We placed no restrictions on timing, dose, duration and co-interventions.

Types of outcome measures

Primary outcomes

1. Treatment efficacy: we determined treatment efficacy from the number of participants who developed PTSD after a minimum period of three months after the traumatic event (APA 1994). We determined diagnosis according to the relevant DSM-IV criteria (APA 1994), as implemented in scales such as the Clinician-Administered PTSD Scale (CAPS) (Blake 1995), and the Comprehensive International Diagnostic Interview (CIDI) (WHO 1997). We also accepted outcomes from studies assigning a probable diagnosis of PTSD using the Posttraumatic Stress

Symptom 10 Questionnaire Inventory (PTSS-10), given evidence that this measure has moderate to high (77%) sensitivity and excellent (97.5%) specificity in diagnosing clinically confirmed cases of PTSD (Weisaeth 1989).

2. Treatment acceptability: we included the total proportion of participants who withdrew from the RCTs due to treatment-emergent side effects in the analysis as a surrogate measure of treatment acceptability, in the absence of other more direct indicators of acceptability.

Secondary outcomes

3. Reduction in PTSD symptoms: we assessed PTSD symptoms and, where available, symptom cluster response, using validated scales such as the CAPS (Blake 1995) and the PTSS-10.

4. Reduction in comorbid symptom responses measured by:
a. depression scales, such as the Hamilton Depression Scale (Hamilton 1959), and the Beck Depression Inventory (Beck 1961);
b. anxiety scales, such as the Hamilton Anxiety Scale (Hamilton 1960).

5. Quality of life measures, such as the MOS 36-Item Short-Form Health Survey (SF-36) (Ware 1992).

6. Measures of functional disability, such as the Sheehan Disability Scale (Sheehan 1996).

7. Side effects: we described the most common drug-related side effects for both the included and excluded studies (defined as those occurring in at least 20% of the participants given medication), as well as significant differences in the rate of occurrence of treatment-emergent side effects between medication and control groups, as part of the narrative review.

Main outcomes of 'Summary of findings' tables

We compiled 'Summary of findings' tables to summarise the best evidence for all relevant outcomes (i.e. experimental versus comparator interventions), and these consisted of the following six elements using a fixed format (Higgins 2011a):

- A list of all important outcomes, both desirable and undesirable.
- A measure of the typical burden of these outcomes (e.g. illustrative risk, or illustrative mean, on control intervention).
- Absolute and relative magnitude of effect (if both are appropriate).
- Numbers of participants and studies addressing these outcomes.
- A grade of the overall quality of the body of evidence for each outcome.
- Space for comments.

Evidence for downgrading studies was based on five factors. If we found a reason for downgrading the evidence, we classified the evidence as 'serious' (downgrading the quality rating by one level) or 'very serious' (downgrading the quality grade by two levels):

- Limitations in the design and implementation of the trial.
- Indirectness of evidence.
- Unexplained heterogeneity or inconsistency of results.
- Imprecision of results.
- High probability of publication bias.

We classified the quality of evidence for each outcome according to the following categories:

- High quality: further research is very unlikely to change our confidence in the estimate of effect.
- Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low quality: we are very uncertain about the estimate.

Timing of outcome assessment

We included data for outcomes from validated measures in the review. We determined treatment efficacy from the number of participants who developed PTSD after a minimum period of three months after the traumatic event (APA 1994). For studies that assessed outcomes at multiple time points (Delahanty 2012; Hoge 2012; Pitman 2002; Shalev 2012; Stein 2007; Zohar 2011a), we synthesised data at the first time point that occurred at least three months after the index traumatic event, consistent with the DSM-IV criteria for chronic PTSD (APA 1994).

Search methods for identification of studies

CCDAN's Specialised Register (CCDANCTR)

The Cochrane Depression, Anxiety and Neurosis Group (CCDAN) maintain two clinical trials registers at their editorial base in Bristol, UK, a references register and a studies-based register. The CCDANCTR-References Register contains over 35,000 reports of randomised controlled trials in depression, anxiety and neurosis. Approximately 60% of these references have been tagged to individual, coded trials. The coded trials are held in the CCDANCTR-Studies Register and records are linked between the two registers through the use of unique Study ID tags. Coding of trials is based on the EU-Psi coding manual. Reports of trials for inclusion in the Group's registers are collated from routine (weekly), generic searches of MEDLINE (January 1950 to date), EMBASE (January 1974 to date) and PsycINFO (January 1967 to date); quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and review-specific searches of additional databases. Reports of trials are also sourced from international trials registers c/o the World Health Organization's trials portal (ICTRP), drug companies and the handsearching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses. Details of CCDAN's generic search strategies can be found on the Group's website.

Electronic searches

We searched the CCDANCTR (Studies and References) (initially to April 2012) on condition alone (due to the ever-increasing list of pharmacological interventions used to prevent and treat PTSD).

Search terms used were: (PTSD or posttrauma* or post-trauma* or "post trauma*" or "combat disorder*" or "stress disorder*").

The Trials Search Co-ordinator (TSC) performed a final (more precise) update search on the CCDANCTR in February 2014,

appending terms for prevention: ("early intervention" or prevent* or prophyla*).
All non-pharmacological (including omega-3) and/or paediatric studies were weeded out, together with those already identified by the author team.

Earlier searches were also conducted by CCDAN's TSC on MEDLINE (March 2011), using terms for PTSD in addition to a sensitive list of drug terms. These searches were instigated when the CCDANCTR was out of date, due to a change over of staff at the editorial base (Appendix 1).

The review authors additionally ran their own searches on PubMed, PsycINFO and EMBASE (March 2011) (Appendix 2). We located ongoing or unpublished trials (December 2013) using the metaRegister of Controlled Trials database (mRCT) (http://www.controlled-trials.com), as well as the WHO clinical trials portal (ICTRP) (http://apps.who.int/trialsearch/) and the National Institutes of Health (NIH) Reporter database (http://projectreporter.nih.gov/reporter.cfm). We selected the NIH ClinicalTrials.gov register as one of the databases searched through the mRCT interface. We entered the search terms 'posttraumatic stress disorder' OR 'post traumatic stress disorder' OR 'PTSD' as search queries for these databases.

We conducted a systematic review search on OVID MEDLINE (April 2012) (Appendix 3).

Searching other resources

Reference lists

We scanned the bibliographies of all identified trials for additional studies.

Personal communication

We also obtained published and unpublished trials from key researchers, as identified by the frequency with which they are cited in the bibliographies of RCTs and open-label studies.

Data collection and analysis

Selection of studies

Two authors (TA and JI) independently assessed RCTs identified from the search for inclusion based on information included in the title and abstract. We subsequently scanned full-text articles agreed upon as potentially eligible. The authors independently collated the data listed under Data extraction and management from RCTs which they both regarded as satisfying the inclusion criteria specified in the Criteria for considering studies for this review section. We listed studies for which additional information was required in order to determine their suitability for inclusion in the review in the Studies awaiting classification table, pending the availability of this information. We resolved any disagreements in the trial assessment and data collation procedures by discussion with a third review author (DS).

Data extraction and management

We designed spreadsheet forms for the purpose of recording descriptive information, summary statistics of the outcome measures and associated commentary. Two review authors (TA and JI) compiled these forms and independently extracted data. Once the data extraction process was complete, we rechecked both data sheets for any discrepancies. If these discrepancies could not be addressed by both review authors, we approached an additional review author (DS) for further clarification. Where information was missing, we contacted the investigators by email in an attempt to obtain this information.

We obtained the following information from each trial:

- Description of the trials, including the primary researcher, the year of publication, source of funding, and the setting and/or location.
- Characteristics of the interventions, including the dose of medication, the period over which it was administered and the name of the particular medication tested.
- Characteristics of trial methodology, including the diagnostic (e.g. DSM-IV (APA 1994)) and exclusionary criteria employed, the screening instrument used (e.g. the Structured Clinical Interview for DSM-IV (SCID) (Spitzer 1996)) for both the primary and comorbid diagnoses, the presence of comorbid major depressive disorder (MDD), the use of a placebo run-in, whether a minimal severity criterion was employed and the number of centres involved.
- Characteristics of participants, including the number of participants randomised to the treatment and control groups, their age and gender distributions, whether they have been treated with the medication in the past (treatment naivety), whether they have a history of trauma, the number of participants in the sample with MDD, the type of trauma to which they were exposed, and the average time between trauma and treatment.
- Outcome measures employed (primary and secondary), and summary continuous (means and standard deviations) and dichotomous (number of responders) data. We included additional information, such as the number of total drop-outs per group as well as the number that dropped out due to side effects. We kept records of whether the data reflected the intention-to-treat (ITT) with last observation carried forward (LOCF) or completer/observed cases (OC) sample, and the minimal period required for inclusion of participants in the LOCF analyses. We also recorded other methods of estimating the outcome for participants who dropped out of the study, such as the mixed-effects (ME) model.

Main comparisons

We planned the following comparisons, based on the protocol for this review (with the post hoc addition of beta-blockers, see Differences between protocol and review):

- Antipsychotics versus placebo
- Benzodiazepines versus placebo
- Beta-blockers versus placebo
- Selective serotonin reuptake inhibitors (SSRIs) versus placebo
- Serotonin and norepinephrine reuptake inhibitors (SNRIs) versus placebo
- Tricyclic antidepressants (TCAs) versus placebo
- Mono-amine oxidase inhibitors (MAOIs) versus placebo
- Other medications versus placebo

Agents tested in the trials included in this review were the beta-blocker propranolol, the steroid hydrocortisone,

the SSRI escitalopram, the anticonvulsant gabapentin and the benzodiazepine temazepam. Accordingly, we restricted comparisons for the treatment and control groups to the following:

- Benzodiazepines versus placebo
- Beta-blockers versus placebo
- SSRIs versus placebo
- Other medications (hydrocortisone, gabapentin) versus placebo

Assessment of risk of bias in included studies

We assessed the risk of bias of each included study using The Cochrane Collaboration 'Risk of bias' tool (Higgins 2011a). We considered the following six domains:

1. Random sequence generation: referring to a random number table or using a computer random number generator?
2. Allocation concealment: was the medication sequentially numbered, sealed or placed in opaque envelopes?
3. Blinding of participants, personnel and outcome assessors for each main outcome or class of outcomes: was knowledge of the allocated treatment or assessment adequately prevented during the study?
4. Incomplete outcome data for each main outcome or class of outcomes: were missing or excluded outcome data adequately addressed?
5. Selective outcome reporting: were the reports of the study free of suggestion of selective outcome reporting?
6. Other sources of bias: was the study apparently free of other problems that could put it at a 'high' risk of bias.

We extracted relevant information from each study report, where provided. We made a judgement on the risk of bias for each domain within and across studies, based on the following three categories: 'low' risk of bias, 'unclear' risk of bias and 'high' risk of bias.

Two independent review authors (TA and JI) assessed the risk of bias in selected studies. We discussed any disagreements with a third review author (DJ). Where necessary, we contacted the authors of the studies for further information. All risk of bias data are presented graphically and described in the text.

Measures of treatment effect

Categorical data

We calculated risk ratio of response to treatment and number needed to treat to benefit (NNTB) for the dichotomous outcomes of interest. We used risk ratio instead of odds ratio, as odd ratios are less easily interpreted. Odds ratios also tend to overestimate the size of the treatment effect relative to risk ratios, especially when the occurrence of the outcome of interest is common (as anticipated in this review, with an expected response greater than 20%) (Deeks 2011). The NNTB is based on the risk ratio and is computed with respect to an assumed incidence of PTSD following trauma exposure in the control group of 10% and 20% (Norris 2007). The NNTB provides a measure of the number of people who require treatment with medication, relative to a control, before a single additional person in the medication group responds to treatment.

Continuous data

We calculated mean differences (MD) for continuous summary data derived from the same scale, such as the Clinician-Administered PTSD Scale (CAPS) for symptom severity. In cases in which a range of scales were employed for each outcome, such as in the assessment of comorbid depression on the Montgomery–Åsberg Depression Rating Scale (MADRS) and Hamilton Depression Scale (HAM-D), we determined the standardised mean difference (SMD). The SMD standardises the differences between the means of the treatment and control groups in terms of the variability observed in the trial.

Unit of analysis issues

Cluster-randomised trials

In cluster-randomised trials, groups of individuals rather than individuals are randomised to different interventions. Analysing treatment response in cluster-randomised trials without taking these groups into account is potentially problematic, as participants within any one cluster often tend to respond in a similar manner, and thus their data can no longer be assumed to be independent of one another. Cluster-randomised trials also face additional risk of bias issues including (a) recruitment bias, (b) baseline imbalance, (c) loss of clusters and (d) non-comparability with trials in which allocation of treatment is randomly assigned on the individual level (Higgins 2011a). No cluster-randomised trials were eligible for inclusion in this review. To prevent unit of analysis errors in future updates of this review, we planned to divide the effective sample size of each comparison group in trials that did not adjust for clustering by the design effect metric (Higgins 2011b), with the intraclass correlation coefficient (ICC) that is incorporated within the design effect set equivalent to the median ICC from published cluster-randomised pharmacotherapy RCTs for anxiety disorders.

Studies with multiple treatment groups

Studies with more than two intervention arms pose difficulties in the analysis of prevention data. We assessed such studies as follows:

Continuous data

We pooled mean values, standard deviations and number of participants for each intervention group across treatment arms and compared them against the control group (Higgins 2011a).

Dichotomous data

We combined experimental intervention groups into a single group for comparison against the control group, or divided out the shared intervention groups approximately evenly among the comparisons (Higgins 2011a).

Cross-over trials

We only included cross-over trials in the calculation of summary statistics when it was (a) possible to extract medication and placebo/comparator data from the first treatment period, or (b) when the inclusion of these data from both treatment periods was justified through a wash-out period of sufficient duration as to minimise the risk of carry-over effects. We assessed the minimum wash-out period required on the basis of the plasma half-life of the particular agent, as determined by consulting the Lundbeck Psychotropics website (Lundbeck 2003).

For cross-over trials in which the wash-out period was regarded as adequate, we only included data from both periods when it was possible to determine the standard error of the mean difference

in response between groups (Elbourne 2002). We obtained the summary statistics required to derive the standard error of interest from the trial report, or for trials for which this information was missing, we imputed them through averaging the relevant statistic from other included cross-over trials with comparable control conditions.

Dealing with missing data

All analyses of dichotomous data were intention-to-treat (ITT). We used the total number of participants randomised to the different comparison groups as the denominator in comparisons of treatment efficacy. We only included data from trials which provided information on the original group size (prior to drop-outs) in the analysis of treatment efficacy. In trial reports in which multiple forms of data imputation were conducted, we gave preference to the inclusion of summary statistics for continuous outcome measures derived from mixed-effects models (ME), followed by last observation carried forward (LOCF) and observed cases (OC) summary statistics (in that order). This is in line with evidence that ME methods are more robust to bias than LOCF analyses (Verbeke 2000). If data on studies, outcomes, summary data, participants or study-level characteristics were missing, we contacted the original investigators.

Assessment of heterogeneity

We assessed heterogeneity by means of the Chi^2 test of heterogeneity to assess whether observed differences in results are compatible with chance alone. A low P value (or a large Chi^2 test relative to its degree of freedom) provides evidence of heterogeneity of intervention effects (variation in effect estimates beyond chance). We also assessed heterogeneity against a P value of 0.10. If the Chi^2 test had a P value of less than 0.10, we interpreted this as evidence of heterogeneity, given the low power of the Chi^2 test when the number of trials is small (Deeks 2011). In addition, we used the I^2 statistic, reported by RevMan, to quantify the inconsistency of the trial results within each analysis (Higgins 2003). Thresholds for the interpretation of I^2 can be misleading, since the importance of inconsistency depends on several factors. A rough guide for interpretation was followed:

- 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.

Assessment of reporting biases

We planned to inspect funnels plots visually for evidence of reporting bias for the treatment efficacy and PTSD symptom reduction outcomes. Funnel plots provide a graphical illustration of the effect estimates of an intervention from individual studies against some measure of the precision of that estimate. However, we decided not to generate funnel plots as this would not have been informative, given the small number of studies included in the meta-analyses of these outcomes. For the same reason, we also decided to forgo additional planned Eggers' regression tests (Egger 1997), to confirm evidence of reporting bias from the funnel plots for the PTSD symptom reduction outcome. Future updates of the review will employ Egger's regression test if there are at least 10 studies providing data on this outcome (Sterne 2011).

Data synthesis

We obtained categorical and continuous treatment effects from a random-effects model. Random-effects analytic models include both within-study sampling error and between-study variation in determining the precision of the confidence interval around the overall effect size, whereas fixed-effect modelling approaches take only within-study variation into account. We expressed the outcomes in terms of an average effect size for each subgroup, as well as by means of 95% confidence intervals. We included a small sample bias corrected version of the Cohen's D effect size estimate, Hedges' g, as well as its 95% confidence intervals in the narrative review of study results that could not be synthesised (provided these data were normally distributed - see paragraph below), to aid in the interpretability of the magnitude of the medication effect. We calculated this statistic using the compute.es package within the R statistical computing language (Del Re 2013).

Evidence that data from individual studies were skewed was grounds for excluding the study from quantitative analysis. For the purposes of this review, the following constituted evidence of skewness: cases in which the difference between the observed mean and the lowest possible value or highest possible value on the scale is less than twice as large as the standard deviation (Deeks 2011), or where data are reported as skewed by the authors. For future updates of this review we plan to obtain individual patient data (where possible) for the purpose of normalising the data by means of log transformation techniques.

Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses to assess the degree to which methodological differences between trials might have systematically influenced differences observed in the primary treatment outcomes (Thompson 1994). Current guidelines recommend at least 10 studies per characteristic used for stratifying subgroups (Deeks 2011). Accordingly, we did not conduct subgroup analyses to determine the effect on the primary outcomes of whether trials were conducted at single or multiple treatment centres, were funded by pharmaceutical companies or included participants with major depression.

Sensitivity analysis

Sensitivity analyses are designed to test the robustness of review authors' conclusions to methodological assumptions made in conducting meta-analyses. We planned to assess whether treatment response varies as a function of the use of treatment response versus non-response as an outcome statistic. We regarded this comparison as necessary in light of evidence that treatment response may result in less consistent outcome statistics than non-response (Deeks 2002), when the control group event rate is higher than 50%. No control group event rate was higher than 50% of the ITT sample for any of the studies included in this review, obviating the need for this analysis.

The dichotomous outcome of treatment response in this review is calculated as the proportion of participants diagnosed with PTSD at follow-up out of the total randomised sample. This effectively counts drop-outs in the comparison groups as responders to medication or placebo. We assessed the effect of the decision to use the randomised sample instead of the more commonly reported completer sample in a post hoc sensitivity analysis (e.g. Analysis 2.2 and Analysis 1.2).

Summary of findings

We presented the main findings of the review, for the primary outcome of treatment efficacy, in Summary of findings for the main comparison and Summary of findings 2 using GRADEpro 3.6 software (http://ims.cochrane.org/gradepro). 'Summary of findings' tables present the main findings of a review in a transparent and simple tabular format. In particular, they provide key information concerning the quality of evidence, the magnitude of effect of the interventions examined and the sum of available data on the main outcomes (Higgins 2011a).

We assessed five factors that decrease the quality level of a body of evidence:

- Limitations in the design and implementation.
- Indirectness of evidence.
- Unexplained heterogeneity or inconsistency of results.
- Imprecision of results.
- High probability of publication bias.

We classified the quality of evidence for each outcome according to the following categories:

- High quality: further research is very unlikely to change our confidence in the estimate of effect.
- Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low quality: we are very uncertain about the estimate.

RESULTS

Description of studies

Results of the search

We found a total of 3992 study reports through the search process (CCDANCTR 2012, OVID MEDLINE 87, mRCT 285, NIH Reporter 941, WHO Trials 667). We scanned each title and abstract (if provided) for eligibility. Seventy-one studies initially seemed relevant, but further inspection excluded 50 of these, leaving 21 studies that potentially met the inclusion criteria. After independent reviewing of the full text for these studies, 12 failed to meet inclusion criteria, leaving nine RCTS eligible for inclusion in the review (see Characteristics of included studies and Figure 1). Two of the nine eligible studies were identified (prior to the final updated search of the CCDANCTR) through searching reference lists (Hoge 2012), and from editorial feedback on the review (Shalev 2012).

Figure 1. Flow diagram.

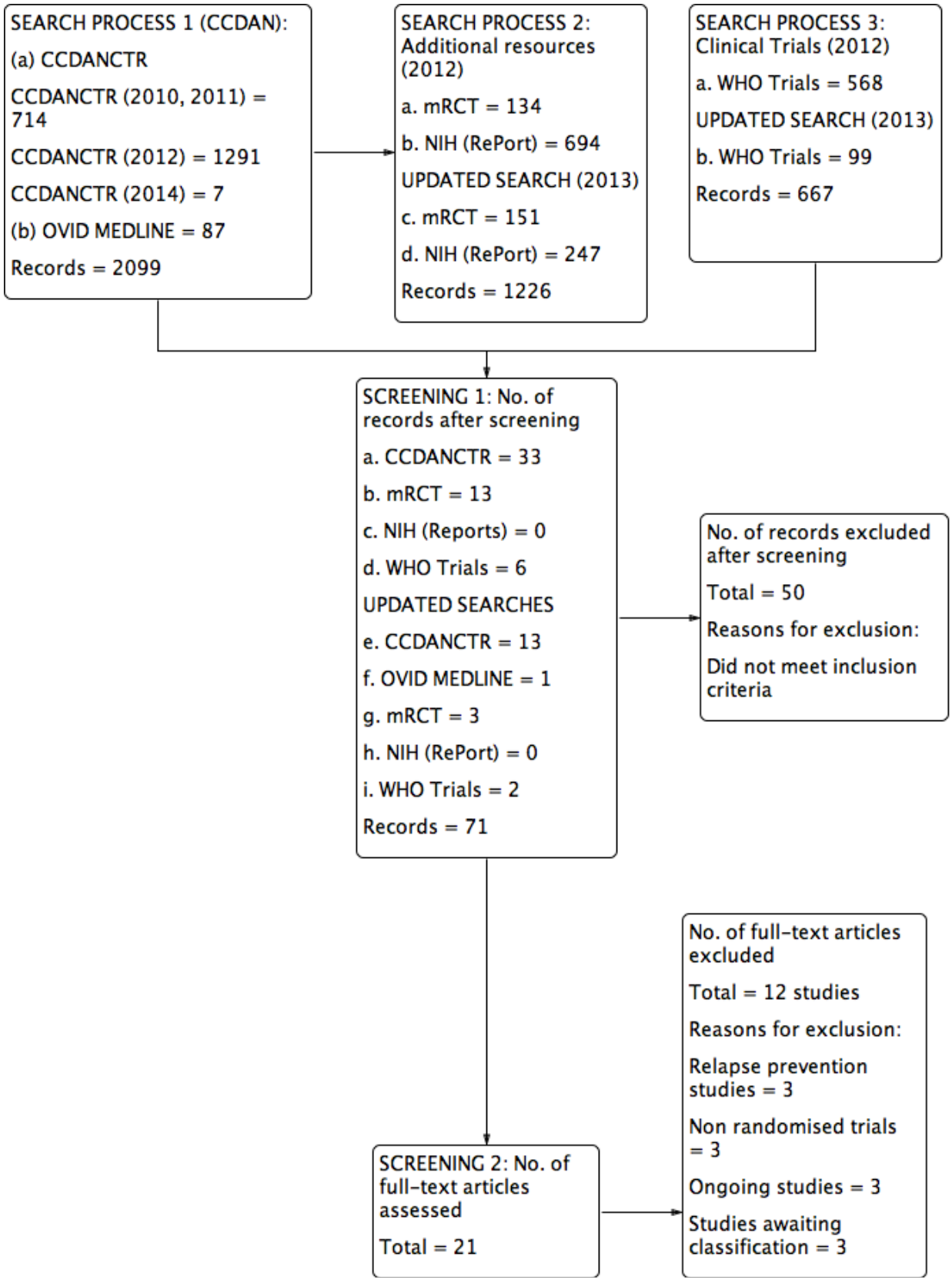
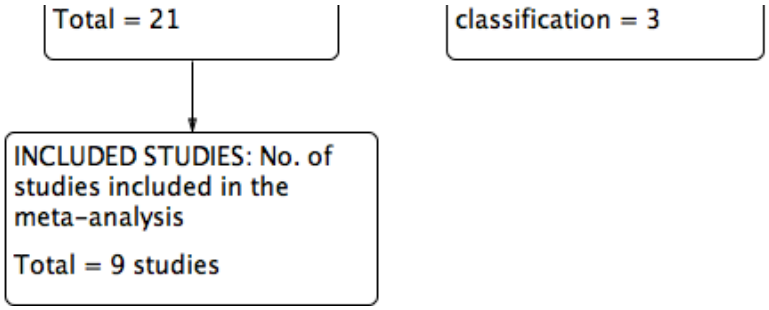


Figure 1. (Continued)



Included studies

Design

The review includes nine short-term RCTs of PTSD prevention. A placebo comparison group was employed in each study, with one study having two medication arms (i.e. propranolol and gabapentin) (Stein 2007). Each study was published in English and supported by a grant and/or pharmaceutical company.

Participants

Three hundred and forty-five participants were included across the nine eligible studies. The average sample size was 38 and ranged from 20 (Schelling 2001) to 64 (Weis 2006). Each study consisted of both males and females, with a mean age of approximately 40 years. Females accounted for 49% of the total proportion of the sample. The participants in each study were exposed to a range of trauma types, including assault (Delahanty 2012; Hoge 2012; Mellman 2002), injury (Delahanty 2012; Hoge 2012; Stein 2007; Zohar 2011a), traffic or work accidents (Delahanty 2012; Hoge 2012; Pitman 2002; Shalev 2012; Zohar 2011a), terrorist attack (Shalev 2012), cardiac surgery (Weis 2006), and septic shock (Schelling 2001).

Participants who were exposed to a traumatic event were assessed according to DSM-IV criteria in six studies (Delahanty 2012; Hoge 2012; Pitman 2002; Schelling 2001; Shalev 2012; Zohar 2011a), and the additional three studies used specified structured or semi-structured measurements (Mellman 2002; Stein 2007; Weis 2006).

Setting

Countries in which studies were conducted included the United States of America (e.g. Boston, San Diego) (Delahanty 2012; Hoge 2012; Mellman 2002; Pitman 2002; Stein 2007), Germany (Schelling 2001; Weis 2006), and Israel (Shalev 2012; Zohar 2011a). Seven studies were single-centre trials (Delahanty 2012; Hoge 2012; Mellman 2002; Schelling 2001; Shalev 2012; Weis 2006; Zohar 2011a), and two studies did not provide sufficient information to determine how many centres were recruited from (Pitman 2002; Weis 2006). Patient recruitment settings included intensive care unit (ICU) wards (Delahanty 2012; Weis 2006), trauma centres (Mellman 2002; Schelling 2001; Stein 2007), and hospital emergency departments (Hoge 2012; Pitman 2002; Shalev 2012; Zohar 2011a).

Interventions

The nine RCTs included four hydrocortisone studies (steroid) (Delahanty 2012; Schelling 2001; Weis 2006; Zohar 2011a), three propranolol studies (beta-blocker) (Hoge 2012; Pitman 2002; Stein 2007) (with Stein 2007 investigating the anxiolytic anticonvulsant gabapentin) and single studies of temazepam (benzodiazepine) (Mellman 2002) and escitalopram (SSRI) (Shalev 2012). The duration of treatment for all pharmacological interventions ranged from a single dose of hydrocortisone (Zohar 2011a) to a 12-week intervention for escitalopram (Shalev 2012). Dosages of hydrocortisone ranged from 40 mg/day (Delahanty 2012) to 140 mg/day (Zohar 2011a), with propranolol administered in doses ranging from 120 mg/day (Stein 2007) to 240 mg/day (Hoge 2012). The maximum dose of temazepam administered at bedtime was 30 mg, while a 10 mg table of escitalopram was administered twice daily in Shalev 2012. In Stein 2007, the maximal daily dosage of gabapentin was 400 mg. The interventions were administered by psychologists (Pitman 2002), psychiatrists (Schelling 2001; Shalev 2012; Zohar 2011a), mental health professionals (Delahanty 2012), and nursing staff (Stein 2007; Weis 2006), as well as multi-disciplinary teams of investigators (Mellman 2002).

Interventions were administered in the majority of studies within the first 12 hours after the traumatic event (Hoge 2012; Pitman 2002; Zohar 2011a), and occurred during the course of the traumatic event in two studies (Schelling 2001; Weis 2006). Medication was only administered within two days after the trauma in Stein 2007, and after an average of 14.3 days and 19.8 days in the case of the trials of temazepam (Mellman 2002) and escitalopram (Shalev 2012), respectively. Interventions occurred concurrently with administration of the study medication in some studies, including the stress hormones epinephrine and norepinephrine in patients who had undergone cardiac surgery with cardiopulmonary bypass (Weis 2006), and a course of antibiotics, fluid resuscitation, mechanical ventilation and norepinephrine in patients treated for septic shock (Schelling 2001). Patients in Schelling 2001 were also sedated with infusions of the benzodiazepine midazolam and the opioid fentanyl. Participants in Pitman 2002 received supportive counselling from the study nurse as appropriate during the course of the study.

Outcomes

The dichotomous outcome of number of participants diagnosed with PTSD, as well as the secondary outcome of reduction in PTSD symptom severity, were assessed for each group using the Clinician-Administered PTSD Scale (CAPS) (Delahanty 2012; Hoge 2012; Mellman 2002; Pitman 2002; Shalev 2012; Zohar 2011a), the Post-Traumatic Stress Syndrome 10-Questions Inventory (PTSS-10Q-I) (Weis 2006), and the Structured Clinical Interview for DSM-IV (SCID-IV) (Schelling 2001) (see Characteristics of included studies). The only study to use different measures of categorical

PTSD diagnosis and symptom severity was Stein 2007, in which the Comprehensive International Diagnostic Interview (CIDI) and the Posttraumatic Stress Disorder Checklist - Civilian Version (Weathers 2001) were used for these purposes, respectively. The follow-up assessments ranged from as early as two weeks after the trauma (Zohar 2011a) to a median of 31 months after the event (Schelling 2001).

Quality of life was assessed using the 36-item Medical Outcomes Study Short Form Survey (SF-36) (Delahanty 2012; Weis 2006). Depression was assessed using the Center for Epidemiological Studies – Depression Scale (CES-D) (Delahanty 2012; Stein 2007), as well as visual analogue scales (VAS) in Zohar 2011a. Zohar 2011a was the only study in which anxiety symptoms was reported as being assessed, using visual analogue scales.

Excluded studies

We excluded six studies from the review. Exclusions were based on study design (Gelpin 1996; Vaiva 2003), and sample characteristics (Davidson 2000; Martenyi 2002; Martenyi 2006; Schelling 2004) (see Characteristics of excluded studies).

Ongoing studies

Three studies are listed as ongoing: Zohar 2009; Zohar 2010; Zohar 2011b (see Characteristics of ongoing studies and Figure 1).

Studies awaiting classification

Three trials were awaiting classification (Azad 2007; Marx 2006; Simon 2005) (see Characteristics of studies awaiting classification and Figure 1).

Ongoing studies

We identified three ongoing randomised, placebo-controlled studies of medication for the prevention of PTSD (Zohar 2009; Zohar 2010; Zohar 2011b). These RCTs are being conducted by the same group, and assess the effectiveness of hydrocortisone (Zohar 2011b), oxytocin (Zohar 2010), and escitalopram (Zohar 2009) in preventing the onset of PTSD. The investigators of these studies require that participants are exposed to a traumatic event, with exposure to trauma assessed within six hours after the traumatic event in two studies (Zohar 2010; Zohar 2011b). All participants are required to be 18 years and older to meet study criteria. The CAPS will be employed for PTSD diagnosis and/or symptom severity assessment in both RCTs for which information on outcome assessment was available (Zohar 2009; Zohar 2010).

Studies awaiting classification

Placebo-controlled studies to be assessed for inclusion in the review, pending additional information, include a RCT on the efficacy of hydrocortisone in 92 high-risk survivors of cardiac surgery, with primary outcomes including immunologic markers, health care-related quality of life and PTSD (Azad 2007), as well as a flexible dose trial of 10 mg to 40 mg of paroxetine over 12 weeks in a recently deployed military veteran sample (Marx 2006). In addition, a 12-week placebo-controlled RCT of escitalopram for participants presenting with ASD criteria (A1 and A2 criteria and at least one additional criterion) after a traumatic injury that occurred in the prior three weeks, was discontinued (Simon 2005).

Risk of bias in included studies

We assessed the risk of bias using The Cochrane Collaboration's 'Risk of bias' tool for allocation concealment, blinding, incomplete outcome data, selective reporting and other potential sources of bias. We classified seven of the included studies as being at high risk for at least one type of bias (see Figure 2 and Figure 3).

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

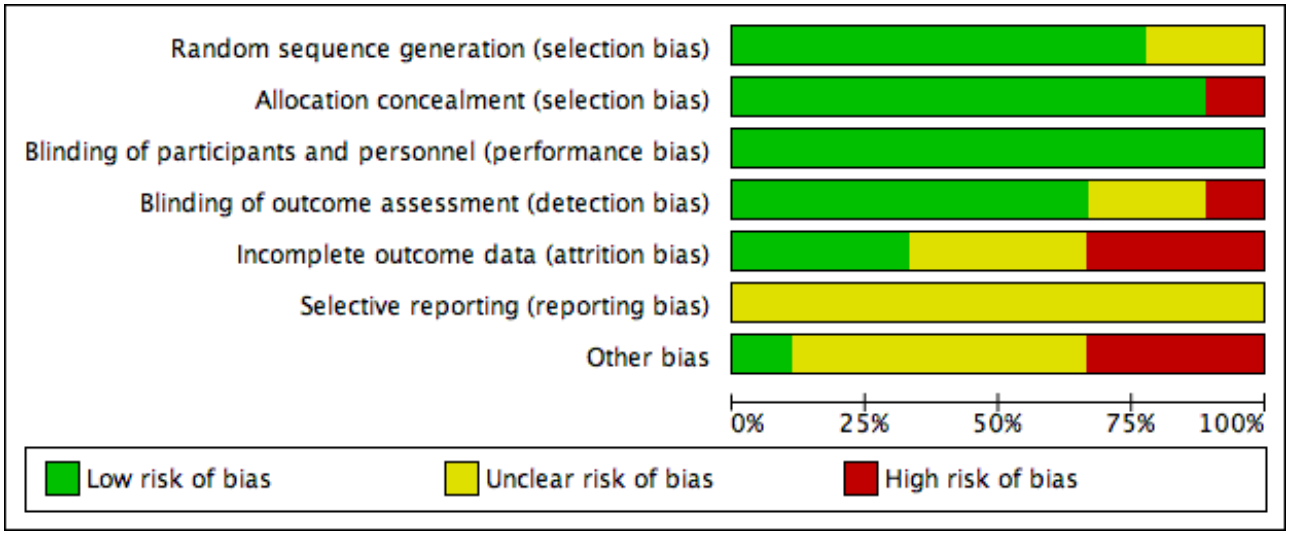
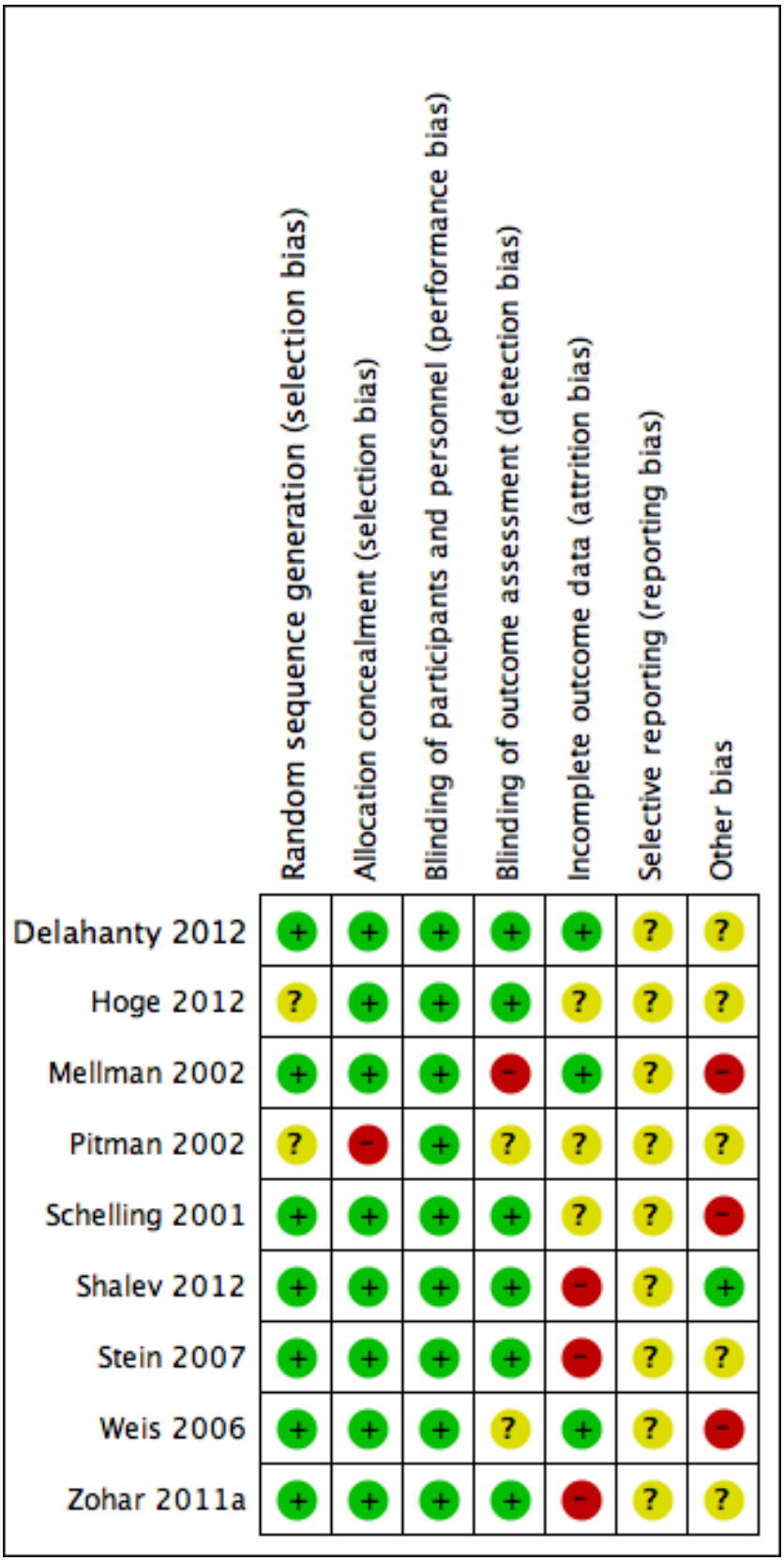


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Randomisation

All included studies described the sequence generation as randomised. Schelling 2001 employed random permutation blocking of participants, while Shalev 2012 utilised an equipoise-stratified randomisation scheme, in which participants were given the option of requesting not to be assigned to two of the four interventions assessed (prolonged exposure, cognitive therapy, escitalopram versus placebo, waiting list control). A central research pharmacy is described as setting up and maintaining the randomisation schedule in Stein 2007. Group assignment was via a computer-generated randomisation list in Weis 2006 and Zohar 2011a, while Mellman 2002 made reference to a predetermined randomisation schedule. Delahanty 2012 employed a random number table to generate the randomisation schedule. We classified these seven studies as 'low' risk, with the risk of selection bias being designated as 'unclear' in the remaining studies.

Allocation concealment

Eight of the studies provided sufficient information to be considered at 'low' risk for selection bias resulting from failure to conceal the agents provided to the study participants. Medication was prepared by a central pharmacy in three studies (Hoge 2012; Mellman 2002; Stein 2007). In Schelling 2001, all syringes of hydrocortisone and placebo were labelled "study medication", while the medication and placebo were prepared by Lundbeck Pharmaceutical and supplied to clinicians by a research associate in Shalev 2012. Weis 2006 described the preparation of the study agents in vials by a study nurse who was not involved in the care of patients participating in the trial. Delahanty 2012 described the use of identical pills/blister packs to conceal the allocation of group assignment from the study investigators. Hydrocortisone or placebo were given intravenously in numbered, identical intravenous bags in Zohar 2011a. We assigned Pitman 2002 a rating of 'high' risk for selection bias, as no information regarding allocation concealment was provided in the study report.

Blinding

Blinding of participants and personnel

We classified all of the studies included in the review as being at 'low' risk of performance bias, as they either described themselves as "double-blinded" (Delahanty 2012; Pitman 2002; Weis 2006; Zohar 2011a), or participants and personnel were explicitly described as blinded in the study report (Schelling 2001; Shalev 2012; Stein 2007), or through correspondence with the trial investigators (Hoge 2012; Mellman 2002).

Blinding of outcome assessors

We classified six of the studies included in the review as being at 'low' risk of detection bias, as they were explicitly described as blinded in the study report (Schelling 2001; Shalev 2012; Stein 2007; Zohar 2011a), or through correspondence with the trial investigators (Delahanty 2012; Hoge 2012). We classified Mellman 2002 as being at 'high' risk, as no information on blinding of the assessors was available for this study, while we rated the risk of bias as 'unclear' for two studies that described the study design as "double-blinded" (Pitman 2002; Weis 2006).

Incomplete outcome data

Three studies failed to provide sufficient information to determine whether the medication and placebo group were comparable with respect to drop-out proportions, or in terms of the demographic and clinical characteristics of those who withdrew (Hoge 2012; Pitman 2002; Schelling 2001), garnering them a rating of 'unclear' risk. Substantially higher proportions of participants withdrew from the medication than the placebo groups in Stein 2007 (propanolol: 29.4%; gabapentin: 28.6%; placebo: 5.9%), Shalev 2012 (escitalopram: 26%; placebo: 60.9%) and Zohar 2011a (hydrocortisone: 40%; placebo: 20%), earning these studies a 'high' risk rating. Studies classified as being at 'low' risk included two RCTs that failed either to detect differences in attrition rates for the comparison groups, or in between-group comparisons of the characteristics of those who withdrew (Delahanty 2012; Weis 2006), and one study in which no participants withdrew prior to follow-up (Mellman 2002). We rated the remaining three studies as being at 'unclear' risk with regard to attrition bias.

Selective reporting

It was unclear as to whether selective reporting took place in any of the included studies, either because the protocol was not available for the study (Delahanty 2012; Mellman 2002; Pitman 2002; Schelling 2001; Shalev 2012; Stein 2007; Weis 2006; Zohar 2011a), or because where the protocol was available, insufficient information was provided on the planned outcomes to be assessed (Hoge 2012).

Other potential sources of bias

Various methodological factors may have impacted on study findings, including the use of concurrent medication (Schelling 2001; Weis 2006) and psychological treatments during the study (Pitman 2002); employment of invasive medical procedures in some trials (Schelling 2001; Weis 2006); failure to identify the index trauma through specification of the DSM-IV PTSD criterion A (Delahanty 2012; Mellman 2002; Schelling 2001; Stein 2007; Weis 2006); and industry funding of the trial (Schelling 2001; Shalev 2012). We reserved ratings of 'high' risk of bias for three studies (Mellman 2002; Schelling 2001; Weis 2006), with all others being classified as being at 'low' risk. In Mellman 2002, termination of follow-up was dependent on the clinical assessment of PTSD-related symptoms, with only 50% of cases followed up at the planned six-week assessment point. For both Schelling 2001 and Weis 2006 participants receiving placebo required higher norepinephrine doses than participants on hydrocortisone. Although the difference in dosage of norepinephrine was not statistically significant in Schelling 2001, the investigators conceded that this may be an alternative explanation of higher PTSD onset in the placebo group, as previous studies have documented higher urinary excretion of norepinephrine in PTSD patients.

Effects of interventions

See: **Summary of findings for the main comparison** Propranolol compared to placebo for preventing post-traumatic stress disorder (PTSD); **Summary of findings 2** Hydrocortisone compared to placebo for preventing post-traumatic stress disorder (PTSD)

See: 'Summary of findings' for the main comparisons of propranolol versus placebo (Summary of findings for the main

comparison) and hydrocortisone versus placebo (Summary of findings 2).

Comparison 1: Benzodiazepines versus placebo

Primary outcome

1.1 Treatment efficacy: number of participants who developed post-traumatic stress disorder (PTSD)

The single trial of temazepam reported a higher proportion of individuals on medication with a diagnosis of PTSD (6/11; 55%) at the final assessment than in the placebo group (3/11; 27%) (Mellman 2002). A post hoc Fisher's exact test of the data provided by the investigators indicates that this difference was not statistically significant (odds ratio (OR) 3.03, P value = 0.387).

1.2 Treatment acceptability: number of participants who withdrew due to treatment-emergent side effects

All patients completed the intervention and were assessed at follow-up in Mellman 2002.

Secondary outcomes

1.3 Reduction in PTSD symptoms

Total symptom severity scores on the Clinician-Administered PTSD Scale (CAPS) decreased from 62.7 (standard deviation (SD) 24.1) at baseline in the medication group and 56.7 (SD 17.8) in the placebo group to 53.3 (SD 19.1) and 44.1 (SD 26.1) at the final assessment, respectively. There was no evidence that temazepam was more effective than placebo in reducing symptom severity (P value = 0.5; Hedges' g = 0.39, 95% confidence interval (CI) -0.48 to 1.25).

1.4 Reduction in comorbid symptom responses

There were no data to determine the effect of medication on comorbid depression or anxiety symptoms.

1.5 Quality of life

There were no data to determine the effect of medication on quality of life.

1.6 Functional impairment

There were no data to determine the effect of medication on functional disability.

1.7 Side effects

There were no data to determine treatment-emergent side effects.

Comparison 2: Beta-blockers versus placebo

Primary outcomes

2.1 Treatment efficacy: number of participants who developed PTSD

Evidence for the efficacy of the beta-blocker propranolol was assessed in three studies with 118 participants (Hoge 2012; Pitman 2002; Stein 2007). There was low quality evidence of an effect of medication on the number of patients diagnosed with PTSD at follow-up (risk ratio (RR) 0.62; 95% CI 0.24 to 1.59; number needed to treat to benefit (NNTB) = 14 to 27; see Analysis 1.1).

2.2 Treatment acceptability: number of participants who withdrew due to treatment-emergent side effects

There were insufficient data to conduct a meta-analysis for this outcome. No participants in Stein 2007 reported stopping medication during the first week of the two-week medication intervention due to treatment-emergent side effects. Neither Hoge 2012 nor Pitman 2002 provided data on the number of participants who withdrew during the treatment phase of the studies.

Secondary outcomes

2.3 Reduction in PTSD symptoms

We did not synthesise PTSD symptom severity outcome data provided for two of the propranolol randomised controlled trials (RCTs) (Hoge 2012; Pitman 2002), due to evidence that the scores were not normally distributed. Taken individually, neither of these trials demonstrated an effect of medication. Pitman 2002 failed to detect a significant difference in mean score between the propranolol and placebo groups on the CAPS at either one month (mean (SD) 27.6 (15.7) versus 35.5 (21.5), respectively) or three months follow-up (21.1 (12.5) versus 20.5 (21.7), respectively). Similarly, no differences were observed for scores on the CAPS in participants receiving placebo or propranolol in Hoge 2012, after either one month (mean (SD) 28.5 (27.1) versus 28.5 (21.5), respectively) or three months (19 (25.8) versus 21.2 (26.1), respectively). Although Stein 2007 did observe an overall reduction in mean Posttraumatic Stress Disorder Checklist–Civilian Version (PCL-C) scores over time, these did not differ by comparison group ($F < 1$).

2.4 Reduction in comorbid symptom responses

There were insufficient data to conduct a meta-analysis for this outcome. Stein 2007 reported that a generalised estimating equation (GEE) analysis of changes in depressive symptoms on the Center for Epidemiological Studies – Depression Scale (CES-D) over time failed to find an effect of propranolol.

2.5 Quality of life

There were no data to determine the effect of medication on quality of life.

2.6 Functional impairment

There were no data to determine the effect of medication on functional disability.

2.7 Side effects

Stein 2007 reported that home nurse visits during the first three days of treatment did not detect symptoms, such as postural hypotension, which required the discontinuation of medication. Hoge 2012 reported minimal side effects for either hydrocortisone or placebo, with one incident of a fall (without serious injury) being attributed to the medication intervention. Pitman 2002 did not provide data on treatment-emergent side effects .

Comparison 3: Selective serotonin reuptake inhibitors (SSRIs) versus placebo

Primary outcomes

3.1 Treatment efficacy: number of participants who developed PTSD

There was no evidence in the single trial of escitalopram that medication was more effective than placebo in preventing the onset of PTSD, with 13/21 (61.9%) of participants receiving medication and 10/18 (55.6%) in the placebo group meeting diagnostic criteria at the five-month assessment (P value > 0.05) (Shalev 2012). Similar results were reported for the nine months post-trauma assessment (8/19 (42.1%) versus 8/17 (47.1%), respectively).

3.2 Treatment acceptability: number of participants who withdrew due to treatment-emergent side effects

Of the 23 participants randomised to 12 weeks of treatment with escitalopram or placebo, more than twice as many participants in the escitalopram arm (13; 56.5%) withdrew prior to the end of the study than in the placebo arm (6; 26.1%). These participants were not contacted to ascertain reasons for study withdrawal (personal communication, Dr. Shalev; 4 December 2013).

Secondary outcomes

3.3 Reduction in PTSD symptoms

There were insufficient data to conduct a meta-analysis for this outcome. Clinician-rated total symptom severity scores on the CAPS at the five-month assessment were similar in the escitalopram and placebo groups (mean (SD): 48.71 (29.63) versus 47.11 (20.13), respectively; Hedges' g = 0.06, 95% CI -0.58 to 0.7) and nine-month post-trauma assessments (47.16 (26.71) versus 45.71 (26.14), respectively; Hedges' g = 0.05, 95% CI -0.61 to 0.72). Similarly, no statistically significant differences were observed in comparisons across groups on the re-experiencing, hyperarousal and avoidance PTSD symptom cluster subscales of the CAPS. Finally, participants' own ratings of their PTSD symptoms, as assessed using the PTSD Symptom Scale – Self-Report Version (PSS-SR), did not differ by group at either time point.

3.4 Reduction in comorbid symptom responses

There were no data to determine the effect of medication on comorbid depression or anxiety symptoms.

3.5 Quality of life

There were no data to determine the effect of medication on quality of life.

3.6 Functional impairment

There were no data to determine the effect of medication on functional disability.

3.7 Side effects

There were no data to determine the effect of medication on treatment-emergent side effects .

Comparison 4: Other medications versus placebo

Primary outcome

4.1 Treatment efficacy: number of participants who developed PTSD

We observed evidence for the efficacy of hydrocortisone in preventing the onset of PTSD in a combined sample of 165 participants across four studies (RR 0.17; 95% CI 0.05 to 0.56; see Analysis 2.1). The size of the medication effect translates to a number needed to treat to benefit (NNTB) of between seven and 13 patients. We deemed the quality of the evidence to be moderate. We conducted an additional post hoc analysis excluding Schelling 2001 and Weis 2006. We considered this necessary given the observation of potential bias introduced through greater administration of norepinephrine to septic shock and cardiac surgery patients receiving placebo than hydrocortisone in these respective RCTs. The combined analysis of PTSD prevention proportions excluding these studies still favoured the hydrocortisone intervention (RR 0.12; 95% CI 0.02 to 0.94).

The administration of the anticonvulsant agent gabapentin, in Stein 2007, was associated with PTSD in two of 10 participants (20%) at four months after physical injury was sustained, compared to four of 16 participants (25%) on placebo, a statistically non-significant difference.

4.2 Treatment acceptability: number of participants who withdrew due to treatment-emergent side effects

No data were provided on the proportion of participants who withdrew from treatment due to side effects in the majority of hydrocortisone trials (Schelling 2001; Weis 2006; Zohar 2011a). Delahanty 2012 observed that one of the 13 participants receiving hydrocortisone who discontinued between randomisation and the one-month assessment complained of dizziness. It was not possible to contact any of the remaining 20 participants (31.3%) across both comparison groups who withdrew prior to the three-month assessment. Although the number of participants who withdrew as a result of treatment-emergent side effects was not reported in the single trial of gabapentin (Stein 2007), the investigators noted that "subjective reporting by subjects indicated that study medications were well tolerated" (p927).

Secondary outcomes

4.3 Reduction in PTSD symptoms

Data were not available for this outcome for two of the hydrocortisone RCTs (Weis 2006; Zohar 2011a). In addition, data from the PTSS-10Q-I at the three-month assessment in Schelling 2001 was not normally distributed and therefore studies could not be pooled in the analysis. Delahanty 2012, Weis 2006 and Zohar 2011a demonstrated the superiority of hydrocortisone compared to placebo in reducing PTSD symptom severity, with substantial differences being observed on the CAPS in Delahanty 2012 after three months (mean of 19.4 versus 31.3, respectively), and on the Post-Traumatic Stress Syndrome 10-Questions Inventory (PTSS-10Q-I) after six months in Weis 2006 (median of 15.5 versus 25.5, respectively). Zohar 2011a reported a significant group difference favouring hydrocortisone at both two weeks and three months after a single dose administration (P value < 0.25 and P value < 0.2, respectively). Finally, Schelling 2001 was not able to detect differences on the PTSS-10Q-I after a median of 31 months post-intervention between the hydrocortisone and control groups (median of 27 and 36 points, respectively).

Stein 2007 reported that symptoms of PTSD did not decline over time in the gabapentin compared to the placebo group. No additional data on this outcome were provided in the study report.

4.4 Reduction in comorbid symptom responses

There were insufficient data to conduct a meta-analysis of the effect of hydrocortisone or gabapentin on comorbid depression or anxiety symptoms. Based on a series of repeated-measures

ANCOVA analyses of outcomes assessed at one and three months post-injury, Delahanty 2012 reported that participants treated with hydrocortisone demonstrated reduced symptoms of depression on the CES-D compared to the control group (F(1,18) = 7.7, P value = 0.01) over time. Rates of major depressive disorder (MDD) assessed using the Comprehensive International Diagnostic Interview (CIDI) in Stein 2007 were similar in the gabapentin and placebo groups four months after the traumatic event (gabapentin: 2/10; placebo: 4/16).

4.5 Quality of life

There were insufficient data to conduct a meta-analysis for this outcome. Delahanty 2012 reported improvements in quality of life assessed using the SF-36 scale over multiple time points (F(1,18) = 5.3, P value = 0.03). Similarly, Weis 2006 reported improvements in the hydrocortisone group compared to placebo on the SF-36 physical and mental summary scores, with statistically significant increases observed in the medication group on seven of the eight subscales of this instrument.

4.6 Functional impairment

There were no data to determine the effect of either hydrocortisone or gabapentin on functional disability.

4.7 Side effects

There were no differences in the number of side effects between the medication and placebo groups in the trials that reported these. With regard to hydrocortisone, Schelling 2001 reported that one individual receiving medication experienced an intestinal haemorrhage that was treated conventionally (personal communication); treatment was reported in Zohar 2011a as being "well tolerated with no noticeable side effects" (p800); Weis 2006 declared the number of patients in their study as being "too small to detect these [side] effects" (p282); and data on side effects were not reported in Delahanty 2012. Information on side effects was not reported for the trial of gabapentin, though all medications tested in this study were described as being very well tolerated, based on subjective patient report (Stein 2007).

Heterogeneity

We found no evidence of heterogeneity for trials of hydrocortisone (Chi^2 = 0.43, P value = 0.93, I^2 = 0%, see Analysis 2.1) and propranolol (Chi^2 = 0.18, P value = 0.91, I^2 = 0%, see Analysis 1.1), when investigating the efficacy of treatment in preventing PTSD onset.

Subgroup analyses

There were insufficient studies to conduct a subgroup analysis (fewer than 10).

Sensitivity analyses

Use of an intention-to-treat (ITT) versus observed cases sample in calculating response to treatment

Effect estimates for the hydrocortisone versus placebo comparisons were similar, regardless of whether the effect estimate was calculated based on the proportion of participants who developed PTSD at follow-up out of the ITT (RR 0.17; 95% CI 0.05 to 0.56) or observed cases sample (RR 0.20; 95% CI 0.06 to 0.64) Analysis 2.2. We observed a similar finding with respect to the propranolol versus placebo comparison (ITT sample: RR 0.62; 95% CI 0.24 to 1.59; observed cases sample: RR 0.73; 95% CI 0.29 to 1.84) Analysis 1.2.

Publication bias

The greatest number of studies in any comparison in this review was equal to four (Analysis 2.1). We regarded this as insufficient to warrant conducting qualitative or quantitative tests that would inform the assessment of publication bias.

DISCUSSION

Summary of main results

The largest number of randomised controlled trials (RCTs) investigating the effectiveness of medication in preventing the onset of post-traumatic stress disorder (PTSD) are for the steroid hydrocortisone and the beta-blocker propranolol. We observed evidence of moderate quality for the efficacy of hydrocortisone in preventing PTSD in four studies following exposure to a traumatic event (see Summary of findings 2). Assuming a baseline onset of PTSD of 10% to 20% for studies that assessed participants a median of four and a half months after trauma exposure, this translates to having to treat seven to 13 patients with hydrocortisone in order for the agent to prevent the onset of PTSD in one patient. A synthesis of the low quality results from three RCTs of propranolol did not support the ability of this agent to prevent the onset of PTSD (see Summary of findings for the main comparison). This was despite promising findings from a series of three open-label studies employing symptom provocation paradigms, in which the repeated administration of propranolol was associated with reduced numbers of participants diagnosed with PTSD (Brunet 2011). The solitary trials of escitalopram, temazepam and gabapentin failed to demonstrate that short-term interventions employing these medications affect the onset of PTSD.

Where provided, drop-outs due to side effects of medication were comparable between the medication and placebo interventions, suggesting that the agents were well tolerated. This may be due to a variety of factors, including (a) the short duration of treatment for many of the trials of hydrocortisone and propranolol in particular, with Zohar 2011a, for instance, administering hydrocortisone at a single session, (b) the fact that treatment often took place at least partly in a controlled environment, such as within trauma centres, where medication response and adherence could be closely monitored, and dosages adjusted accordingly, and (c) that dosages were in the low range for agents that were administered over extended periods, such as the administration of 20 mg/day of escitalopram over 12 weeks (Shalev 2012). Conclusions that medications are well tolerated should be regarded as preliminary, however, given that data on treatment-emergent side effects were often not reported, regardless of whether these led to study withdrawal.

Reductions in PTSD symptom severity were observed in three of the four studies of hydrocortisone, with null findings reported for all of the propranolol studies, as well as for the trials of escitalopram, gabapentin and temazepam. A narrative review indicates that hydrocortisone may improve quality of life (Delahanty 2012; Weis 2006), and possibly reduce symptoms of depression (Delahanty 2012), in individuals who have been treated within 12 hours of the traumatic event.

Overall completeness and applicability of evidence

Completeness of evidence

Reviews of the body of evidence for pharmacotherapy of PTSD have concluded that selective serotonin reuptake inhibitors (SSRIs) are first-line medication agents for the treatment of PTSD (Ipser 2011), with promising findings for the selective noradrenergic reuptake inhibitor (SNRI) venlafaxine and the atypical antipsychotic risperidone. Despite a comprehensive search, we were only able to find a single trial testing the efficacy of a SSRI medication (escitalopram) in preventing PTSD. The efficacy of other medication classes that are frequently considered for treating PTSD in the prevention of the onset of this disorder, such as the tricyclic antidepressants (TCAs) and mono-amine oxidase inhibitors (MAOIs), has also not been investigated.

Limited data were available to assess the effect of medication on comorbid symptoms of depression and anxiety, as well as quality of life. None of the included studies assessed post-treatment changes in functional ability. Additionally, the paucity of studies and missing data hampered our ability to assess the degree to which methodological differences between studies might have systematically influenced differences observed in the primary treatment outcome. Accordingly, our conclusions are limited to a small range of drugs and many of our review questions remain unanswered.

Applicability of evidence

The outcomes of this review may be generalisable to a diverse range of settings. Studies were conducted in the United States of America (Delahanty 2012; Mellman 2002; Pitman 2002; Stein 2007), Germany (Schelling 2001; Weis 2006), and Israel (Zohar 2011a), in both out- and inpatient settings, with interventions targeting both males and females across a wide age range. Differences in treatment delivery, as well as the background and training of study investigators and outcome assessors, increases the likelihood that the findings of this review are applicable to a range of developed and developing nation contexts.

Quality of the evidence

We included nine studies with 345 participants in the review. Seven of the included RCTs possessed a high risk of bias related to at least one aspect of study design, with weaknesses most commonly observed with respect to allocation concealment and differential attrition in the medication and control groups. In addition, the effects of medication may have been confounded in a number of studies of patients in emergency care, trauma centre and surgery settings who were receiving other medications concurrently with the intervention to prevent PTSD (Schelling 2001; Weis 2006).

We judged the evidence for the efficacy of hydrocortisone in preventing PTSD to be of moderate quality (see Summary of findings 2). Accordingly, further research is likely to have an important impact on our confidence in the estimate of this agent's treatment effect, and may even change that estimate. The low quality rating of the corresponding estimate for propranolol indicates that the size of the non-significant effect of this agent in preventing PTSD is likely to change. This reflects shortcomings in the data set contributing to this outcome, including the small number of studies, missing data and small samples included in these studies. These shortcomings are likely to be equally pertinent with respect to the null findings for the trials of escitalopram, temazepam and gabapentin. Another potential explanation for the observation that the outcomes assessed in this review appeared to be relatively insensitive to the effects of medications may be the relatively low background rate of PTSD in the samples that constituted the evidence base for this review, as discerned from the proportion of individuals in the placebo groups who were diagnosed with chronic PTSD (31.6%).

The absence of any evidence that the benzodiazepine temazepam prevents PTSD or reduces PTSD symptoms is consistent with prior negative findings reported for a non-randomised controlled trial of clonazepam or alprazolam (Gelpin 1996). Nevertheless, the limitations of the temazepam study (its small size (N = 21), the fact that assessments of PTSD were conducted less than three months after the trauma event, that in one half of the cases the intervention was terminated when clinical judgement indicated the initiation of other medication treatment, and that participants were not required to endorse the Diagnostic and Statistical Manual (DSM-IV) criterion A for PTSD) suggest that conclusive evidence regarding the efficacy of benzodiazepines in preventing PTSD awaits further controlled studies.

Potential biases in the review process

We minimised overall bias in this review process through conducting an extensive search for studies meeting rigorous methodological inclusion criteria, and through repeated attempts to obtain missing data from the trial investigators. Nevertheless, the small number of eligible studies compromised our ability to assess the extent to which biases, with respect to which studies were published, might have influenced the review findings. Furthermore, the post hoc addition of propranolol may have also introduced bias as a result of the small number of trials we found, and may be susceptible to publication bias, though this was not tested for. It is also noteworthy that all seven included RCTs that provided information on the number of sites recruited from were classified as single-site studies. Single-site RCTs may provide biased estimates of treatment effect, as a recent meta-analysis demonstrated that the size of these estimates are larger than those observed with multi-centre trials (Dechartres 2011).

Agreements and disagreements with other studies or reviews

The conclusions of the review are only partially consistent with those arrived at by other systematic reviews on the effects of pharmacological interventions to prevent PTSD (Bisson 2010; Sones 2011). For instance, Bisson 2010 determined that evidence for the effectiveness of hydrocortisone and various other medications was inconclusive, with cognitive behavioural techniques identified as the most beneficial intervention to prevent PTSD. Similar conclusions were reached in a review conducted by Forneris 2013. Sones 2011, on the other hand, suggested that several pharmacological interventions for PTSD prevention might be of benefit, including propranolol, morphine, glucocorticoids and SSRIs, based on a review of RCTs and open-label studies. These studies differed from the current review in that they included data from preventative studies containing patients diagnosed with PTSD. The finding of minimal effect of the benzodiazepine temazepam in reducing the onset of PTSD following trauma exposure is consistent with an earlier study (Gelpin 1996), in which the sequential administration of clonazepam (mean 2.7 mg/day) or

alprazolam (mean 2.5 mg/day) to emergency department trauma-exposed patients, on average within a week after trauma exposure, failed to reduce PTSD symptoms, as assessed using the Mississippi Rating Scale for Combat-Related PTSD-civilian version.

Other Cochrane reviews on interventions to prevent PTSD have been conducted, with a focus on single-session psychological debriefing interventions (Rose 2002), multiple-session early psychological interventions (Roberts 2010), and psychosocial interventions (De Silva 2009; Peñalba 2009). This review represents an extension of this body of work, with a specific focus on pharmacological interventions for the prevention of PTSD development.

AUTHORS' CONCLUSIONS

Implications for practice

The only agent for which there was preliminary evidence of efficacy in the prevention of post-traumatic stress disorder (PTSD) following trauma exposure was hydrocortisone. Absence of evidence for the efficacy of propranolol, escitalopram, gabapentin and temazepam in preventing PTSD or reducing symptom severity argues against their routine use for this indication. This is particularly the case given the low quality of the evidence for propranolol, resulting partly from methodological shortcomings that were also apparent in single trials of gabapentin and temazepam. Although the limited data on treatment-emergent side effects suggest that all of the medications assessed were well tolerated by patients, this should be balanced against the additional complications in administering these medications in emergency department and trauma clinic settings (including possible interactions with other medications being administered to treat the trauma). Based on these considerations, and pending further research, we believe there is not sufficient evidence at this stage to endorse any medication for the prevention of PTSD.

Implications for research

This review highlights the need for additional randomised controlled trials (RCTs) to evaluate the effectiveness of medications to prevent PTSD, including those agents assessed in this review (hydrocortisone, propranolol, escitalopram, gabapentin and temazepam). Methodological limitations of the studies included in this review, and formalised using the GRADE approach, include small sample size, no description of methods to conceal medication allocation adequately and differences in attrition rate observed between comparison groups. Where possible, these limitations should be addressed in future studies.

RCTs of medication to prevent PTSD are challenging on many fronts, including the unique ethical considerations involved in medicating individuals prior to presentation with a trauma-associated psychiatric diagnosis, as well as difficulties in recruiting participants from this patient population. By pooling participants across multiple centres, future studies would ensure sufficient power to investigate the effect of a number of factors that may affect treatment response, including the optimal clinical window after trauma exposure for the initiation of treatment, dosage and duration of treatment, and the moderating effect of clinical (e.g. trauma type) and demographic factors (e.g. age, gender, ethnicity) in predicting response to medication.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Delahanty 2012

Methods	Design: randomised, double-blind, placebo-controlled pilot study Duration of intervention: 16 days (including 6-day taper off) Follow-up: 1 and 3 months Placebo run-in: no
Participants	Sample size: 64 participants were randomised to hydrocortisone and placebo Mean age: 30.6 (10.7) Gender: 42 males and 22 females were included in the study Ethnicity: 14% African-American and 2% Native American Type of trauma: motor vehicle accidents, falls, assault, and pedestrian and/or car accidents Diagnostic measure: DSM-IV Inclusion criteria: participants consisted of 64 injury victims, who met criterion A for exposure to a traumatic event, ranging in age from 18 to 56 who were admitted as trauma inpatients at a Midwestern Level-1 trauma unit. Participants were required to have a minimum score of 27 on the Peritraumatic Dissociative Experiences Questionnaire - Self Report Exclusion criteria: Quote: "Glasgow Coma Scale (GCS) score of less than 14; exposure to a traumatic event that occurred more than 12 hours before initial medication dose could be given or inability to initiate first medication dose within 12 hours of event; allergy to cortisol or medical/medicinal contraindications to cortisol administration; pregnant or breast-feeding; exposure to a trauma of a potentially ongoing nature (e.g. domestic violence); presence of injuries requiring delayed operative procedures; patient reported corticosteroid use in the previous 6 months; and/or patient had injuries that required treatment with steroids" Drop-outs: 21 (12/31 in the medication group and 9/33 in the placebo group) Number of participants with MDD: data not provided
Interventions	Pharmacological intervention: Quote: "Following consent, the nurse administered the first oral dose [20mg Hydrocortisone (Cortef®, Pharmacia) or placebo capsules] within twelve hours of hospital admission. Participants continued to take either the 20mg hydrocortisone or placebo capsules every twelve hours (bid) for 10 days, followed by a 6-day taper period to avoid any potential adrenal suppression. The medication regimen was tapered by halving the dose every two days"
Outcomes	Primary outcomes: Clinician-Administered PTSD Scale (CAPS), 36-Item Short-Form Health Survey (SF-36) and the Center for Epidemiological Studies – Depression Scale (CES-D) Secondary outcomes: not specified
Notes	Industry-funded: yes. Funding for this study was provided by the National Institute of Mental Health (R34 MH73014) and the Ohio Board of Regents Medication provided by industry: no Any of the authors work for industry: no
Risk of bias	

Delahanty 2012 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised to either hydrocortisone or placebo. The investigators indicated in response to a request for additional information that "a random number table was used to generate the randomization sequence" (11 December 2013)
Allocation concealment (selection bias)	Low risk	The investigators indicated in response to a request for additional information that "the group into which a participant was allocated was concealed from the study investigators via identical pills/blister packs. They were prepared by the hospital's pharmacist who was a co-author - he maintained the blind so that, in case of adverse reaction, the blind could be broken quickly - he had no contact with any of the participants" (11 December 2013)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding procedures were not specified, but the study was described as double-blinded. Quote: "Following eligibility determination, participants were consented in-hospital and randomly assigned, in double-blind fashion, to either a 10-day course (plus a 6-day taper period) of hydrocortisone or placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigators indicated in response to a request for additional information that "individuals who assessed the study outcomes were blinded to the group to which participants had been assigned"
Incomplete outcome data (attrition bias) All outcomes	Low risk	The most common reason for loss to follow-up in both the hydrocortisone and placebo group was inability to contact the participants at follow-up (11/12 drops on hydrocortisone and 9/9 on placebo). Quote: "There were no differences between drop-outs and participants who were retained through the protocol on any study variable. There was no differential drop out between the hydrocortisone and placebo groups"
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available
Other bias	Unclear risk	No other source of bias was identified for this study

Hoge 2012

Methods	Design: randomised, double-blind, placebo-controlled pilot study Duration of intervention: an initial dose was given at the emergency department, followed by a 19-day treatment course at home Follow-up: 1 and 3 months Placebo run-in: no
Participants	Sample size: 43 participants were randomised to propranolol and placebo Mean age: 33.5 (10.2) Gender: 18 males and 23 females were included in the study Ethnicity: data not provided Type of trauma: emergency department Diagnostic measure: DSM-IV

Hoge 2012 *(Continued)*

	Inclusion criteria: Quote: "Participant candidates had to experience an event that met the DSM-IV PTSD A.1 (stressor) and A.2 (response) criteria." "The initial eligibility criterion of an ED admission heart rate of 80 BPM or greater was done away with, and the requirement that the traumatic event occur no earlier than 4 h prior to first dose of study medication was extended to from 4 to 12 hours, due to recruitment difficulties" Exclusion criteria: Quote: "These included physical injury that would complicate participation, hospital stay longer than overnight (the great majority of participants were discharged from the ED the same day), head injury with loss of consciousness, a medical condition that contraindicated the administration of propranolol (e.g., asthma), use of medications with potentially dangerous interactions with propranolol, previous adverse reaction to a β-blocker, blood alcohol concentration above 0.02% or presence of substances of abuse on saliva testing, pregnancy, traumatic event reflecting ongoing victimization, contraindicating psychiatric condition such as psychotic, bipolar, major depressive, or posttraumatic stress disorder from another event, suicidality or homicidality, unwillingness or inability to come to Boston for the research visits, or treating physician did not concur with enrollment in the study" Drop-outs: 9 of 43 (20.9%). Group-specific drop-out rates were not provided Number of participants with MDD: 3/20 (15%) on placebo and 3/21 (14.3%) on propranolol
Interventions	Pharmacological intervention: Quote: "Following screening, each participant was randomized to receive an initial oral dose of either 40 mg short-acting propranolol or placebo. One hour after this first dose, if systolic blood pressure had not fallen by 10 mmHg or more, or to below 100 mmHg, an additional oral dose of 60 mg long-acting propranolol or placebo was given; all participants received both doses. Participants continued taking long-acting propranolol (or placebo) at home over a 19-day course, starting with 120 mg every morning and evening for 10 days, and then tapering to 120 mg in the morning and 60 mg in the evening for 3 days, then 60 mg in the morning and 60 mg the evening for 3 days, then 60 mg in the morning only ×3 days, after which the study medication was discontinued"
Outcomes	Primary outcomes: Physiological Reactivity, Peritraumatic Emotional Distress Inventory, Clinician Administered PTSD Scale (CAPS) Secondary outcomes: not specified
Notes	Industry-funded: no Medication provided by industry: no Any of the authors work for industry: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information about generation of the randomisation sequence was not provided. Quote: "Following screening, each participant was randomized to receive an initial oral dose of either 40 mg short-acting propranolol or placebo"
Allocation concealment (selection bias)	Low risk	Lead author confirmed that "the research pharmacy makes up the active drug and placebo to look the same" (E. Hoge; personal correspondence: 26 November 2013)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No description of blinding is provided in the study report, though the protocol for this study (NCT00158262) describes this study as "Double Blind (Subject, Investigator)". Lead author confirmed that "subjects, the psychologist who did the SCID, and the study nurses who had contact with patients, were all blinded to treatment allocation through the use of blinded medication" (E. Hoge; personal correspondence: 26 November 2013)
Blinding of outcome assessment (detection bias)	Low risk	No description of outcome assessment blinding is provided in the study report. Lead author confirmed that "subjects, the psychologist who did the SCID,

Hoge 2012 *(Continued)*

All outcomes		and the study nurses who had contact with patients, were all blinded to treatment allocation through the use of blinded medication" (E. Hoge; personal correspondence: 26 November 2013)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Proportion and characteristics of participants who dropped out by group is not described. Nevertheless, the total proportion of drop-outs (20.9%) is relatively low, suggesting that drop-out rates may not have biased the outcomes
Selective reporting (reporting bias)	Unclear risk	The outcomes are not described in the study protocol available on ClinicalTrials.gov (NCT00158262)
Other bias	Unclear risk	No other source of bias was identified for this study

Mellman 2002

Methods	Design: randomised, placebo-controlled trial Duration of intervention: 7 days Follow-up: the final assessment for the trial was 6 weeks after the initial assessment Placebo run-in: no
Participants	Sample size: 22 participants were randomised to temazepam and placebo Mean age: 36.1 (11.4) Gender: 14 men and 8 females Ethnicity: 18 Hispanic, 2 white and 2 black participants Type of trauma: motor vehicle accidents, industrial accidents and impersonal assaults Diagnostic measure: DSM-IV Inclusion criteria: participants were recruited from a much larger pool of injured patients on the basis of having recall of the incident and endorsing at least moderate impairment of sleep initiation or maintenance and meeting full criteria for at least 2 PTSD symptoms clusters (DSM-IV) during a structured interview assessment, and the ability and willingness to provide written informed consent Exclusion criteria: intoxication at the time of the incident, brain injury and pre-existing active psychiatric disorders Drop-outs: 0 Number of participants with MDD: 0
Interventions	Pharmacological intervention: Quote: "Subjects were randomly assigned to placebo taken at bedtime for seven nights or 30mg of temazepam at bedtime for five nights followed by 15mg for two nights"
Outcomes	Primary outcomes: CAPS and sleep diary measure Secondary outcomes: not specified
Notes	Industry-funded: yes. Supported by grant MH54006 from the National Institute of Mental Health, Bethesda Medication provided by industry: no Any of the authors work for industry: no

Mellman 2002 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Predetermined randomisation schedule
Allocation concealment (selection bias)	Low risk	Medication schedule was known only to the research pharmacist (TA Mellman; personal correspondence: 09 September 2011)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Medication was placed in identical capsules (TA Mellman; personal correspondence: 09 September 2011)
Blinding of outcome assessment (detection bias) All outcomes	High risk	No information was provided on the blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no drop-outs reported during this study
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available for this study
Other bias	High risk	Study was terminated at 6 weeks after initial assessment, or in 50% of cases when non-study medications were indicated. Quote: "The final assessment for the trial was 6 weeks after the initial assessment or, in one half of cases, just prior to initiating nonstudy medication, which was initiated on the basis of the clinical judgment of the investigators when insomnia and/or other PTSD-related symptoms that were distressing to the subject did not diminish during or shortly after the trial (intent-to-treat analysis)"

Pitman 2002

Methods	Design: randomised, double-blind, pilot study Duration of intervention: 19 days (including a 9-day taper-off period) Follow-up: 1 and 3 months Placebo run-in: no
Participants	Sample size: 41 participants were randomised to propranolol and placebo Mean age: 34.3 (11) Gender: 20 males and 21 females Ethnicity: not specified Type of trauma: motor vehicle accidents Diagnostic measure: DSM-IV Inclusion criteria: patients were included if: Quote: "(a) had just experienced a traumatic event that met the DSM-IV PTSD A.1 (stressor) and A.2 (response) criteria; (b) had a heart rate (HR) of 80 beats per

Pitman 2002 *(Continued)*

	minute (BPM) or greater at the time of ED presentation; (c) were without serious physical injury, systolic blood pressure under 100 mm Hg, substance intoxication, pregnancy or lifetime history of congestive heart failure, heart block or bronchial asthma; (d) upon mental status examination were found competent to understand the purpose of the study and the nature of the procedures; and (e) gave written informed consent after the procedures had been fully explained" Exclusion criteria: serious physical injury, systolic blood pressure over 100 mm Hg, substance intoxication, pregnancy or lifetime history of congestive heart failure, heart block or bronchial asthma Drop-outs: 7/18 on propranolol and 8/23 on placebo at the 3-month assessment Number of participants with MDD: 0
Interventions	Pharmacological intervention: patients were randomised to begin, within 6 hours of the event, a 10-day course of double-blind propanolol versus placebo 40 mg 4 times daily
Outcomes	Primary outcome: Clinician-Administered PTSD Scale (CAPS) Secondary outcomes: not specified
Notes	Industry-funded: yes. Supported by US Public Health Service Grant #MH58671 Medication provided by industry: no Any of the authors work for industry: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomly assigned to treatment and comparison. However, the procedure was not specified
Allocation concealment (selection bias)	High risk	The study did not report on how the intervention was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was described as "double-blind", though no information was provided on which parties were blinded and how blinding was achieved
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was described as "double-blind", though no information was provided on which parties were blinded and how blinding was achieved
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Equivalent numbers of drop-outs were reported at the 3-month assessment for the propranolol and placebo groups. No information was provided on the reasons for study withdrawal, and whether they differed by group, however
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available for this trial
Other bias	Unclear risk	No other source of bias was identified for this study

Schelling 2001

Methods	Design: prospective, randomised, double-blind study

Schelling 2001 *(Continued)*

	Duration of intervention: hydrocortisone was administered for a median of 18 days (range: 14 to 35 days) Follow-up: median assessment for PTSD at 31 months (range: 21 to 49 months) Placebo run-in: no
Participants	Sample size: 20 participants were randomised to propranolol and placebo Mean range: 52 (23 to 76) Gender: 8 males and 12 females Ethnicity: not specified Type of trauma: septic shock Diagnostic measure: SCID-IV Inclusion criteria: Quote: "Patients who had fulfilled the criteria for hyperdynamic septic shock as proposed by the American college of chest physicians/society of critical care medicine" Exclusion criteria: psychiatric diseases (including alcohol and drug abuse) and those who could not complete a questionnaire in German language Drop-outs: 50% (20/40) of the randomised sample (11/20 in the hydrocortisone and 9/20 in the placebo group) Number of participants with MDD: 0 (participants were excluded for "pre-existing psychiatry disease")
Interventions	Pharmacological intervention: Quote: "Patients were prospectively and randomly assigned to receive either placebo or hydrocortisone with a loading dose of 100mg given intravenously over 30 minutes, followed by a continuous infusion of 1.8mg/kg/hour. This dose was kept constant for six days. When septic shock was reversed the dose of hydrocortisone was reduced to .08mg for an additional six days and then tapered in steps of 24mg per day."
Outcomes	Primary outcomes: Structured Clinical Interview for DSM-IV (SCID-IV), Post-Traumatic Stress Syndrome 10-Questions Inventory (PTSS-10Q-I) (German version) and the traumatic memory questionnaire Secondary outcomes: not specified
Notes	Industry-funded: yes. Supported by grants from Hoffman-La Roche, Grenzach-Wyhlen and the Eli-Lilly International Foundation, Bad Homburg, in Germany Medication provided by industry: unclear Any of the authors work for industry: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "In this study, patients were prospectively randomised to receive either stress doses of hydrocortisone or placebo (saline). Patients were assigned to random permuted blocks (G. Schelling; personal correspondence: 15/09/2011)"
Allocation concealment (selection bias)	Low risk	Quote:"Fifty-milliliter syringes containing 100 mg of hydrocortisone-21-hemisuccinate (Upjohn, Heppenheim, Germany) diluted in physiologic saline solution or placebo were prepared daily and labelled study medication"

Schelling 2001 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The patients were blinded regarding the facts that their interviewers were psychiatrists and that the aim of the interviews was the diagnosis of PTSD. They were told that their interviewers were doctors with special training in interviewing techniques and that the object of the interviews was their memories from intensive care treatment and their current emotional well-being"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "For the interviews, the psychiatrists were blinded with regard to treatment characteristics (group assignment, principal diagnoses, traumatic duration of treatment, etc.). They were informed only that the patients were long-term survivors of care"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Exclusions were conducted after randomisation for this study, making it difficult to determine whether participants who did not survive to follow-up (5 on hydrocortisone and 6 on placebo) would have been excluded. The exclusion/drop-out rates were similar between the groups (11/20 and 9/20 in the hydrocortisone and placebo groups, respectively), though no information was provided regarding differences between those who were assessed and those who were not
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available for this trial
Other bias	High risk	Funding for study provided by pharmaceutical companies. Additionally, participants receiving placebo required higher norepinephrine doses than participants on hydrocortisone (though this difference was not statistically significant). The authors concede that this may be an alternative explanation of higher PTSD onset in the placebo group, as previous studies have documented higher urinary excretion of norepinephrine in PTSD patients

Shalev 2012

Methods	Design: prospective, randomised, double-blind study. Assignment to 1 of 4 treatment arms (prolonged exposure, cognitive therapy, escitalopram or placebo, and waiting list) Duration of intervention: escitalopram or placebo was administered for 12 weeks Follow-up: follow-up assessments were conducted at 5 months and 9 months after trauma exposure. Quote: "The first clinical assessment took place a mean (SD) 19.8 (5.2) days after the traumatic event" Placebo run-in: no
Participants	Sample size: 46 participants were randomised to propranolol or placebo Mean range: 38.1 (12.1) Gender: 23 males and 23 females Ethnicity: not specified Type of trauma: motor vehicle accident, terrorist attack and other Diagnostic measure: CAPS Inclusion criteria: Quote: "All survivors of qualifying events who met all criteria for PTSD, including the DSM-IV A2 criterion (exposure to a traumatic event that was responded to with fear, helplessness, or horror), but not the 1 month duration criterion Individuals who did not meet criterion A, but only B, C, and D for PTSD were classified as having partial PTSD, and included as part of a separate analysis"

Shalev 2012 *(Continued)*

	Exclusion criteria: Quote: "Current or past psychosis or bipolar disorder, a current substance abuse problem, other conditions requiring urgent attention (e.g., suicidal ideations or acute grief), or chronic PTSD or if they started treatment elsewhere" Drop-outs: 6/23 (26.1%) on escitalopram and 13/23 (56.5%) on placebo completed the 8 sessions of treatment, with 1 additional participant on placebo not providing data for the 5-month post-trauma assessment Number of participants with MDD: 18 (78.3%) and 12 (52.2%) in the escitalopram and placebo arms, respectively
Interventions	Pharmacological intervention: Quote: "An initial dose of 1 tablet (10 mg) daily was increased to 2 tablets after 2 weeks of treatment. Trained psychiatrists provided 4 weekly sessions (weeks 1-4) followed by 4 biweekly sessions (weeks 6-12). At the end of our study, 8 participants with PTSD who received placebo were invited to receive PE"
Outcomes	Primary outcome: Clinician-Administered PTSD Scale (CAPS) Secondary outcomes: PTSD Symptom Scale – Self-Report Version (PSS-SR), Clinician-Administered PTSD Scale (CAPS, structured interview) and Beck Depression Inventory (BDI)
Notes	Industry-funded: yes. Funding was provided by Lundbeck Pharmaceuticals Ltd. (Denmark) Medication provided by industry: unclear Any of the authors work for industry: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An equipoise-stratified randomisation procedure was employed, though no information is provided on how this randomisation sequence was generated. Quote: "The equipoise-stratified randomization is a method for randomly allocating participants to interventions in treatment studies that include more than 2 arms ... It allows potential participants to decline treatment options that they do not desire and to be randomly assigned to the remaining arms. By making that choice, each participant assigns himself or herself to a "stratum" which consists of all the options that he or she finds equally acceptable"
Allocation concealment (selection bias)	Low risk	Quote: "Concealed tablets of either 10 mg of escitalopram or placebo were prepared and coded by Lundbeck Pharmaceuticals (Copenhagen, Denmark) and were supplied to clinicians by a research associate"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and those administering the medication were blinded. Quote: "Trained psychiatrists provided 4 weekly sessions (weeks 1-4) followed by 4 biweekly sessions (weeks 6-12). The concealment was broken and added to the study's data file at the end of the study". Quote: "To separate the pharmacological effect of an SSRI from that of receiving medication and psychiatric care, this blinded group [SSRIs versus placebo comparison] includes both the active agent and placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	5-month (CA-2) and 9-month (CA-3) assessments were blinded. Quote: "Because those who conducted the CA-2 and CA-3 were blinded to treatment attendance and adherence, the resulting comparisons include completers, partial completers, and noncompleters and thereby represent the total yield of participants randomly assigned to an intervention"
Incomplete outcome data (attrition bias)	High risk	A greater proportion of participants dropped out from the placebo (14/23; 60.9%) than the escitalopram (6/23; 26%) arms at the 5-month assessment.

Shalev 2012 *(Continued)*

All outcomes		These participants were not contacted to obtain information on their reasons for withdrawing from treatment" (AY Shalev; personal correspondence: 5 December 2013)
Selective reporting (reporting bias)	Unclear risk	The protocol for this study was not available
Other bias	Low risk	Funding for study provided by industry. Additionally, in the equipoise-stratified randomisation scheme employed, participants could indicate 2 of the 4 treatment arms they did not want to be assigned to. A large proportion of eligible participants (42.6%) refused treatment with escitalopram or placebo. Since industry funding and self exclusion from the medication arms would be expected to bias the study finding towards an effect for medication, we have interpreted the absence of such an effect as an indication that bias did not occur

Stein 2007

Methods	Design: proof-of-concept-study; double-blind, randomised, placebo-controlled trial Duration of intervention: 14 days (including the up-titration, treatment and taper phases) Follow-up: 1, 4 and 8 months Placebo run-in: no
Participants	Sample size: 48 participants were randomised to propranolol, gabapentin and placebo Mean age: 29.4 (10.10) Gender: 26 males and 22 females Ethnicity: Quote: "The sample was ethnically diverse: 40% Hispanic, 35% White non-Hispanic, 10% African American, 10% Asian, and 4% Native American" Type of trauma: Quote: "The most common type of injury was a motor vehicle collision followed by falls, burns, pedestrian versus automobile, assault, and other (e.g. surfing)" Diagnostic measure: specified structured or semi structured measurement Inclusion criteria: Quote: "Potential participants were men and women ages 18-65 who were admitted to the University of California San Diego (UCSD) Level 1 Surgical Trauma Centre during the 39-month period from October 2001 through December 2004. Admission to this service reflected a severe physical injury requiring specialized, emergent trauma care" Exclusion criteria: Quote: "The most common reasons for exclusion were (a) living outside the region such that home monitoring could not be arranged, (b) too medically unstable to participate, (c) did not speak English, or (d) too old or too young" Drop-outs: 5/17 for propranolol, 4/14 for gabapentin and 1/17 on placebo, as inferred from number of people assessed for PTSD at the 4-month follow-up assessment Number of participants with MDD: data not provided
Interventions	Pharmacological intervention: 14 days of propranolol, gabapentin or placebo, administered within 48 hours of injury to patients admitted to a surgical trauma centre. Propranolol was started at 20 mg for 3 times daily and up-titrated over 2 days to 40 mg. Gabapentin was started at 300 mg and up-titrated over 2 days to 400 mg

Stein 2007 *(Continued)*

Outcomes	Primary outcomes: the Acute Stress Disorder Scale (ASDS), the Comprehensive International Diagnostic Interview (CIDI), the Center for Epidemiologic Studies Depression Scale (CES-D) and the Posttraumatic Stress Disorder Checklist–Civilian Version (PCL-C) Secondary outcomes: not specified
Notes	Industry-funded: yes. Supported by NIMH grants MH62037 (R21) and MH64122 (K24) to MBS Medication provided by industry: no Any of the authors work for industry: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised to receive propranolol, gabapentin or placebo. Quote: "A randomised schedule was set up and maintained by the UCSB Research Pharmacy"
Allocation concealment (selection bias)	Low risk	Quote: "When a subject was enrolled, the study nurse notified one of the attending physicians on the Trauma Service, who authorized the Research Pharmacy to provide the medication supplies (according to the randomization schedule) to the subject"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All study medications were supplied in identical capsules. Quote: "All study medications were supplied in identical capsules to avoid breaking the blind study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The study nurse, who was blinded to treatment allocation, conducted assessments"
Incomplete outcome data (attrition bias) All outcomes	High risk	A higher proportion of drop-outs was observed in the medication groups (propanolol: 29.4% and gabapentin: 28.6%) versus placebo (5.9%). Investigators employed a GEE modelling approach to try and accommodate missing data. No data on reasons for study withdrawal were provided, though. Quote: "And finally, although our rate of follow-up (≈80% at 4 months) was satisfactory, the possibility of differential drop-out across groups creates a missing data problem that even the use of GEE analyses may not solve"
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available for this trial
Other bias	Unclear risk	No other source of bias was identified for this study

Weis 2006

Methods	Design: prospective, randomised, double-blind trial Duration of intervention: 4 days Follow-up: 6 months Placebo run-in: no
Participants	Sample size: 36 participants were randomised to hydrocortisone and placebo

Weis 2006 *(Continued)*

	Mean age: 68.5 (range 63 to 73) Gender: 8 males and 28 females Ethnicity: not specified Type of trauma: cardiac surgery Diagnostic measure: specified structured or semi structured measurement Inclusion criteria: Quote: "The study was performed in high-risk patients undergoing CS with CPB. High risk was defined as a preoperative left ventricular ejection fraction of less than 35% or an expected duration of CPB of greater than 97 minute" Exclusion criteria: Quote: "Patients were excluded from the study if they met the following criteria before surgical intervention: pregnancy, emergency operation, hepatic dysfunction (bilirubin 3 mg/dL), renal dysfunction (plasma creatinine 2 mg/dL), a positive serologic test result for HIV, manifest insulin-dependent diabetes mellitus, an extracardial septic focus, chronic or acute inflammatory disease, and inability to provide informed consent. In addition, patients who required glucocorticoids other than hydrocortisone were excluded" Drop-outs: 5/19 in the medication group and 3/17 in the placebo group. 2 of these participants were not technically drop-outs, but were not included in the analysis due to missing data Number of participants with MDD: not assessed
Interventions	Pharmacological intervention: Quote: "Hydrocortisone administration started with a loading dose (100 mg over 10 minutes administered intravenously) before induction of anesthesia, followed by a continuous infusion of 10mg/h for 24 hours (postoperative day [POD] 1), which was reduced to 5mg/h on POD 2 and then tapered to 3 X 20 mg administered intravenously on POD 3 and 3 X 10 mg administered intravenously on POD 4"
Outcomes	Primary outcomes: the Short Form (36) Health Survey (SF-36) and Posttraumatic Symptom Scale (PTSS-10). Evaluation of traumatic memories: all patients were asked to complete a structured and validated questionnaire, evaluating different categories of traumatic memory from ICU therapy Secondary outcomes: not specified
Notes	Industry-funded: unclear Medication provided by industry: unclear Any of the authors work for industry: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were randomly assigned to one of two treatment groups with the use of a computer-generated randomisation list"
Allocation concealment (selection bias)	Low risk	Quote: "The vials were prepared by a study nurse who was not involved in the care of patients participating in the trial"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was described as "double-blind", though no information was provided on which parties were blinded and how blinding was achieved. Quote: "One group of patients received stress doses of hydrocortisone (Pharmacia & Upjohn, Erlangen, Germany; the hydrocortisone group) and patients from the other group (the placebo group) received normal saline in identical vials in a double-blind fashion"

Weis 2006 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was described as "double-blind", though no information was provided on which parties were blinded and how blinding was achieved. Quote: "One group of patients received stress doses of hydrocortisone (Pharmacia & Upjohn, Erlangen, Germany; the hydrocortisone group) and patients from the other group (the placebo group) received normal saline in identical vials in a double-blind fashion"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar proportions of patients withdrew from the hydrocortisone (5/19; 26.3%) and placebo (3/17; 17.6%) groups. Between-group comparisons on patient and treatment characteristics for the fully randomised sample as well as the sample excluding drop-outs were virtually identical, suggesting that outcomes for the drop-outs would have been similar to those retained in the study. Quote: "There were no significant differences with regard to patient or treatment characteristics between included or excluded patients"
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available for this trial
Other bias	High risk	Participants receiving hydrocortisone required significantly lower norepinephrine doses (to "counteract vasodilatory hypotension") than participants on placebo. As noted for the similar finding in Schelling 2001, this might provide an alternative explanation of higher PTSD onset in the placebo group, as previous studies have documented higher urinary excretion of norepinephrine in PTSD patients

Zohar 2011a

Methods	Design: randomised, double-blind, placebo-controlled pilot study Duration of intervention: single dose 1.5 to 5 hours after the traumatic event Follow-up: 2 weeks, 1 month and 3 months after the trauma Placebo run-in: no
Participants	Sample size: 25 participants were randomised to hydrocortisone and placebo Mean age: 35.16 (14) Gender: 14 males and 11 females Ethnicity: not specified Type of trauma: traffic accidents, work accidents and snake bites Diagnostic measure: specified structured or semi structured measurement Inclusion criteria: Quote: "Seventy consecutive patients who were exposed to a traumatic event, experienced either acute stress reaction or sub-threshold acute stress reaction, and met the DSM-IV PTSD A.1 (stressor) and A.2 (response) criteria (fulfilling criteria A, 2 of the symptoms in criteria B, 3 out of 4 of criteria C, D, E, and F, and meeting criterion H of the ASD criteria set out in DSM-IV) were recruited from the emergency department at the Chaim Sheba Medical Center" Exclusion criteria: Quote: "Exclusion criteria included serious physical injury (a score of 3 or above on the Abbreviated Injury Scale), brain trauma, substance abuse disorders, cardiac pacemaker implant, a history of epilepsy, neurosurgery, chronic medical conditions of any sort. Medication specific exclusion criteria included hypersensitivity to hydrocortisone, pregnancy, or treatment for asthma" Drop-outs: 6/15 (40%) on hydrocortisone and 2/10 (20%) on placebo

Zohar 2011a *(Continued)*

	Number of participants with MDD: MDD was not assessed
Interventions	Pharmacological intervention: Quote: "Hydrocortisone or placebo was given between 1.5 and 5.5 hours following the traumatic event. Patients received hydrocortisone intravenously in a single bolus at a dose ranging from 100 to 140mg based on body weight: 100 mg for weights of 60–69kg, 120 mg for weights of 70–89kg, and 140mg for weights of 90–99kg"
Outcomes	Primary outcomes: Clinician-Administered PTSD Scale (CAPS), visual analogue scales for anxiety (VAS-A) and depression (VAS-D) Secondary outcomes: not specified
Notes	Industry-funded: no Medication provided by industry: no Any of the authors work for industry: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The participants were randomised by a predetermined program, and entered in a double blind, placebo-controlled design"
Allocation concealment (selection bias)	Low risk	Quote from Dr. Hagit (11 December 2013): "Hydrocortisone or placebo was given intravenously and has been prepared by another physician. IV bags were numbered and were the same for both treatments"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Although described as double-blinded, the procedure employed was not specified. Quote: "The participants were randomised by a predetermined program, and entered in a double blind, placebo-controlled design"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessment was blinded. Quote: "Ratings of ASD and PTSD symptoms, anxiety, and depression were carried out at 4 time points — before the intervention, at 2 weeks, 1 month and 3 months after the trauma — by an expert investigator who was blind to the treatment condition"
Incomplete outcome data (attrition bias) All outcomes	High risk	A larger proportion of participants were excluded from the hydrocortisone (6/15; 40%) than the placebo groups (2/10; 20%). No information was provided regarding the reasons for treatment withdrawal
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available for this trial
Other bias	Unclear risk	No other source of bias was identified for this study

BPM: beats per minute
CAPS: Clinician-Administered PTSD Scale
CPB: cardiopulmonary bypass
CS: cardiac surgery
DSM-IV: Diagnostic and Statistical Manual IV
ED: emergency department
GEE: generalised estimating equation
ICU: intensive care unit
MDD: major depressive disorder
NIMH: National Institute of Mental Health
PTSD: post-traumatic stress disorder

SCID-IV: Structured Clinical Interview for DSM-IV
SD: standard deviation
SSRI: selective serotonin reuptake inhibitor

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

Study	Reason for exclusion
Davidson 2000	Relapse prevention study; participants were already diagnosed with PTSD
Gelpin 1996	Non-randomised trial and no placebo control group
Martenyi 2002	Relapse prevention study; participants were already diagnosed with PTSD
Martenyi 2006	Relapse prevention study; participants were already diagnosed with PTSD
Schelling 2004	No comparison group
Vaiva 2003	Participants were not randomised to treatment

PTSD: post-traumatic stress disorder

Characteristics of studies awaiting assessment *[ordered by study ID]*

Azad 2007

Methods	Prospective, interventional, randomised, double-blind, placebo-controlled study
Participants	92 high-risk patients after cardiac surgery
Interventions	Hydrocortisone in stress doses versus placebo
Outcomes	Primary outcomes: immunologic markers, health care-related quality of life, PTSD Secondary outcomes: early clinical outcome parameters
Notes	Primary outcomes were assessed at 1.5 years. Secondary outcomes were assessed at 1 year

Marx 2006

Methods	Randomised, parallel-group, double-blind, controlled study
Participants	12 veterans, 18 to 55 years of age
Interventions	Paroxetine 10 mg to 40 mg (flexible dosing) versus placebo x 12 weeks
Outcomes	Primary outcome: improvement in PTSD symptoms as determined by the Clinician Administered PTSD Scale (CAPS) Secondary outcomes: short PTSD Rating Interview, Connor Davidson Resilience Scale, Hospital Anxiety and Depression Scale, Clinical Global Impressions of Severity and of Improvement Scales, Symptom Checklist 90 and the Sheehan Disability Scale (SDS)
Notes	Primary outcome assessed at baseline and at 12 weeks. All secondary outcomes assessed at 12 weeks of intervention

Simon 2005

Methods	Double-blind, flexible-dose, placebo-controlled study
Participants	60 study participants meeting criteria for the A1, A2 and at least 1 additional ASD criterion (i.e., B, C and or D criteria), as determined by the Acute Stress Disorder Interview upon initial evaluation
Interventions	Escitalopram (10 to 40 mg/day) versus placebo x 12 weeks
Outcomes	Primary outcome: symptoms of post-traumatic stress disorder, symptoms of acute stress disorder Secondary outcome: Clinical Global Improvement
Notes	—

ASD: acute stress disorder
PTSD: post-traumatic stress disorder

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

Zohar 2009

Trial name or title	PTSD prevention using escitalopram
Methods	Allocation: randomised Intervention model: parallel assignment Masking: double-blind (subject, investigator) Primary purpose: prevention
Participants	Ages eligible for study:18 years to 65 years Genders eligible for study: both Accepts healthy volunteers: no
Interventions	Pharmacological intervention: 10 to 20 mg/day of escitalopram versus 1/2 capsules of placebo
Outcomes	Primary outcome: CAPS Secondary outcomes: no information provided
Starting date	June 2005
Contact information	Contact: Joseph Zohar, MD: jzohar@post.tau.ac.il
Notes	Assessment of primary outcome at 1-year follow-up

Zohar 2010

Trial name or title	The efficacy of a single dose of intranasal oxytocin in the prevention of post traumatic stress disorder (PTSD)
Methods	Study type: interventional Allocation: randomised

Zohar 2010 *(Continued)*

	Endpoint classification: efficacy study Intervention model: parallel assignment Masking: double-blind (subject, caregiver, investigator, outcomes assessor) Primary purpose: prevention
Participants	Ages eligible for study: 18 67 years Genders eligible for study: both Inclusion criteria: (1) Persons over the age of 18, who have been exposed to an event meeting the DSM-IV "A.1" criterion for trauma exposure, expressing marked anxiety, and/or emotional distress and/or dissociation, as assessed by the visual analogue scales; (2) the traumatic event occurred up to 6 hours prior to the arrival to the emergency room; (3) the person can and is willing to provide written, informed consent to participate in the study
Interventions	Pharmacological intervention: oxytocin and placebo - saline nasal spray
Outcomes	Primary outcome: the primary outcome measure is DSM-IV diagnosis of PTSD at the end of the trial Secondary outcome: the secondary outcome measure is the severity of PTSD as expressed by the Clinician Administered PTSD Scale (CAPS), at the end of the trial
Starting date	February 2010
Contact information	Contact: Joseph Zohar, MD: jzohar@post.tau.ac.il Contact: Shlomit Cwikel-Hamzany, MD: shlomitch@gmail.com
Notes	—

Zohar 2011b

Trial name or title	Randomized placebo-controlled trial of hydrocortisone in PTSD prophylaxis
Methods	Study type: interventional Allocation: randomised Endpoint classification: efficacy study Intervention model: parallel assignment Masking: double-blind (subject, caregiver, investigator, outcomes assessor) Primary purpose: prevention
Participants	Ages eligible for study: no information provided Genders eligible for study: no information provided Inclusion criteria: no information provided
Interventions	Pharmacological intervention: single injection of 90 to 140 mg (proportioned to body weight) of hydrocortisone
Outcomes	Primary outcome measures: no information provided

Zohar 2011b *(Continued)*

	Secondary outcome measures: no information provided
Starting date	August 2011
Contact information	Contact: Joseph Zohar, MD; jzohar@post.tau.ac.il Program Officer: Farris K. Tuma; ftuma@mail.nih.gov
Notes	—

CAPS: Clinician-Administered PTSD Scale
DSM-IV: Diagnostic and Statistical Manual IV
PTSD: post-traumatic stress disorder

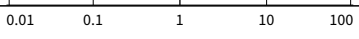
DATA AND ANALYSES

Comparison 1. Propranolol versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment efficacy	3	118	Risk Ratio (IV, Random, 95% CI)	0.62 [0.24, 1.59]
2 Sensitivity analysis - observed cases	3	97	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.29, 1.84]

Analysis 1.1. Comparison 1 Propranolol versus placebo, Outcome 1 Treatment efficacy.

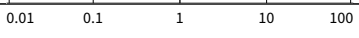
Study or subgroup	Propranolol n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Hoge 2012	2/22	4/21		34.73%	0.48[0.1,2.34]
Pitman 2002	1/18	2/23		16.28%	0.64[0.06,6.5]
Stein 2007	3/17	4/17		48.99%	0.75[0.2,2.86]
Total (95% CI)	**57**	**61**		**100%**	**0.62[0.24,1.59]**
Total events: 6 (Propranolol), 10 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.18, df=2(P=0.91); I^2=0%					
Test for overall effect: Z=0.99(P=0.32)					



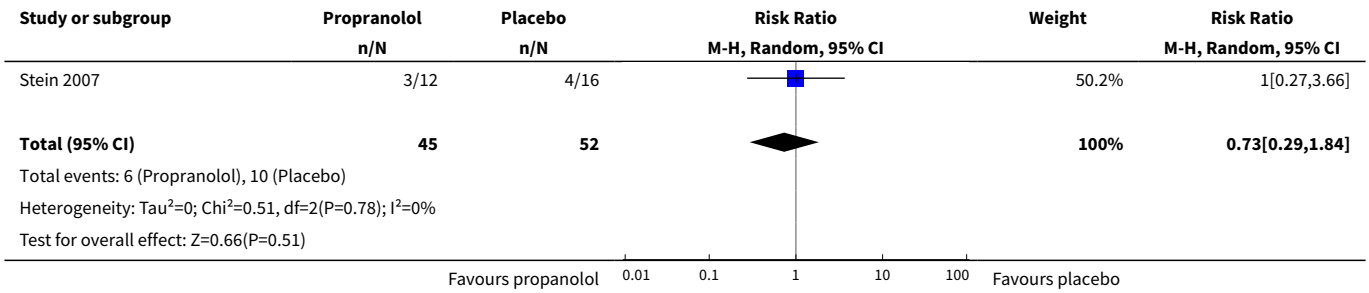
Favours propranolol — Favours placebo

Analysis 1.2. Comparison 1 Propranolol versus placebo, Outcome 2 Sensitivity analysis - observed cases.

Study or subgroup	Propranolol n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Hoge 2012	2/22	4/21		33.43%	0.48[0.1,2.34]
Pitman 2002	1/11	2/15		16.36%	0.68[0.07,6.61]



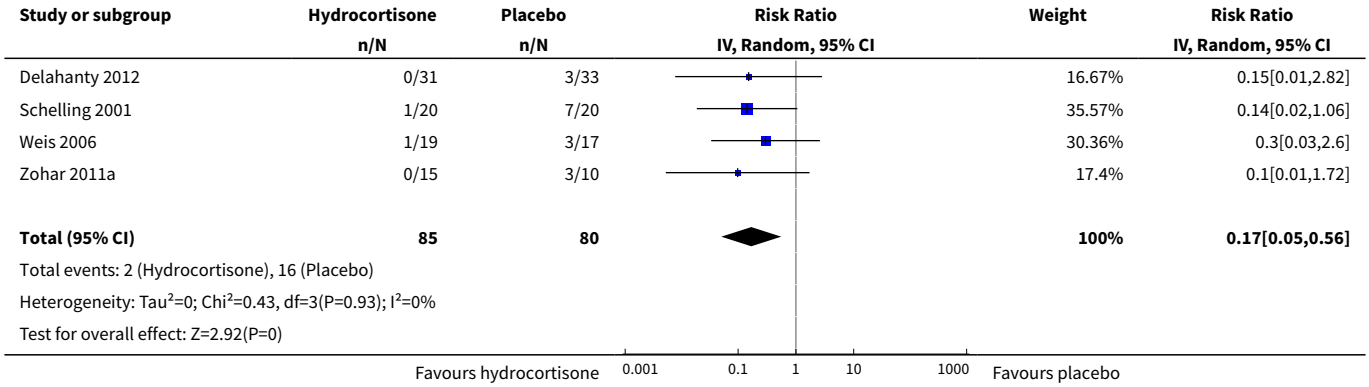
Favours propanolol — Favours placebo



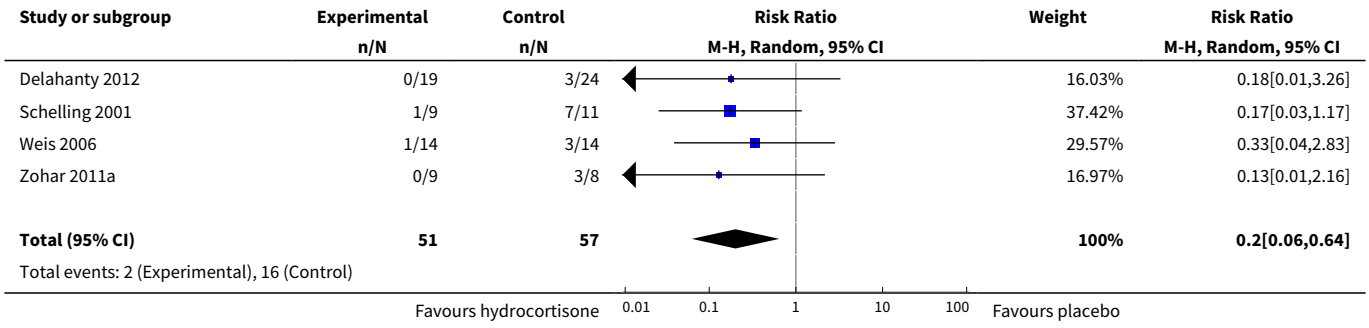
Comparison 2. Hydrocortisone versus placebo

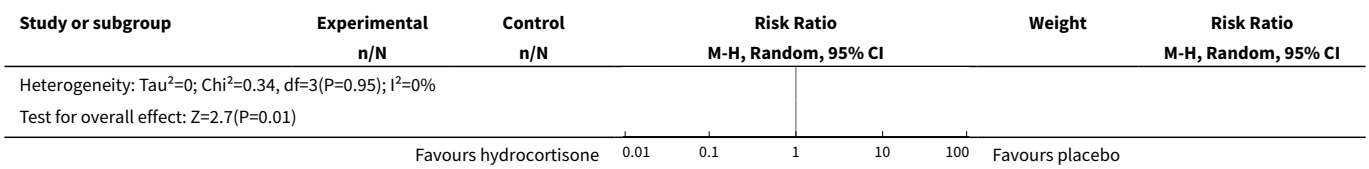
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment efficacy	4	165	Risk Ratio (IV, Random, 95% CI)	0.17 [0.05, 0.56]
2 Sensitivity analysis - observed cases	4	108	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.06, 0.64]

Analysis 2.1. Comparison 2 Hydrocortisone versus placebo, Outcome 1 Treatment efficacy.



Analysis 2.2. Comparison 2 Hydrocortisone versus placebo, Outcome 2 Sensitivity analysis - observed cases.





APPENDICES

Appendix 1. Search strategy (OVID MEDLINE, EMBASE)

CCDAN's Trials Search Co-ordinator (TSC) ran the following searches on OVID MEDLINE and EMBASE:

(i) OVID MEDLINE (2004 to March 2011)

1. ((serotonin or norepinephrine or noradrenaline or dopamine or neurotransmitter) adj (uptake or reuptake or re-uptake)).mp.
2. (antiadrenergic or anti-adrenergic).mp.
3. (5-hydroxytrypotophan or Acetylcarnitine or Alaproclate or alprazolam or Amersergide or Amiflamine or Amineptine or Amitriptyline or Amoxapine or anticonvulsant* or Antidepress* or antipsychotic* or anxiolytic* or Aripiprazole).mp.
4. (Befloxatone or Benactyzine or Benzodiazepine* or Brofaromine or Bupropion or Butriptyline).mp.
5. (Carbazepine or Caroxazone or cck-4 or Chlorimipramine or Chlorphenamidine or Chlorpoxiten or Cilosamine or Cimoxatone or Citalopram or Clomipramine or clonidine or Clorgyline or Clovoxamine or Cyproheptadine or d-Cycloserine).mp.
6. (Deanol or Demexiptiline or Deprenyl or Desipramine or Desvenlafaxine or Dibenzipin or Diclofensine or divalproex or dopamin* or Dosulepin or Dothiepin or Doxazosin or Doxepin or Duloxetine).mp.
7. (Escitalopram or Etoperidone or Femoxetine or Fenfluramine or flumazenil or Fluotracen or fluoxetine or Fluparoxan or fluphenazine or Fluvoxamine or Furazolidone or Guanfacine).mp.
8. (haloperidol or Harmaline or Harmine or hydrocortisone or Idazoxan or Imipramine or inositol or Iprindole or Iproniazid or Isocarboxazid or lamotrigine).mp.
9. (Lithium carbonate or Lithium compounds or Litoxetine or Lofepramine).mp.
10. (MAOI* or Maprotiline or medicat* or Medifoxamine or Melitracen or Metapramine or Metyrapone or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Monoamine Oxidase Inhibitor*).mp.
11. (Naloxone or Naltrexone or Nefazodone or Nialamide or Nomifensine or noradrenerg* or Norfenfluramine or Nortriptyline or Noxiptiline or Olanzapine or Opipramol or Oxaflozane or Oxaprotiline or Oxcarbazepine).mp.
12. N-Methyl-3,4-methylenedioxyamphetamine/
13. (Pargyline or Paroxetine or pharmacother* or Phenelzine or Pheniprazine or Piribedil or Pirlindole or Pivagabine or Pizotyline or Prazosin or Pregabalin or Procaine or Propranolol or Prosulpride or Protriptyline or psychotropic*).mp.
14. (Quetiapine or Quinupramine or Quipazine or Reboxetine or Risperidone or Ritanserin or Rolipram).mp.
15. (Selegiline or seroto* or Sertraline or Setiptiline or SNRI* or SSRI* or Sulpiride).mp.
16. (Teniloxine or Tetrindole or Thiazesim or Thozalinone or Tiagabine or Tianeptine or Toloxatone or Tomoxetine or Topiramate or Tranylcypromine or Trazodone or tricyclic* or Trimipramine or Tryptophan).mp.
17. (Venlafaxine or Viloxazine or Viqualine or Yohimbine or Zimeldine).mp.
18. exp Stress Disorders, Traumatic/dt
19. or/1-18
20. exp Stress Disorders, Traumatic/
21. ((post-traumatic or post traumatic or posttraumatic) and disorder*).tw.
22. PTSD.tw.
23. or/20-22
24. randomized controlled trial/
25. controlled clinical trial/
26. randomi#ed.ti,ab.
27. randomly.ab.
28. placebo$.tw.
29. trial.ab.
30. drug therapy.fs.
31. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$ or dummy)).mp.
32. (control$ adj3 (trial$ or study or studies$ or group$)).tw.
33. (animals not (humans and animals)).sh.
34. or/24-32
35. 34 not 33

36. 19 and 23 and 35
37. (2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$).ed,yr.
38. 36 and 37

(ii) OVID EMBASE (2004 to February 2010)

1. ((seroton* or norepinephrine or noradrenaline or dopamin* or neurotransmitter) adj (uptake or reuptake or re-uptake)).mp.
2. (5-hydroxytrypotophan or acetylcarnitine or alaproclate or alprazolam or amersergide or amiflamine or amineptine or amitriptyline or amoxapine or anticonvulsant* or antidepress* or antipsychotic* or anxiolytic*).mp.
3. (befloxatone or benactyzine or benzodiazepine* or brofaromine or bupropion or butriptyline).mp.
4. (caroxazone or cck-4 or chlorimipramine or chlorphenamidine or chlorpoxiten or cilosamine or cimoxatone or citalopram or clomipramine or clonidine or clorgyline or clovoxamine or cyproheptadine or d-cycloserine).mp.
5. (deanol or demexiptiline or deprenyl or desipramine or desvenlafaxine or dibenzipin or diclofensine or divalproex or dopamin* or dosulepin or dothiepin or doxepin or duloxetine).mp.
6. (escitalopram or etoperidone or femoxetine or fenfluramine or flumazenil or fluotracen or fluoxetine or fluparoxan or fluphenazine or fluvoxamine or furazolidone).mp.
7. (haloperidol or harmaline or harmine or hydrocortisone or idazoxan or imipramine or inositol or iprindole or iproniazid or isocarboxazid or lamotrigine).mp.
8. (lithium carbonate or lithium compounds or litoxetine or lofepramine).mp.
9. (maoi* or maprotiline or medicat* or medifoxamine or melitracen or metapramine or metyrapone or mianserin or milnacipran or minaprine or mirtazapine or moclobemide or monoamine oxidase inhibitor*).mp.
10. (naloxone or naltrexone or nefazodone or nialamide or nomifensine or noradrenerg* or norfenfluramine or nortriptyline or noxiptiline or olanzapine or opipramol or oxaflozane or oxaprotiline).mp.
11. (pargyline or paroxetine or pharmacother* or phenelzine or pheniprazine or piribedil or pirlindole or pivagabine or pizotyline or prazosin or procaine or propranolol or prosulpride or protriptyline or psychotropic*).mp.
12. (quetiapine or quinupramine or quipazine or reboxetine or risperidone or ritanserin or rolipram).mp.
13. (selegiline or seroto* or sertraline or setiptiline or snri* or ssri* or sulpiride).mp.
14. (teniloxine or tetrindole or thiazesim or thozalinone or tiagabine or tianeptine or toloxatone or tomoxetine or topiramate or tranylcypromine or trazodone or tricyclic* or trimipramine or tryptophan).mp.
15. (venlafaxine or viloxazine or viqualine or yohimbine or zimeldine).mp.
16. or/1-15
17. posttraumatic stress disorder/
18. ((post-traumatic or post traumatic or posttraumatic) and disorder*).tw.
19. ptsd.tw.
20. or/17-19
21. major clinical study/
22. randomized controlled trial/
23. randomization/
24. placebo/
25. randomi#ed.ti,ab.
26. placebo$.tw.
27. trial$.ti,ab.
28. randomly.ab.
29. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$ or dummy)).mp.
30. (control$ adj3 (trial$ or study or studies$)).tw.
31. ((animal or nonhuman) not (human and (animal or nonhuman))).de.
32. or/21-30
33. 32 not 31
34. 16 and 20 and 33
35. (2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$).yr,em.
36. 34 and 35

Appendix 2. Additional author searches (PubMed, PsycINFO, EMBASE)

The authors ran additional searches (all years to March 2011) on the following databases, using the following terms:

(iii) PubMed
(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR ("latin square" [tw]) OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animal [mh] NOT

human [mh]) AND (Stress Disorders, Traumatic [mh] OR "acute stress disorder" [tw] OR ASD [tw] OR "posttraumatic stress disorder" [tw] OR "post traumatic stress disorder" [tw] OR PTSD [tw]) AND (prevent* [tw] OR prophy* [tw]).

(iv) PsycINFO
PsycINFO was searched using the following search query: ("randomisation" OR "randomization") OR "controlled" AND ("post traumatic stress disorder" OR "PTSD")

(v) EMBASE
EMBASE was searched using the following search strategy: (random* OR "controlled") AND ("post traumatic stress disorder" OR "PTSD") AND (prevent*)

Appendix 3. Systematic reviews search: PTSD/drug therapy (OVID MEDLINE)

1. (((systematic or structured or evidence or trials).ti. and ((review or overview or look or examination or update$ or summary).ti. or review.pt.)) or (meta analysis.pt. or meta analysis/ or "0266-4623".is.) or (reviewed systematically or systematically reviewed).tw. or (1469-493X or 1366-5278 or 1530-440X).is.) not ((animals/ not humans/) or letter.pt.)
2. ("review" or "review academic" or "review tutorial").pt.
3. (medline or medlars or embase or pubmed).tw,sh.
4. (scisearch or psychinfo or psycinfo).tw,sh.
5. (psychlit or psyclit).tw,sh.
6. cinahl.tw,sh.
7. ((hand adj2 search$) or (manual$ adj2 search$)).tw,sh.
8. (electronic database$ or bibliographic database$ or computeri#ed database$ or online database$).tw,sh.
9. (pooling or pooled or mantel haenszel).tw,sh.
10. (retraction of publication or retracted publication).pt.
11. (peto or dersimonian or der simonian or fixed effect).tw,sh.
12. or/3-11
13. 2 and 12
14. meta-analysis.pt.
15. meta-analysis.sh.
16. (meta-analys$ or meta analys$ or metaanalys$).tw,sh.
17. (systematic$ adj5 review$).tw,sh.
18. (systematic$ adj5 overview$).tw,sh.
19. (quantitativ$ adj5 review$).tw,sh.
20. (quantitativ$ adj5 overview$).tw,sh.
21. (quantitativ$ adj5 synthesis$).tw,sh.
22. (methodologic$ adj5 review$).tw,sh.
23. (methodologic$ adj5 overview$).tw,sh.
24. (integrative research review$ or research integration).tw.
25. or/14-24
26. (1 or 13 or 25)
27. stress disorders, traumatic/ or combat disorders/ or stress disorders, post-traumatic/ or stress disorders, traumatic, acute/
28. (PTSD or posttrauma* or post-trauma* or post trauma* or stress disorder* or combat disorder*).tw.
29. or/27-28
30. dt.fs.
31. (26 and 29 and 30)

HISTORY

Protocol first published: Issue 4, 2006
Review first published: Issue 7, 2014

Date	Event	Description
2 November 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Jonathan Ipser compiled the background and methods sections of the protocol, and assisted in making changes to the review in response to editorial feedback. Dan Stein assisted in this process and also served as a co-ordinator for the protocol. Taryn Amos compiled the original version of the review, including the data analysis section.

DECLARATIONS OF INTEREST

Potential conflicts of interest for individual review authors

Taryn Amos has no known conflict of interest outside of her employment by the MRC Unit on Anxiety and Stress Disorders.

Jonathan Ipser has no known conflict of interest.

Dan Stein has received research grants and/or consultancy honoraria from AstraZeneca, Eli-Lilly, GlaxoSmithKline, Lundbeck, Orion, Pfizer, Pharmacia, Roche, Servier, Solvay, Sumitomo and Wyeth. He has participated in a number of ongoing studies and has presented data from some of these studies on behalf of the sponsoring companies.

SOURCES OF SUPPORT

Internal sources

- University of Cape Town, Cape Town, South Africa.
- MRC Research Unit on Anxiety and Stress Disorders, Cape Town, South Africa.

External sources

- MRC Research Unit on Anxiety and Stress Disorders, Cape Town, South Africa.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We removed the third objective stated in the protocol, namely to assess whether depression is a predictor of treatment response in the prevention of PTSD, from the review, as it taps into risk rather than preventative factors for the onset of PTSD.

The timing of the outcome event was not made explicit in the protocol for the review. It has now been stated in the text that for studies that assessed outcomes at multiple time points (Delahanty 2012; Hoge 2012; Pitman 2002; Shalev 2012; Stein 2007; Zohar 2011a), we synthesised data at the first time point that was consistent with chronic PTSD, in which the assessment occurred after at least three months after the index traumatic event.

The original protocol imposed an age range criterion for eligible studies of 18 to 65 years. We decided to remove the restriction on the maximum age of the sample, as this allowed us to include data from a number of studies that would otherwise have been excluded (Schelling 2001; Weis 2006). While medications might be expected to metabolise at a different rate in paediatric samples, there is no evidence that PTSD is less likely to occur in populations over 65 years of age than in middle age, or that the effects of medication in this older age group will differ substantially from younger adults.

The original protocol described comparisons between medication and placebo arms, as well as alternative 'standard' medication therapy. The review was restricted to placebo-controlled studies, as we only found one placebo-controlled RCT that included an active medication control arm (Stein 2007).

We have moved treatment acceptability from a secondary to a primary outcome for this review. This is in keeping with recommendations within the *Cochrane Handbook for Systematic Reviews of Interventions* that primary outcomes of a review should include negative as well as positive outcomes (Section 4.5) (Higgins 2011a), and in recognition that side effects are particularly salient when considering prophylactic studies.

Clinical response to treatment was included as a secondary outcome in the original protocol, as assessed using the Clinical Global Impressions Scale - Improvement Item (Guy 1976) or related scales. In light of the tendency of studies to report reductions in PTSD symptom severity instead of more general responses to treatment, we have instead replaced this outcome in the review with reductions in PTSD symptom severity (as assessed using scales such as the CAPS and the PTSS-10).

Heterogeneity of treatment response and symptom severity was not assessed by means of Deeks' stratified test of heterogeneity (Deeks 2001), as planned in the original protocol, nor was this assessed visually from the forest plot of relative risk, given the small number of studies. We did not conduct planned subgroup analyses to assess the extent to which the primary outcomes were affected by (a) source of trial funding, (b) whether trials were conducted at a single centre or across multiple centres, or (c) whether depressed individuals were included in the sample, for the same reason.

We have expanded the list of medication categories under Types of interventions to include beta-blockers, to account for the large number of studies assessing the efficacy of propranolol in preventing the onset of PTSD.

In the protocol it was stated that treatment efficacy of medication in preventing PTSD would be determined using the number of cases diagnosed according to DSM criteria. In the review we decided to broaden this outcome to include data from studies assigning a probable diagnosis of PTSD using the Posttraumatic Stress Symptom 10 Questionnaire Inventory (PTSS-10), as this measure has demonstrated moderate to high (77%) sensitivity and excellent (97.5%) specificity in diagnosing clinically confirmed cases of PTSD (Weisaeth 1989).

The small number of participants in the included studies in this review means that evidence of outcome data that are not normally distributed might be particularly problematic. There was no procedure in place in the protocol to address skewed data. We have now added a description of such a procedure to the data synthesis component of the methods section. In addition, we have indicated that we intend to obtain individual patient data (where possible) for the purpose of normalising the data by means of log transformation techniques in future updates of the review.

We computed Hedges' g effect size estimate and 95% confidence intervals where study results for the PTSD symptom reduction outcome were described as part of a narrative review. Although not originally part of the protocol, we added this to the review to aid interpretability, as per the recommendation provided as part of editorial feedback on a draft version of the review.

We added to the review a sensitivity analysis to detect the influence of using the ITT sample as the denominator in calculating risk ratios for the primary outcome of PTSD prevention, rather than the observed cases sample that was reported in the study publications, based on feedback provided by an anonymous reviewer of the manuscript for the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic beta-1 Receptor Antagonists [therapeutic use]; Amines [therapeutic use]; Anti-Anxiety Agents [therapeutic use]; Anti-Inflammatory Agents [therapeutic use]; Antidepressive Agents, Second-Generation [therapeutic use]; Citalopram [therapeutic use]; Cyclohexanecarboxylic Acids [therapeutic use]; Gabapentin; Hydrocortisone [therapeutic use]; Propranolol [therapeutic use]; Randomized Controlled Trials as Topic; Stress Disorders, Post-Traumatic [*prevention & control]; Temazepam [therapeutic use]; gamma-Aminobutyric Acid [therapeutic use]

MeSH check words

Adult; Aged; Humans; Middle Aged; Young Adult