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[Intervention Review]

Early pharmacological interventions for prevention of post-traumatic stress disorder (PTSD) in individuals experiencing acute traumatic stress symptoms

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ABSTRACT

Background

Acute traumatic stress symptoms may develop in people who have been exposed to a traumatic event. Although they are usually self-limiting in time, some people develop post-traumatic stress disorder (PTSD), a severe and debilitating condition. Pharmacological interventions have been proposed for acute symptoms to act as an indicated prevention measure for PTSD development. As many individuals will spontaneously remit, these interventions should balance efficacy and tolerability.

Objectives

To assess the efficacy and acceptability of early pharmacological interventions for prevention of PTSD in adults experiencing acute traumatic stress symptoms.

Search methods

We searched the Cochrane Common Mental Disorders Controlled Trial Register (CCMDCTR), CENTRAL, MEDLINE, Embase and two other databases. We checked the reference lists of all included studies and relevant systematic reviews. The search was last updated on 23 January 2023.

Selection criteria

We included randomised controlled trials on adults exposed to any kind of traumatic event and presenting acute traumatic stress symptoms, without restriction on their severity. We considered comparisons of any medication with placebo, or with another medication. We excluded trials that investigated medications as an augmentation to psychotherapy.

Data collection and analysis

We used standard Cochrane methodological procedures. Using a random-effects model, we analysed dichotomous data as risk ratios (RR) and calculated the number needed to treat for an additional beneficial/harmful outcome (NNTB/NNTH). We analysed continuous data as

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mean differences (MD) or standardised mean differences (SMD). Our primary outcomes were PTSD severity and dropouts due to adverse events. Secondary outcomes included PTSD rate, functional disability and quality of life.

Main results

We included eight studies that considered four interventions (escitalopram, hydrocortisone, intranasal oxytocin, temazepam) and involved a total of 779 participants. The largest trial contributed 353 participants and the next largest, 120 and 118 participants respectively. The trials enrolled participants admitted to trauma centres or emergency departments. The risk of bias in the included studies was generally low except for attrition rate, which we rated as high-risk. We could meta-analyse data for two comparisons: escitalopram versus placebo (but limited to secondary outcomes) and hydrocortisone versus placebo.

One study compared escitalopram to placebo at our primary time point of three months after the traumatic event. There was inconclusive evidence of any difference in terms of PTSD severity (mean difference (MD) on the Clinician-Administered PTSD Scale (CAPS, score range 0 to 136) -11.35, 95% confidence interval (CI) -24.56 to 1.86; 1 study, 23 participants; very low-certainty evidence), dropouts due to adverse events (no participant left the study early due to adverse events; 1 study, 31 participants; very low-certainty evidence) and PTSD rates (RR 0.59, 95% CI 0.03 to 13.08; NNTB 37, 95% CI NNTB 15 to NNTH 1; 1 study, 23 participants; very low-certainty evidence). The study did not assess functional disability or quality of life.

Three studies compared hydrocortisone to placebo at our primary time point of three months after the traumatic event. We found inconclusive evidence on whether hydrocortisone was more effective in reducing the severity of PTSD symptoms compared to placebo (MD on CAPS -7.53, 95% CI -25.20 to 10.13; I^2 = 85%; 3 studies, 136 participants; very low-certainty evidence) and whether it reduced the risk of developing PTSD (RR 0.47, 95% CI 0.09 to 2.38; NNTB 14, 95% CI NNTB 8 to NNTH 5; I^2 = 36%; 3 studies, 136 participants; very low-certainty evidence). Evidence on the risk of dropping out due to adverse events is inconclusive (RR 3.19, 95% CI 0.13 to 75.43; 2 studies, 182 participants; low-certainty evidence) and it is unclear whether hydrocortisone might improve quality of life (MD on the SF-36 (score range 0 to 136, higher is better) 19.70, 95% CI -1.10 to 40.50; 1 study, 43 participants; very low-certainty evidence). No study assessed functional disability.

Authors' conclusions

This review provides uncertain evidence regarding the use of escitalopram, hydrocortisone, intranasal oxytocin and temazepam for people with acute stress symptoms. It is therefore unclear whether these pharmacological interventions exert a positive or negative effect in this population. It is important to note that acute traumatic stress symptoms are often limited in time, and that the lack of data prevents the careful assessment of expected benefits against side effects that is therefore required.

To yield stronger conclusions regarding both positive and negative outcomes, larger sample sizes are required. A common operational framework of criteria for inclusion and baseline assessment might help in better understanding who, if anyone, benefits from an intervention. As symptom severity alone does not provide the full picture of the impact of exposure to trauma, assessment of quality of life and functional impairment would provide a more comprehensive picture of the effects of the interventions. The assessment and reporting of side effects may facilitate a more comprehensive understanding of tolerability.

PLAIN LANGUAGE SUMMARY

Medicines to prevent post-traumatic stress disorder for people with acute traumatic stress symptoms

Key messages

- Acute stress symptoms are common after a traumatic experience. They are usually time-limited. However, for some people, they may persist or progress to a condition known as post-traumatic stress disorder (PTSD). Medicines have been proposed to prevent later PTSD.

- We found data for four medicines: escitalopram, an antidepressant; hydrocortisone, a hormone that reduces the immune response and is involved in the body's response to stress; oxytocin, a hormone that could lessen the response to stress; and temazepam, a drug used to reduce anxiety. They were all compared to placebo (dummy pills).

- For all the medicines, it is unclear if they have an effect on the probability of having PTSD, on the severity of PTSD or any harmful effects.

What are acute stress symptoms?

Individuals who have experienced a traumatic event may exhibit psychological symptoms, also known as acute traumatic stress symptoms, shortly after the event. These symptoms include intrusive memories or nightmares, an inability to feel positive emotions, an altered sense of reality, efforts to avoid distressing memories or reminders of the traumatic event, sleep disturbances and being in a state of heightened alertness to possible threats.

Why are they important for post-traumatic stress disorder?

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Acute traumatic stress symptoms often go away with time, but for some individuals they persist or worsen until they develop the condition PTSD. PTSD can have a debilitating effect on the lives of those affected and their loved ones.

What did we want to find out?

For people exposed to a traumatic event and who have acute traumatic stress symptoms, are medicines more effective than placebo (dummy pills) or other medicines in:

- reducing the severity of symptoms of PTSD?
- reducing the number of people that stop taking the medication because they have side effects?
- reducing the probability of developing PTSD?
- reducing the repercussions on the activities of daily living?

What did we do?

We searched scientific databases for studies in which adult participants were randomly assigned to a medicine for acute traumatic stress symptoms. We considered any kind of traumatic event.

We compared and summarised the studies according to the medicine they used, and rated our confidence in the evidence, based on factors such as study methods and sizes. We considered data collected at three months after the people experienced the traumatic event for the main results, as this is a critical time for clinicians and patients to decide on treatment if symptoms have progressed to PTSD.

What did we find?

We included eight studies, involving 779 participants. The studies took place in trauma centres and emergency departments. The studies considered four medications: escitalopram, an antidepressant; hydrocortisone, a hormone that reduces the immune response and is involved in the body's response to stress; oxytocin, a hormone that could lessen the response to stress; and temazepam, a drug used to reduce anxiety. They were all compared to placebo.

What did the evidence tell us?

Based on three studies, we do not know if hydrocortisone compared to placebo has an effect on the severity of PTSD symptoms, the number of people who have PTSD, quality of life or the risk of stopping the medication because of side effects. We found only one study with data on escitalopram, and we do not know its effect on PTSD severity, the number of people stopping the medication because of side effects or the number of people with PTSD. Similarly, we found only one study with data on intranasal oxytocin, with inconclusive evidence of an effect on PTSD severity. The study on temazepam did not collect data at three months after the traumatic event.

What are the limitations of the evidence?

We have little or very little confidence in the evidence because the studies were few and small.

How up-to-date is this evidence?

The evidence is up-to-date to January 2023.

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SUMMARY OF FINDINGS

Summary of findings 1. Escitalopram compared to placebo for the prevention of PTSD in individuals experiencing acute traumatic stress symptoms

Escitalopram compared to placebo for prevention of PTSD in individuals experiencing acute traumatic stress symptoms

Patient or population: adults experiencing acute traumatic stress symptoms
Setting: emergency departments
Intervention: escitalopram
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with escitalopram				
PTSD severity at 3 months	The mean PTSD severity at 3 months was 23.73 on the CAPS	MD 11.35 lower on the CAPS (24.56 lower to 1.86 higher)	-	23 (1 RCT)	⊕⊖⊖⊖ Very low[a,b]	-
Dropouts due to adverse events at 3 months	Study population		Not estimable	31 (1 RCT)	⊕⊖⊖⊖ Very low[a,c]	-
	0 per 1000	0 per 1000 (0 to 0)				
PTSD rate at 3 months	Study population		RR 0.59 (0.03 to 13.08)	23 (1 RCT)	⊕⊖⊖⊖ Very low[a,d]	-
	67 per 1000	39 per 1000 (2 to 872)				
Functional disability at 3 months - not measured	-	-	-	-	-	-
Quality of life at 3 months - not measured	-	-	-	-	-	-

*__The risk in the intervention group__ (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; **MD**: mean difference; **PTSD**: post-traumatic stress disorder; **RCT**: randomised controlled trial; **RR**: risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

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Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for high risk of attrition bias in the included studies.
[b]Downgraded two levels for imprecision as far fewer than 400 participants have been included.
[c]Downgraded two levels for imprecision because the optimal sample size is not met as the number of participants is very small.
[d]Downgraded two levels for imprecision as the optimal sample size is not met, and the CI includes both appreciable benefit and harm.

Summary of findings 2. Hydrocortisone compared to placebo for prevention of PTSD in individuals experiencing acute traumatic stress symptoms

Hydrocortisone compared to placebo for prevention of PTSD in individuals experiencing acute traumatic stress symptoms

Patient or population: adults experiencing acute traumatic stress symptoms
Setting: emergency department/trauma unit patients
Intervention: hydrocortisone
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with hydrocortisone				
PTSD severity at 3 months	The mean PTSD severity at 3 months was 25.68 on the CAPS	MD 7.53 lower on the CAPS (25.2 lower to 10.13 higher)	-	136 (3 RCTs)	⊕⊖⊖⊖ Very low[a,b,c]	-
Dropouts due to adverse events at 3 months	Study population		RR 3.19 (0.13 to 75.43)	182 (2 RCT)	⊕⊕⊖⊖ Low[d]	-
	0 per 1000	0 per 1000 (0 to 0)				
PTSD rate at 3 months	Study population		RR 0.47 (0.09 to 2.38)	136 (3 RCTs)	⊕⊖⊖⊖ Very low[a,d]	-
	138 per 1000	65 per 1000 (12 to 330)				
Functional disability at 3 months - not measured	No study reported this outcome		-	-	-	-

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Quality of life at 3 months	The mean quality of life at 3 months was 28.3 on the SF-36 general health scale	MD 19.7 higher on the SF-36 general health scale (1.1 lower to 40.5 higher)	-	43 (1 RCT)	⊕⊖⊖⊖ Very low[c,e]	-

*__The risk in the intervention group__ (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; **SF-36**: Short-Form Health Survey; **MD**: mean difference; **PTSD**: post-traumatic stress disorder; **RCT(s)**: randomised controlled trial(s); **RR**: risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for high risk of attrition bias in the included studies.
[b]Downgraded one level for inconsistency as there is a rather wide difference in the point estimates of effect among the included studies.
[c]Downgraded two levels for imprecision as far fewer than 400 participants have been included, and the CI includes both appreciable benefit and harm.
[d]Downgraded two levels for imprecision as the optimal sample size is not met, and the CI includes both appreciable benefit and harm.
[e]Downgraded one level for high risk of attrition bias in the included study.

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BACKGROUND

Description of the condition

Acute traumatic stress symptoms are psychological manifestations that can precipitate in individuals exposed to traumatic events. Experiences that entail a threat, actual or perceived, to life or physical integrity are generally recognised as possible traumatic events. According to the description of acute stress disorder (ASD) and post-traumatic stress disorder (PTSD) in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5), potentially traumatic events "include, but are not limited to, exposure to war as a combatant or civilian, threatened or actual physical assault, threatened or actual sexual violence, being kidnapped, being taken hostage, terrorist attack, torture, incarceration as a prisoner of war, natural or human-made disasters, and severe motor vehicle accidents" (APA 2013). With some limitations regarding the nature of the traumatic incident, witnessing a trauma, learning that a relative or close friend was exposed to trauma, or being exposed to aversive details about a trauma (as in the course of professional duties) may also constitute a traumatic event. As stated by the DSM-5, this list is not comprehensive and many different traumatic events have proved capable of precipitating traumatic stress symptoms.

There is currently some complexity in the definition of acute traumatic stress symptoms. The two main mental health classification systems have many similarities in defining the manifestations of psychological distress that occur in the period after a traumatic experience. However, they differ in how they frame their timing. The DSM-5 describes acute stress symptoms in the context of acute stress disorder, an entity that can only be diagnosed when a certain number of symptoms are present, when there are significant limitations in functioning, and in the period between three days and one month after the traumatic event. The symptoms recognised by the DSM-5 are grouped into five categories (APA 2013):

- **Intrusion symptoms**: recurrent unwanted intrusive memories, distressing dreams, dissociative reactions as flashbacks, psychological distress at cues that symbolise or resemble the traumatic event.
- **Negative mood**: inability to experience positive emotions.
- **Dissociative symptoms**: an altered sense of reality, inability to remember an important aspect of the traumatic event.
- **Avoidance symptoms**: efforts to avoid distressing memories, thoughts or feelings related to the traumatic event, or efforts to avoid external reminders of the traumatic event.
- **Arousal symptoms**: sleep disturbance, irritability, hypervigilance, problems concentrating, exaggerated startle response.

Previously, DSM-IV-TR also put a different emphasis on dissociation symptoms (APA 2000).

The International Classification of Diseases, 11th revision (ICD-11) includes the manifestations of psychological distress following a traumatic event in the category of acute stress reaction (ASR), which, unlike ASD in the DSM-5, is a non-diagnosable entity that covers the days immediately following the traumatic event (WHO 2019). ASR is self-limited and usually resolves within a week or a month in the case of prolonged traumatic events. The psychological manifestations listed are similar to those in the DSM-5.

Beyond the differences in classification systems, manifestations of psychological distress following a traumatic event are common and usually temporary. However, some people continue to experience symptoms of acute stress and may develop ASD in the short term, or PTSD if symptoms are present for more than a month after the traumatic event. It should be noted that while individuals with ASD have a high risk of progressing to PTSD, the majority of individuals with PTSD did not previously meet all of the ASD diagnostic criteria (Bryant 2011). Acute traumatic stress symptoms are therefore relevant for two reasons: because they are distressing in themselves, and because they can be a target for indicated prevention of PTSD, a severe and debilitating disorder.

Factors leading to PTSD development are complex and not fully understood, but it is clear that multiple and interconnected systems are involved (Kelmendi 2016; Koch 2014; Lee 2016; Pitman 2012), with the contribution of biological and psychological mechanisms (Besnard 2012; Nickerson 2013).

Description of the intervention

Interventions for acute traumatic stress symptoms can be divided into two main categories, psychological and pharmacological: this review will focus on the latter. Psychological and pharmacological interventions can be combined and there are several reviews that have addressed early psychosocial interventions (Bryant 2007; Kearns 2012; Qi 2016; Roberts 2019).

With respect to pharmacological interventions for acute traumatic stress symptoms, randomised controlled trials (RCTs) have investigated drugs belonging to different classes. This is because researchers have investigated both those interventions employed in PTSD treatment and those regarded as possibly effective on the basis of knowledge about the development and maintenance of traumatic memories and post-traumatic symptoms. Previous meta-analyses on PTSD prevention, which included early interventions in people with acute traumatic stress symptoms, reported medications belonging to the following drug classes (Amos 2014; Astill Wright 2019; Sijbrandij 2015):

- Glucocorticoids are synthetic analogues of cortisol, a hormone involved in immunity and stress response. Glucocorticoids can be administered in several ways, including orally, intravenously and intramuscularly. Trials testing steroids for PTSD prevention have used either single-dose administration or a course of a few days in individuals with severe physical conditions (Delahanty 2013; Schelling 2001; Weis 2006). Hydrocortisone, along with some other steroids, is also included in the World Health Organization (WHO) Model List of Essential Medicines (WHO 2017), and is therefore expected to be commonly available in several global contexts.
- Beta-blockers are medications that exert a competitive antagonism towards endogenous catecholamines by binding to the beta adrenergic receptors. Beta-blockers' main employment is in cardiology; however, some trials have tested propanolol on a three-week time span for PTSD prevention (Hoge 2012; Pitman 2002; Stein 2007). Propranolol is also included in the WHO Model List of Essential Medicines (WHO 2017).
- Benzodiazepines are minor tranquillisers which, by binding to the $GABA_A$ receptor, enhance the anxiolytic effects of the

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neurotransmitter gamma-aminobutyric acid (GABA). A small trial has investigated a short course of temazepam, but found an increase in PTSD onset rather than a decrease (Mellman 2002).

- Oxytocin is a pituitary hormone with roles in sociability and stress regulation, as well as its more widely known role in childbirth (Qi 2016). It can also be administered as a medication, and a trial has investigated oxytocin administered as a single intranasal dose as early intervention (van Zuiden 2017).
- Selective serotonin reuptake inhibitors (SSRIs) are drugs mostly employed in depressive and anxious disorders. SSRIs have yielded good results in PTSD treatment, but there is uncertainty about whether they are effective in reducing the incidence of PTSD (Shalev 2012; Zohar 2018).
- Mood stabilisers/anticonvulsants are a broad group of drug agents with effects in treating/preventing seizures. Some of them are effective in bipolar disorder and have anxiolytic properties. The anticonvulsant gabapentin has been included in trials of PTSD prevention (Stein 2007).
- Opioids are primarily employed in pain relief, but they have been proposed for PTSD after a large retrospective study on US soldiers with combat injury found an association between morphine administration and lower later PTSD incidence (Holbrook 2010).
- Omega-3 fatty acids are essential fatty acids that humans are unable to synthesise de novo. They have been the subject of investigation with regard to their potential role in depressive and anxiety symptoms (Matsuoka 2011).

How the intervention might work

The biological mechanisms underlying PTSD provide several possible targets. Different rationales can potentially explain the efficacy of the investigated drugs.

Glucocorticoids

Glucocorticoids are involved in both hormonal stress response and memory formation. The hypothalamic-pituitary-adrenal (HPA) axis has been a long-time focus in the field of PTSD and a role for hydrocortisone in facilitating extinction learning has been hypothesised (Hruska 2014). In a rodent model, a negative association has been found between a high dose of steroids and prevalence of PTSD-like behaviour in rats exposed to predator scent stress (Cohen 2008), and consistent results were found in a morphological study (Zohar 2011). There is also epidemiological evidence that lower urinary cortisol levels in the immediate aftermath of trauma are associated with future PTSD symptoms (Delahanty 2000; McFarlane 1997).

Beta-blockers

A role for adrenaline in the formation of traumatic memories has long been postulated (Pitman 1989; Ressler 2020). It has been argued that a surge in adrenaline concentration, in conjunction with trauma, results in a strong emotional memory and fear conditioning that could prime PTSD. Later human studies supported a role for the beta adrenergic system in memory storing and in the enhanced memories associated with emotional arousal (Cahill 1994; Southwick 1999), and for propranolol to limit this process (Reist 2001).

Benzodiazepines

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

Opioids

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

Oxytocin

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

SSRIs

SSRI antidepressants are generally considered the first-line pharmacological treatment for PTSD (ISTSS 2018; NICE 2018; Stein 2006), and might thereby have a putative role in the prevention of the disorder. SSRIs enhance serotonergic neurotransmission by inhibiting the re-uptake of serotonin from the synapsis as mediated by the SERT transporter (Leonard 2000). Further downstream mechanisms are likely responsible for the beneficial effects of SSRIs, as these effects develop only after a few weeks of treatment. An increased expression of the specific downstream genes is currently supposed to induce dendritic spine formation, synaptogenesis and neurogenesis (Licznerski 2013; Santarelli 2003).

Mood stabilisers/anticonvulsants

As for SSRIs, mood stabilisers/anticonvulsants might have a putative role in PTSD prevention, considering their employment as adjuvant/second-line treatment for anxiety disorders (Van Ameringen 2004), and a trial of gabapentin has been reported in a previous meta-analysis of PTSD prevention (Stein 2007). Gabapentin administration increases the release of the neurotransmitter GABA from brain glial cells (Lydiard 2003). Imbalances in the GABAergic system have been reported in people with PTSD and other anxiety disorders (Meyerhoff 2014).

Omega-3 fatty acid compounds

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

Why it is important to do this review

Up to 80% of the adult population in the USA have been exposed to a possible traumatic event (Breslau 2012), and estimates are similar for Europe (de Vries 2009). Acute traumatic stress symptoms can

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progress to ASD and, more importantly from a prognostic point of view, to PTSD. Despite the abundance of clinical and putative biological risk factors for PTSD and various predictive strategies being tested (Galatzer-Levy 2014; Karstoft 2015; Kessler 2014), in clinical practice there is currently no effective way to predict who will develop PTSD after a traumatic experience. In addition to the affliction from acute traumatic stress symptoms, PTSD represents a heavy burden for the people affected, those around them, health systems and society. Data from the World Health Organization World Mental Health Survey Initiative show the 12-month prevalence of PTSD to be 1.1% and the lifetime prevalence to be 3.9% (Karam 2014; Koenen 2017). Prevalence rates in displaced populations (Bogic 2015; Turrini 2017), and populations exposed to conflict (Steel 2009), are even higher. Moreover, PTSD is associated with poor general health status and unemployment (Zatzick 1997).

Early pharmacological interventions for acute traumatic stress symptoms may serve in both acute symptom relief and as indicated prevention of PTSD. It is thus relevant to assess these interventions in terms of PTSD symptoms. Investigating these interventions is also relevant because the risk-to-benefit ratio needs to be carefully assessed: drugs will entail possible side effects for all those receiving them, while for some people acute traumatic stress symptoms are self-limiting.

OBJECTIVES

To assess the efficacy and acceptability of early pharmacological interventions for prevention of PTSD in adults experiencing acute traumatic stress symptoms.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) comparing one medication with placebo or one medication with another. We considered trials for inclusion irrespective of language or publication status. We found no cross-over trials, for which we had planned to consider the first randomised phase only. We did not consider quasi-random methods of allocation (such as alternation, date of birth or case record number) to be eligible.

Types of participants

Individuals

We included trials on individuals with all of the following characteristics.

- History of any traumatic event
- Presenting acute traumatic stress symptoms, without restriction on their severity
- Aged 18 and older

We have excluded from this review trials not targeting symptomatic patients after exposure to traumatic events. These trials have been included in a parallel review on universal PTSD prevention (Bertolini 2022).

Setting

We considered trials performed in any type of setting.

Subset data

We planned to include trials in which only a portion of the sample meets the above criteria, provided that the relevant data could be gained from the study report or by contacting the authors, and that the effect of randomisation was not affected by doing so. We did not find studies that allowed this.

Types of interventions

We considered any pharmacological intervention administered with the intention of treating acute traumatic stress symptoms or preventing the onset of PTSD or PTSD symptoms within a period of three months from the trauma, as the DSM-5 regards this timing as relevant for the evolution of symptoms into PTSD (APA 2013). We have set no restriction regarding dose, duration or administration route of the intervention, nor on the presence of any co-medication not related to traumatic stress symptoms. We have not considered trials where the experimental medication was used as an augmentation agent to ongoing psychotherapy (e.g. cognitive enhancers).

Based on our knowledge of the literature, we expected to find drugs from the following pharmacological groups.

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

Types of comparison

We included studies using both placebo and any active pharmacological comparison. We have not considered studies comparing pharmacological interventions with only psychosocial interventions (i.e. with no other pharmacological or placebo arm).

We included studies that met the above criteria, irrespective of whether they reported any of our outcomes of interest.

Types of outcome measures

Primary outcomes

1. **PTSD severity (continuous)**: using the mean score on a validated rating scale such as the Clinician-Administered PTSD Scale (CAPS) (Blake 1995), or the Posttraumatic Stress Disorder Checklist (PCL) (Weathers 2001), the Comprehensive International Diagnostic Interview (CIDI) (WHO 1997), or any other validated rating scale to assess symptom severity.
2. **Dropouts due to adverse events (dichotomous)**: we considered the number of participants who left the assigned arms early due to side effects, out of the number of randomised individuals.

Secondary outcomes

1. **PTSD rate (dichotomous)**: we considered PTSD rates, as measured by a DSM or International Classification of Diseases (ICD) defined diagnosis made with a clinician-administered measure.

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2. **Depression severity (continuous)**: we considered the severity of depressive symptoms, using the score on validated scales such as the MADRS (Montgomery 1979), or the Hamilton Depression Rating Scale (Hamilton 1960), or the Beck Depression Inventory (Beck 1961), or any other validated scale.
3. **Anxiety severity (continuous)**: we considered the severity of the anxiety symptoms using the score on validated scales such as the Covi Anxiety Scale (CAS) (Covi 1984), or the Beck Anxiety Inventory (Beck 1988), or the Spielberger State-Trait Anxiety Inventory (Spielberger 1970), or the Hamilton Anxiety Rating Scale (Hamilton 1959), or any other validated scale.
4. **Functional disability (continuous)**: we considered validated scales such as the Sheehan Disability Scale (Sheehan 1996), or any other validated scale.
5. **Quality of life (continuous)**: we considered validated scales such as the Medical Outcomes Study (MOS) 36-Item Short-Form Health Survey (SF-36) (Ware 1992), or any other validated scale to assess quality of life.
6. **Dropouts for any reason (dichotomous)**: we considered the number of participants who leave the assigned arms early for any reason, out of the number of randomised individuals.

Hierarchy of outcome measures

The hierarchy of outcome measure scales has followed the order above. As we expected that clinician-administered scales would be more frequently employed, in the case of trials employing validated scales that are different from those mentioned above, for homogeneity reasons we have given priority to clinician-administered scales over self-reported ones.

Timing of outcome measures

We have synthesised data at three months after exposure to the traumatic event, operationalised as the time point closest to three months of follow-up (from two to four months of follow-up). In addition, we have included data at study endpoint as a secondary time point.

Search methods for identification of studies

We used the same search strategy as that used for the Cochrane review of early pharmacological interventions for preventing post-traumatic stress disorder (Bertolini 2022).

Specialised register: the Cochrane Common Mental Disorders Controlled Trials Register (CCMDCTR)

Cochrane Common Mental Disorders (CCMD) maintained a specialised register of randomised controlled trials (RCTs), the CCMDCTR, to June 2016. This register contains over 40,000 reference records (reports of RCTs) for anxiety and depressive disorders, bipolar disorder, eating disorders, self-harm and other mental disorders within the scope of CCMD. The CCMDCTR is a partially studies-based register, with more than 50% of the reference records tagged to 12,600 study records, individually coded for participant, intervention, comparison and outcome (PICO). Reports of trials for inclusion in the register were collated from (weekly) generic searches of MEDLINE (1950-), Embase (1974-) and PsycINFO (1967-), quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and review-specific searches of additional databases. Reports of trials were also sourced from international trial registries, drug companies, handsearching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses. An example of the CCMD core search strategy for MEDLINE can be found in Appendix 1.

The CCMD trials register fell out of date with the relocation of the group from the University of Bristol to York University in June 2016.

Electronic searches

CCMDCTR-studies and references register

We have cross-searched the CCMDCTR studies and references register for condition alone, using the following terms:

(*PTSD or posttrauma* or post-trauma* or "post trauma*" or "combat disorder*" or "stress disorder**") (all years to June 2016).

Biomedical database search

To account for the period after the CCMDCTR fell out-of-date, the CCMD Information Specialists conducted additional searches in the following bibliographic databases, using relevant subject headings (controlled vocabularies) and search syntax, appropriate to each resource (see Appendix 2 for details of the search strategy).

- Cochrane Central Register of Controlled Trials (CENTRAL 2023, Issue 1) in the Cochrane Library (June 2016 to 23 January 2023);
- MEDLINE Ovid (June 2016 to 23 January 2023);
- Embase Ovid (June 2016 to 23 January 2023);
- PsycINFO Ovid (June 2016 to 23 January 2023);
- Published International Literature On Traumatic Stress (PILOTS) EBSCO (June 2016 to 23 January 2023).

The search was designed for all of the reviews on PTSD within the scope of CCMD. After deduplication, at least two members of the CCMD editorial base staff screened the search results in Covidence (see Appendix 2 for inclusion and exclusion criteria applied at this stage). A first search was run in March 2018, with updates in March 2019 and November 2020 (see Appendix 2). Due to changes in the editorial CCMD group, the last update on 23 January 2023 was run by an Information Specialist (HF) with near identical search strategies but with some minor changes that were made to the strategy for CENTRAL to accommodate changes in how the database reads search terms (see Appendix 3). As Wolters Kluwer later informed of a data processing issue that affected the Ovid database starting 23 January, the Ovid Embase search was re-run on 23 February 2023 using the fix provided by Wolters Kluwer. See Appendix 3 for details of the search strategy for this update. The Cochrane Central Register of Controlled Trials (CENTRAL) comprises records retrieved from PubMed/MEDLINE, Embase, ClinicalTrials.gov, WHO ICTRP, all Cochrane Review Groups' Specialised Registers and records identified by handsearching various biomedical sources.

Searching other resources

We checked the reference lists of all included studies and relevant systematic reviews.

Data collection and analysis

Selection of studies

We imported all records obtained via the electronic search, plus the handsearch, into Endnote software (EndNote) in order to remove

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all duplicates. Three review authors (FB, LR and GO) worked in duplicate and independently. We screened the titles and abstracts of all potential papers and coded them as 'retrieve' or 'not retrieve', obtained the full-text publication of the records coded as 'retrieve', and assessed the inclusion and exclusion criteria. We resolved any disagreements through discussion or, if necessary, by involving a third review author (NM).

Data extraction and management

Three review authors (FB, LR and GO), working independently and in duplicate, extracted data from the included trials. We used a data extraction sheet developed in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (hereafter referred to as the *Cochrane Handbook*), section 7.5 (Higgins 2011a). We based the extraction sheet on the one we used for the parallel review (Bertolini 2022), and piloted it on one trial. We collected the following data:

- First author, year of publication, journal, source of funding, notable conflict of interest of authors, total duration of study, number of centres and location.
- Methodological characteristics of the trial: randomisation, blinding, allocation concealment, number of arms, follow-up time points.
- Sample characteristics: study setting, type of traumatic event, criteria for enrolling, age, gender, number of participants randomised to each arm, baseline acute traumatic stress symptoms, history of previous trauma.
- Intervention details: time from the traumatic event to treatment, medication employed, period over which it has been administered, dosage range, mean dosage prescribed.
- Outcomes: time points of outcome assessment, instrument used to assess PTSD symptoms, instrument used to assess PTSD rate, instrument used to assess depression symptoms, instrument used to assess anxiety, instrument used to assess functional disability, outcome measure employed by original trial (primary and secondary), data for continuous (means and standard deviation or standard error if standard deviation is not provided) and dichotomous variables of interest, number of total dropouts, number of dropouts due to pharmacological side effect, whether the data reflect an intention-to-treat (ITT) model, methods of estimating the outcome for participants who dropped out (last observation carried forward (LOCF) or completer/observed case (OC) approach, or other).

We resolved disagreements by consensus or by involving a fourth author (CB). We would have sought assistance from Cochrane Common Mental Disorders for studies that required translation.

Assessment of risk of bias in included studies

Three review authors (FB, LR and GO), working independently and in duplicate, assessed the risk of bias for each study according to the criteria outlined in the *Cochrane Handbook* (Higgins 2011b). We resolved disagreements through discussion or, if necessary, by involving a third review author (NM). We have assessed the risk of bias according to the following domains:

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

We have rated each source of bias as high, low or unclear, with reasons to justify the rating.

Dichotomous data

For dichotomous data, we have calculated risk ratio (RR) estimates and their 95% confidence interval (CI). RRs are more easily interpreted than odds ratios (ORs) (Boissel 1999), and as there is a risk clinicians may interpret ORs as RRs (Deeks 2002), this may lead to an overestimation of the effect. We also calculated the number needed to treat for an additional beneficial/harmful outcome (NNTB/NNTH).

Continuous data

For continuous data, we have calculated mean differences (MDs) and their 95% CI, where data were measured on the same scale. For studies that employed different scales, we have used standardised mean differences (SMDs). We gave preference to endpoint measures, considering the nature of the review (prevention) and that endpoint data are easier to interpret from a clinical point of view. In the case of reporting of change score measures only, we had planned, if sufficient data had been reported, to convert change scores into endpoint data using the standard formulas reported in the *Cochrane Handbook* (Deeks 2011), but this was unnecessary.

Cross-over trials

We included no cross-over trials in this review. For this design, we had planned to consider only the first phase, as the carry-over effect cannot be excluded for a prevention measure, regardless of appropriate washout times.

Cluster-randomised trials

We found no cluster-randomised trials eligible for inclusion in this review. For eligible cluster-RCTs that had not appropriately adjusted for the correlation between participants within clusters, we had planned to contact trial authors to obtain an estimate of the intracluster correlation coefficient (ICC), or to impute using estimates from the other included trials or from similar external trials. We planned to conduct a sensitivity analysis in the case of imputation of ICCs to examine the impact on estimates.

Multiple treatment groups studies

We compared each arm with placebo separately and included each pair-wise comparison separately. In the case of pooling different interventions together, we had planned the following methods to prevent 'double-counting', in accordance with the *Cochrane Handbook*, section 16.5.4 (Higgins 2011c). In the case of dichotomous variables, we would split the comparison group evenly amongst the intervention groups; in the case of continuous variables, we would only divide the total number of participants and leave the mean and standard deviations (SDs) unchanged.

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Dose-ranging studies

We did not include studies with multiple arms with the same medication administered at different doses or for a different length of time. For these trials, we had planned to pool these intervention groups into a single one, as recommended by the *Cochrane Handbook*, section 16.5.4 (Higgins 2011c).

Dealing with missing data

As a first measure, we tried to contact study investigators to obtain missing data. When this was unsuccessful, we employed the following approaches.

Dichotomous data

We planned to use ITT data analysed on a 'once randomised, always analysed' basis, and for studies that did not perform an ITT analysis, to assume a negative outcome (i.e. onset of PTSD) for individuals lost to follow-up. However, given the high attrition rates of some trials and that none used ITT analyses, we felt that this approach risked estimates being further distant from the true value. Therefore, we decided to consider the number of participants with the event divided by the number of analysed participants (i.e. 'observed cases'), and we added a sensitivity analysis with the number of participants with the event divided by the number of randomised participants.

Continuous data

We used ITT data when reported, favouring multiple imputations or mixed-effects models where different imputation strategies had been used. In the context of prevention, last observation carried forward (LOCF) provides the least conservative option and therefore observed cases (OC) were preferred. For studies not reporting ITT analyses, we have not imputed missing data for continuous outcomes, as this usually requires access to individual participant data.

Missing statistics

In the case of missing statistics, we had planned to calculate SDs when only P values, CIs, standard errors etc. were reported, but this was not possible. We also planned to calculate the arithmetic mean of SDs for studies using the same scale as the one with the missing SDs (as in Furukawa 2006), but again this was not possible.

Assessment of heterogeneity

We have assessed heterogeneity by means of:

- visual inspection of the overlap of the CIs for individual studies in the forest plot;
- the Chi^2 test, with a P value set at 0.10;
- the I^2 statistic: in accordance with the suggestion in the *Cochrane Handbook*, section 9.5.2 (Deeks 2011), we have followed a rough guide for interpretation as follows: 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity.

We have also taken into account the magnitude and direction of effects.

Assessment of reporting biases

We included fewer than 10 studies per outcome per comparison. If more than 10 studies had been included per primary outcome, we would have:

- visually inspected the relative funnel plots, tested them for asymmetry and investigated possible reasons for funnel plot asymmetry;
- employed Egger's regression test (Egger 1997).

Methods for pair-wise meta-analysis

We have performed standard pair-wise meta-analysis with a random-effects model for every comparison with at least two studies, using Review Manager 5 (Review Manager 2014). We used a random-effects model as we were expecting clinical heterogeneity.

Methods for network meta-analysis

We had planned to perform a network meta-analysis subject to feasibility. In consideration of the limited number of included studies and the lack of direct comparisons, we judged the network meta-analysis infeasible.

Subgroup analysis and investigation of heterogeneity

For the primary outcomes only, we planned to assess the impact on the effectiveness of subgrouping by setting (e.g. acute and emergency departments, surgery or intensive care survivors) and by patients with a diagnosis of ASD and patients not fulfilling ASD criteria. Different settings may represent different types of traumatic events and specific populations. Patients fulfilling ASD criteria may be expected to have a greater risk of developing PTSD as compared to those not fulfilling ADS criteria. Subgroup analyses were not feasible due to the number of included studies per each comparison.

Sensitivity analysis

We planned to conduct sensitivity analysis for all outcomes. We have investigated the impact of excluding studies at high risk of bias, defined by unclear or missing allocation concealment or unclear or missing blinding of outcome assessors. The following additional pre-planned sensitivity analyses could not be carried out due to lack of data: impact of using ITT data versus completers data; impact of excluding cluster-RCTs.

Summary of findings and assessment of the certainty of the evidence

We planned to present the results using a summary of findings table for each comparison. However, given the trials we included, we prioritised the comparisons of escitalpram versus placebo and hydrocortisone versus placebo, as these are likely to be the most important comparisons for decision-makers. Summary of findings tables for oxytocin compared to placebo and temazepam compared to placebo can be found in Table 1 and Table 2. The summary of findings tables considered the primary time point of three months after the traumatic event and the following outcomes:

- PTSD severity
- Dropouts due to adverse events
- PTSD rate

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- Functional disability
- Quality of life

We used the five GRADE 'certainty assessment' domains (risk of bias, inconsistency, indirectness, imprecision and publication bias) to assess the certainty of the evidence in consideration of the studies that provided data for the specific outcome. We used the GRADEpro software (GRADEpro GDT 2015), and applied the methods and recommendations from the *Cochrane Handbook*, section 11.5 (Schünemann 2011). Three review authors (FB, LR and GO) independently graded the certainty of the evidence. We resolved any disagreements through discussion or, if required, by consulting a third review author (NM). We used footnotes to justify the downgrading of the evidence. We noted comments to aid the reader, when suitable. We categorised the certainty of the evidence as high (further research is not likely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on the estimate of effect and may change it), low (further research is very likely to have an important impact on the estimate of effect and is likely to change it), or very low (the estimate of effect is very uncertain).

RESULTS

Description of studies

Results of the search

The initial search identified 3339 titles and abstracts, and later update searches identified an additional 2208 and 5566 titles and abstracts (see Figure 1 for study flow diagram). We screened each title (and abstract if available) for eligibility. A total of 114 full texts were further inspected, which included 15 eligible studies reported in 37 references. Of these, seven are ongoing studies, leaving eight studies that we have included in the review. Fifty-one studies were not eligible for this review (Excluded studies). Of these, 13 have been considered in the parallel review on universal PTSD prevention (Bertolini 2022).

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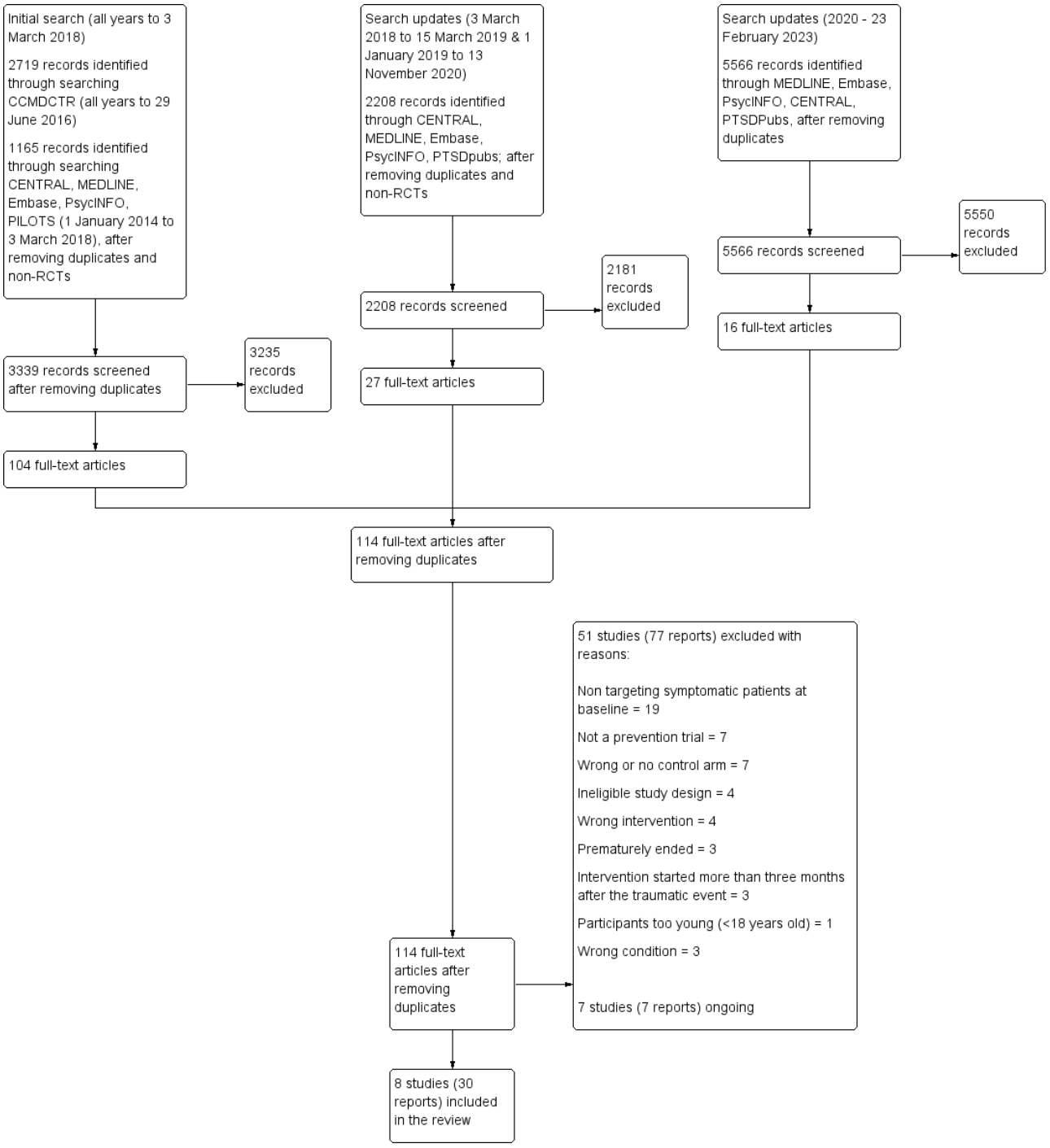
Figure 1. PRISMA flowchart



Included studies

See Characteristics of included studies.

Design

All of the included RCTs compared one active pharmacological intervention against placebo. Shalev 2012 had three additional arms comparing non-pharmacological interventions, which have not been considered for this review.

Participants, traumatic events and setting

The studies recruited a total of 779 participants, with Zohar 2018 contributing 353, Van Zuiden 2017 120 and Carmi 2022 118 participants.

Two studies recruited participants from level 1 trauma centres (Delahanty 2013; Mellman 2002), and six studies considered patients from emergency departments (Carmi 2022; Shalev 2012; Suliman 2015; Van Zuiden 2017; Zohar 2011; Zohar 2018). Participants were exposed to a range of traumatic events, of

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both unintentional and intentional nature, including motor vehicle accidents, work injures, assaults and terrorist attacks.

Two studies were multicentric (Van Zuiden 2017; Zohar 2018), six were single-centre (Carmi 2022; Delahanty 2013; Mellman 2002; Shalev 2012; Suliman 2015; Zohar 2011).

Two studies were conducted in the USA (Delahanty 2013; Mellman 2002), three in Israel (Carmi 2022; Shalev 2012; Zohar 2011), one in both Israel and South Africa (Zohar 2018), one in South Africa only (Suliman 2015) and one in the Netherlands (Van Zuiden 2017).

Assessment of acute traumatic stress symptoms

Six studies considered modified DMS-IV criteria for either ASD or PTSD for participants to be included (Carmi 2022; Mellman 2002; Shalev 2012; Suliman 2015; Zohar 2011; Zohar 2018). Two studies used scales for participants to be included: Delahanty 2013 used the 10-item Peritraumatic Dissociative Experiences Questionnaire Self-Report Version and Van Zuiden 2017 used the Trauma Screening Questionnaire and the Peritraumatic Distress Inventory (PDI) screening questionnaire.

Four studies assessed baseline traumatic stress symptoms as measured with the Clinician-Administered PTSD Scale (CAPS) (Shalev 2012; Suliman 2015; Van Zuiden 2017; Zohar 2018). For the remaining four studies, Carmi 2022 used the VAS Distress and VAS Anxiety scales; Delahanty 2013 used the Peritraumatic Distress Inventory (PDI) and the Peritraumatic Dissociative Experiences Questionnaire Self-Report Version (PDEQ); Mellman 2002 specified the number of participants meeting full ASD criteria; Zohar 2011 used the VAS Anxiety scale. Please see Characteristics of included studies for details of the scores for each participant group.

Interventions

The studies focused on four active interventions: three studies were on hydrocortisone (Carmi 2022; Delahanty 2013; Zohar 2011), one studied temazepam, a benzodiazepine (Mellman 2002), three studies assessed escitalopram, an SSRI antidepressant (Shalev 2012; Suliman 2015; Zohar 2018), and one studied oxytocin (Van Zuiden 2017). All the trials employed placebo as a comparison.

Hydrocortisone was prescribed either as a tablet for a 10-day course of 20 mg twice daily followed by a six-day taper period (Delahanty 2013), or as a single intravenous bolus at a body weight-determined dose (Carmi 2022; Zohar 2011; please see the included studies table for details of the intravenous dosing used by these trials). Hydrocortisone was administered within six (Carmi 2022), 12 (Delahanty 2013) or 5.5 (Zohar 2011) hours from the traumatic event. Temazepam was prescribed as a single 30 mg tablet at bedtime for five nights followed by five additional nights at 15 mg, starting at a mean of 14.3 days from the traumatic event (Mellman 2002). Escitalopram was titrated to a dose of 20 mg per day, with an overall duration of intervention ranging from 12 to 24 weeks (Shalev 2012; Suliman 2015; Zohar 2018). In Shalev 2012 and Zohar 2018, escitalopram was started within one month from the traumatic event, while Suliman 2015 does not report the exact time of the start of the intervention. Oxytocin was provided as intranasal administration of five puffs of 4 IU per nostril twice a day, for eight days, starting at a mean of 8.9 days from the traumatic event (Van Zuiden 2017).

Outcome measures

All the studies assessed PTSD severity and did so with the CAPS. Six studies used the CAPS to also establish the presence of PTSD (Carmi 2022; Delahanty 2013; Mellman 2002; Shalev 2012; Suliman 2015; Zohar 2011). Depression severity was assessed by a number of scales: the MADRS (Carmi 2022 at 13 months, a time point at which the same outcome was also measured with the VAS-D; Suliman 2015, which also measured the same outcome with the VAS-D; Zohar 2018), the Center for Epidemiological Studies - Depression Scale (CES-D) (Delahanty 2013), the Beck Depression Inventory (BDI) (Shalev 2012), the Hospital Anxiety and Depression Scale (HADS) (Van Zuiden 2017) and the Visual Analogue Scales for Depression (VAS-D) (Carmi 2022 at three and 13 months; Zohar 2011). Five studies assessed anxiety severity, four with the Visual Analogue Scale for Anxiety (VAS-A) (Carmi 2022; Suliman 2015; Zohar 2011; Zohar 2018) and one with the Hospital Anxiety and Depression Scale (HADS) (Van Zuiden 2017). Only one study measured functional disability (Shalev 2012), and did so with the Structured Clinical Interview for DSM-IV Global Assessment of Functioning (SCID-IV GAF). Only one study measured the quality of life (Delahanty 2013) and did so with the Short Form (36) Health Survey (SF-36). We sought and received additional outcome data from the authors of Suliman 2015 (please see the Characteristics of included studies table for further details).

Timing of outcome assessment

Five studies assessed outcomes at the review primary time point of three months after the traumatic experience (Carmi 2022; Delahanty 2013; Suliman 2015; Van Zuiden 2017; Zohar 2018). Timing of outcome assessment overall generally occurred between 6 and 56 weeks after the traumatic event, with one study reaching three years after the traumatic event (Shalev 2012).

Excluded studies

We excluded 51 studies from this review. Thirteen studies published up to 2020 that did not target symptomatic individuals at baseline (thus investigating universal prevention strategies) have been considered in a parallel Cochrane review (Bertolini 2022); the last search update identified six additional studies to these. Among the excluded studies, seven were not included because they had no or an ineligible control arm (IRCT20190919044819N2; Matsumura 2011; Matsuoka 2010; NCT04467086; Nishi 2012; Schelling 2004; Yang 2011), as we sought studies comparing an active intervention with another or placebo. In addition to these trials, the most common reason for exclusion was the focus not being on prevention (seven studies), followed by ineligible study design (four studies), not investigating an intervention of interest to the review (four studies), intervention started later than three months after the traumatic event occurred (three studies), study ended prematurely (three studies), focused on ineligible conditions (three studies) and considered participants under 18 years of age (one study). See Characteristics of excluded studies.

Ongoing studies

We found seven currently ongoing studies (EUCTR-000088-12-DE; McMullan 2020; NCT01039766; NCT03997864; NCT04071600; NCT04274361; NCT04924166). See Characteristics of ongoing studies.

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Risk of bias in included studies

See Figure 2 and Figure 3 for further details.

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

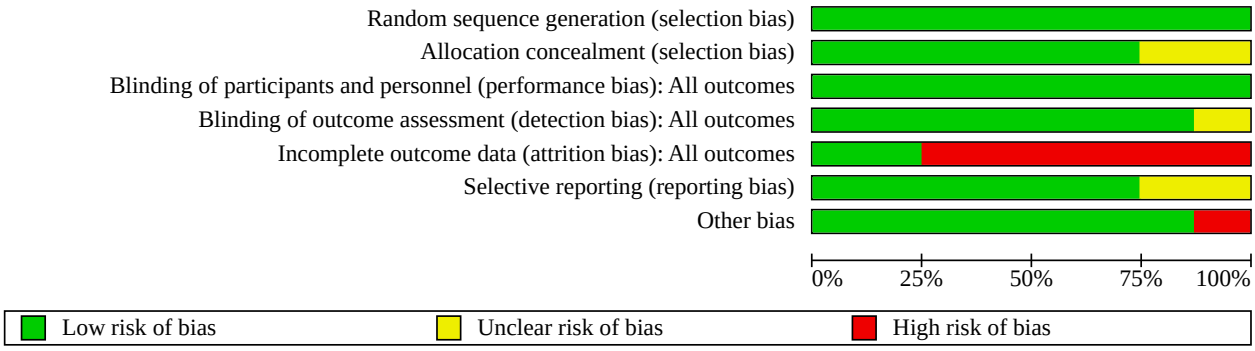

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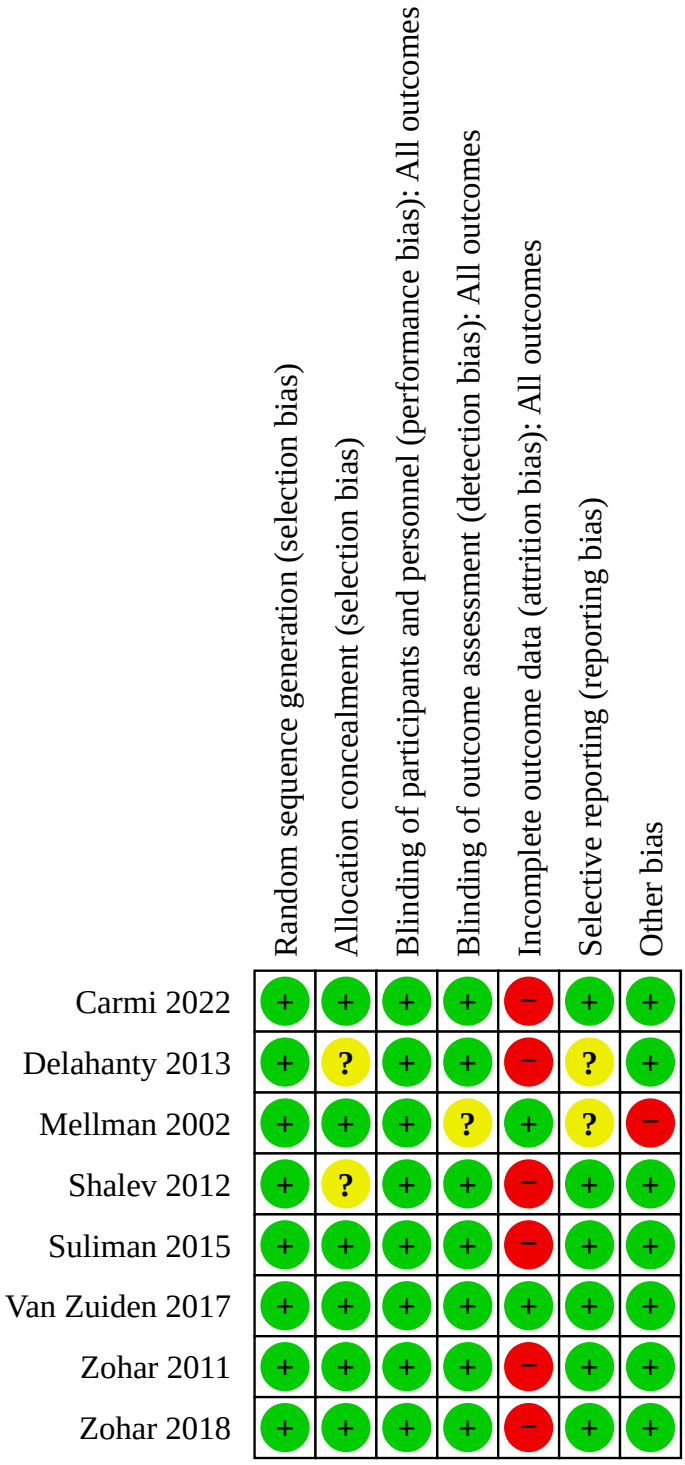
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



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Random sequence generation

All the included studies described the process of randomisation in sufficient detail to be judged at low risk of bias.

Allocation concealment

Six studies reported procedures that clearly resulted in or implied the concealment of the randomisation list (Carmi 2022; Mellman 2002; Suliman 2015; Van Zuiden 2017; Zohar 2011; Zohar 2018); we judged these studies at low risk of bias. Two studies did not report procedures in sufficient detail to ensure that allocation concealment was in place (Delahanty 2013; Shalev 2012); we judged these studies at unclear risk of bias.

Blinding

All the studies reported blinding of participants, and we judged them at low risk of bias.

All but one study reported blinding of outcome assessors; we judged these studies at low risk of bias. Mellman 2002 did not provide information on blinding of outcome assessors, and we judged this study at unclear risk of bias.

Incomplete outcome data

Only two studies reported low attrition rates for the outcomes of interest (Mellman 2002; Van Zuiden 2017); we judged these studies at low risk of bias. All the remaining studies had attrition rates over 20% (Carmi 2022; Delahanty 2013; Shalev 2012; Suliman 2015; Zohar 2011; Zohar 2018); we judged these studies at high risk of bias.

Selective reporting

Six studies were registered on ClinicalTrials.gov and appropriately reported the outcomes as listed in the original registration entry (Carmi 2022; Shalev 2012; Suliman 2015; Van Zuiden 2017; Zohar 2011; Zohar 2018); we judged these studies at low risk of bias. For two studies, a previously published protocol or trial registration was not available (Delahanty 2013; Mellman 2002); we judged these studies at unclear risk of bias.

Other potential sources of bias

For all but one study we found no additional sources of concern; we judged these studies at low risk of bias. For Mellman 2002, the only published source is a short letter to the editor. Due to the concerns related to the short reporting, we judged this study at high risk of bias.

Effects of interventions

See: **Summary of findings 1** Escitalopram compared to placebo for the prevention of PTSD in individuals experiencing acute traumatic stress symptoms; **Summary of findings 2** Hydrocortisone compared to placebo for prevention of PTSD in individuals experiencing acute traumatic stress symptoms

See Summary of findings 1 for escitalopram compared to placebo; Summary of findings 2 for hydrocortisone compared to placebo; Table 1 for oxytocin compared to placebo; Table 2 for temazepam compared to placebo.

Comparison 1: Escitalopram versus placebo

Three studies compared escitalopram to placebo (Shalev 2012; Suliman 2015; Zohar 2018).

Primary outcomes

1. PTSD severity

Three months after the traumatic event

One study assessed the severity of PTSD symptoms after three months with the CAPS (Suliman 2015). The evidence from this small study was inconclusive as to whether escitalopram is more effective in reducing the severity of PTSD symptoms compared to placebo, as these data are based on only one small study, with the confidence interval rather wide and including the null effect (MD -11.35, 95% CI -24.56, 1.86, score range 0 to 136; 1 study, 23 participants; very low-certainty evidence; Analysis 1.1). We downgraded this outcome to very low-certainty evidence due to the risk of attrition bias and very serious imprecision of the effect estimate, as far fewer than 400 participants were included.

Study endpoint

Three studies assessed PTSD severity, after 24 weeks (Suliman 2015), after 56 weeks (Zohar 2018) and after three years from the traumatic event (Shalev 2012). All studies used the CAPS. It is unclear whether escitalopram is less effective in reducing the severity of PTSD symptoms compared to placebo, as the confidence interval is very wide and includes the null effect (MD 3.34, 95% CI -10.72 to 17.39, I^2 = 81%, scale range 0 to 136; 3 studies, 255 participants; Analysis 1.2). When we excluded studies at overall high risk of bias (Shalev 2012), we found similar results (MD 4.07, 95% CI -15.06 to 23.20, I^2 = 90%; 2 studies, 227 participants).

2. Dropouts due to adverse events

Three months after the traumatic event

One study provided data on dropouts due to adverse events after three months (Suliman 2015). The evidence from this small study is inconclusive as to whether there is a difference between escitalopram and placebo, as for both groups no participant left the study early due to adverse events (very low-certainty evidence; Analysis 1.3). We downgraded this outcome to very low-certainty evidence because of the risk of attrition bias in the included study and very serious imprecision, as the optimal sample size is not met because the number of participants is very small.

Study endpoint

The same study provided data on dropouts due to adverse events at 56 weeks (Suliman 2015). Again, it is unclear whether there is a difference between escitalopram and placebo, as still no dropouts due to adverse events had been registered in either of the intervention groups (Analysis 1.4).

Secondary outcomes

1. PTSD rate

Three months after the traumatic event

One study provided data on the number of participants with PTSD after three months from the traumatic event (Suliman 2015). The evidence from this small trial is inconclusive as to whether there is a difference between escitalopram and placebo in the risk of having PTSD as the confidence interval is rather wide and includes the null

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effect (RR 0.59, 95% CI 0.03 to 13.08; NNTB 37, 95% CI NNTB 15 to NNTH 1; 1 study, 23 participants; very low-certainty evidence; Analysis 1.5). We downgraded this outcome to very low-certainty evidence because of the risk of attrition bias in the included study and very serious imprecision, as the optimal sample size is not met, and the CI includes both appreciable benefit and harm. We conducted a sensitivity analysis exploring the effect of considering cases divided by the number of randomised participants instead of dividing by the number of analysed participants. This sensitivity analysis showed similar results (RR 0.45, 95% CI 0.02 to 10.30; NNTB 33, 95% CI NNTB 18 to NNTH 2; 1 study, 31 participants; Analysis 1.6).

Study endpoint

Two studies provided data on the rate of participants with PTSD at 56 weeks (Suliman 2015) and three years after the traumatic event (Shalev 2012). It is unclear whether there is a difference between escitalopram and placebo in the risk of having PTSD as the number of participants is very limited, and the CI is wide and includes the null effect (RR 1.15, 95% CI 0.49 to 2.71; NNTH 30, 95% CI NNTB 9 to NNTH 3; 2 studies, 47 participants; Analysis 1.7). We conducted a sensitivity analysis exploring the effect of considering cases divided by the number of randomised participants instead of dividing by the number of analysed participants. This sensitivity analysis showed similar results (RR 1.00, 95% CI 0.38 to 2.65; NNTB incalculable, 95% CI NNTB 11 to NNTH 4; 2 studies, 77 participants; Analysis 1.8). We did not perform the planned sensitivity analysis excluding studies at high risk of bias (Shalev 2012), as it would have left only one study (Suliman 2015).

2. Depression severity

Three months

One study assessed depression severity as measured with the MADRS after three months (Suliman 2015). Escitalopram may reduce the severity of depression symptoms compared to placebo (MD -5.07, 95% CI -9.75 to -0.39, scale range 0 to 60; 1 study, 23 participants; Analysis 1.9). However, these data are based on a single trial with a very small number of participants and the CI includes values below the minimum clinically important difference for the scale (Duru 2008; Masson 2013).

Study endpoint

Two studies assessed depression severity at 56 weeks as measured with the MADRS (Suliman 2015) and at three years after the traumatic event as measured with the BDI (Shalev 2012). It is unclear whether escitalopram reduces the severity of depression symptoms compared to placebo, as the number of participants is limited and the CI includes the null effect (SMD -0.50, 95% CI -1.09 to 0.09, scale range 0 to 60; I^2 = 0%; 2 studies, 47 participants; Analysis 1.10). We did not perform the planned sensitivity analysis excluding studies at high risk of bias (Shalev 2012), as it would have left one study only (Suliman 2015)

3. Anxiety severity

Three months

One study assessed anxiety severity as measured with the VAS-A after three months (Suliman 2015). It is unclear whether escitalopram reduces the severity of anxiety symptoms compared to placebo as these data are based on only one small study and the confidence interval includes the null effect (MD -1.02, 95% CI -2.39 to 0.35, scale range 0 to 10; 1 study, 23 participants; Analysis 1.11).

Study endpoint

One study assessed anxiety severity as measured with the VAS-A at 56 weeks after the traumatic event (Suliman 2015). It is unclear whether there is a difference between escitalopram and placebo as these data are based on only one small study and the confidence interval is rather wide and includes the null effect (MD -0.13, 95% CI -1.65 to 1.39, scale range 0 to 10; 1 study, 19 participants; Analysis 1.12).

4. Functional disability

Three months

No study reported data on functional disability at this time point.

Study endpoint

Two studies assessed functional disability (Shalev 2012; Suliman 2015), with Suliman 2015 not reporting data in sufficient detail to meta-analyse. Based on the data from Shalev 2012, it is unclear whether escitalopram is more effective in reducing functional disability as the trial is very small and the CI includes the null effect (MD on the SCID-IV GAF (higher is better) 1.06, 95% CI -7.16 to 9.28, scale range 0 to 100); 1 study, 28 participants; Analysis 1.13). Suliman 2015 assessed functional disability on the Sheehan disability scale. Data were not reported in sufficient detail to meta-analyse. Mean scores across groups diminished at 24 weeks in a statistically significant manner between participants receiving escitalopram and placebo (-5.58, standard error (SE) ± 1.58 and -8.25 SE ± 1.26, respectively, P < 0.01) (on the Sheehan disability scale, lower scores reflect less disability, scale range 0 to 30). It should be noted that the escitalopram group had lower scores at baseline compared to the placebo group (8.83 SE ± 6.46 and 14.41 SE ± 7.75, respectively, P = 0.05).

5. Quality of life

No study assessed this outcome.

6. Dropouts for any reason

Three months

One study provided data on the number of participants leaving the study for any reason (Suliman 2015). It is unclear whether escitalopram increases the risk of leaving the study early compared to placebo, as the trial was small and the CI includes the null effect (RR 2.31, 95% CI 0.67 to 7.98; NNTH 5, 95% CI NNTB 18 to NNTH 1; 1 study, 31 participants; Analysis 1.14).

Study endpoint

Three studies provided data on the number of participants leaving the study at various time points: after 24 weeks (Suliman 2015), after 56 weeks (Zohar 2018) and after three years (Shalev 2012). Escitalopram may not increase nor decrease the risk of leaving the study for any reason (RR 0.97, 95% CI 0.78 to 1.20; NNTH 76, 95% CI NNTB 11 to NNTH 10; I^2 = 0%; 3 studies, 430 participants; Analysis 1.15). When we excluded studies at overall high risk of bias (Shalev 2012), we found similar results (RR 0.94, 95% CI 0.75 to 1.19, NNTH 37, 95% CI NNTB 12 to NNTH 9; I^2 = 0%; 2 studies, 384 participants).

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Comparison 2: Hydrocortisone versus placebo

Three studies compared hydrocortisone to placebo (Carmi 2022; Delahanty 2013; Zohar 2011). Carmi 2022 assessed the outcomes at three and 13 months after the traumatic event, while Delahanty 2013 and Zohar 2011 only assessed the outcomes at three months after the traumatic event. Carmi 2022 appears to be a consistent outlier in many of the outcomes.

Primary outcomes

1. PTSD severity

Three months after the traumatic event

Three studies assessed PTSD severity after three months from the traumatic event, as measured with the CAPS (Carmi 2022; Delahanty 2013; Zohar 2011). The evidence is inconclusive on whether hydrocortisone is more effective in reducing the severity of PTSD symptoms compared to placebo, as these data are based on three small studies and the effect estimate is imprecise as the confidence interval is wide and includes the null effect (MD -7.53, 95% CI -25.20 to 10.13, scale range 0 to 136; I^2 = 85%; 3 studies, 136 participants; very low-certainty evidence; Analysis 2.1). We downgraded this outcome to very low-certainty evidence because of risk of attrition bias in the included studies, inconsistency in the point estimate of the effect across the studies and the imprecision of the effect estimate. When we excluded studies at overall high risk of bias (Delahanty 2013), we found similar results (MD -5.81, 95% CI -35.15 to 23.53; I^2 = 90%; 2 studies, 93 participants).

Study endpoint

Three studies assessed PTSD severity, at three months (Delahanty 2013; Zohar 2011) and at 13 months (Carmi 2022) from the traumatic events. All studies used the CAPS. It is unclear whether hydrocortisone is more effective in reducing the severity of PTSD symptoms compared to placebo, as these data are based on three small studies and the confidence interval includes the null effect (MD -9.69, 95% CI -21.91 to 2.53, scale range 0 to 136; I^2 = 72%; 3 studies, 156 participants; Analysis 2.2). When we excluded studies at overall high risk of bias (Delahanty 2013), we found similar results (MD -9.55, 95% CI -30.67 to 11.58; I^2 = 83%; 2 studies, 113 participants).

2. Dropouts due to adverse events

Three months after the traumatic event

Two studies reported on the number of participants leaving the study due to adverse events (Carmi 2022; Delahanty 2013). The evidence is inconclusive on whether there is a difference between hydrocortisone and placebo, as these data are based on two small studies and the confidence interval is very wide and includes the null effect (RR 3.19, 95% CI 0.13 to 75.43; 2 studies, 182 participants; low-certainty evidence; Analysis 2.3). We downgraded this outcome to low-certainty for imprecision as the optimal sample size is not met, and the CI includes both appreciable benefit and harm. We did not perform the planned sensitivity analysis excluding studies at overall high risk of bias (Delahanty 2013), as it would have left only one study (Carmi 2022).

Study endpoint

Two studies reported on the number of participants leaving the study due to adverse events at three months (Delahanty 2013) and 13 months (Carmi 2022) after the traumatic event. The evidence is inconclusive on whether there is a difference between hydrocortisone and placebo, as these data are based on two small studies and the confidence interval is very wide and includes the null effect (RR 3.19, 95% CI 0.13 to 75.43; 2 studies, 182 participants; low-certainty evidence; Analysis 2.4). We did not perform the planned sensitivity analysis excluding studies at overall high risk of bias (Delahanty 2013), as it would have left one study only (Carmi 2022).

Secondary outcomes

1. PTSD rate

Three months after the traumatic event

Three studies provided data on the number of participants with PTSD after three months from the traumatic event (Carmi 2022; Delahanty 2013; Zohar 2011). It is unclear whether hydrocortisone reduces the risk of having PTSD as compared to placebo, as these data are based on only three small studies, and the confidence interval is rather wide and includes the null effect (RR 0.47, 95% CI 0.09 to 2.38; NNTB 14, 95% CI NNTB 8 to NNTH 5; I^2 = 36%; 3 studies, 136 participants; very low-certainty evidence; Analysis 2.5). We downgraded this outcome to very low-certainty evidence because of the risk of attrition bias in the included studies and because the optimal sample size is not met, and the CI includes both appreciable benefit and harm. We conducted a sensitivity analysis exploring the effect of considering cases divided by the number of randomised participants instead of dividing by the number of analysed participants. This sensitivity analysis showed similar results (RR 0.41, 95% CI 0.05 to 3.02; NNTB 19, 95% CI NNTB 12 to NNTH 6; 3 studies, 207 participants; Analysis 2.6). When we excluded studies at overall high risk of bias (Delahanty 2013), we found similar results (RR 0.56, 95% CI 0.06 to 5.14; NNTB 16, 95% CI NNTB 7 to NNTH 2; I^2 = 54%; 2 studies, 93 participants).

Study endpoint

Three studies provided data on the number of participants with PTSD, at three months (Delahanty 2013; Zohar 2011) and at 13 months (Carmi 2022) from the traumatic events. It is unclear whether hydrocortisone reduces the risk of having PTSD as compared to placebo, as these data are based on only three small studies, and the confidence interval is rather wide and includes the null effect (RR 0.48, 95% CI 0.14 to 1.63; NNTB 15, 95% CI NNTB 9 to NNTH 12; I^2 = 8%; 3 studies, 156 participants; Analysis 2.7). We conducted a sensitivity analysis exploring the effect of considering cases divided by the number of randomised participants instead of dividing by the number of analysed participants. This sensitivity analysis showed similar results (RR 0.39, 95% CI 0.08 to 1.83; NNTB 17, 95% CI NNTB 11 to NNTH 12; 3 studies, 207 participants; Analysis 2.8). When we excluded studies at overall high risk of bias (Delahanty 2013), we found similar results (RR 0.50, 95% CI 0.09 to 2.91; NNTB 15, 95% CI NNTB 8 to NNTH 4; I^2 = 35%; 2 studies, 113 participants).

2. Depression severity

Three months after the traumatic event

Three studies provided data on depression severity as measured with the CES-D (Delahanty 2013) and VAS-D (Carmi 2022; Zohar 2011) at three months after the traumatic event. It is unclear whether hydrocortisone decreases the severity of depression symptoms as compared to placebo as these data are based on three

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small studies and the confidence interval includes the null effect (SMD -0.49, 95% CI -1.40 to 0.42; I^2 = 82%; 3 studies, 136 participants; Analysis 2.9). When we excluded studies at overall high risk of bias (Delahanty 2013), we found similar results (SMD -0.37, 95% CI -1.79 to 1.05; I^2 = 84%; 2 studies, 93 participants).

Study endpoint

Three studies provided data on depression severity as measured with the CES-D at three months after the traumatic event (Delahanty 2013) and with the VAS-D at three months (Zohar 2011) and at 13 months after the traumatic event (Carmi 2022). It is unclear whether hydrocortisone decreases the severity of depression symptoms as compared to placebo as these data are based on three small studies and the confidence interval includes the null effect (SMD -0.51, 95% CI -1.38 to 0.36; I^2 = 81%; 3 studies, 156 participants; Analysis 2.10). When we excluded studies at overall high risk of bias (Delahanty 2013), we found similar results (SMD -0.40, 95% CI -1.74 to 0.94; I^2 = 83%; 2 studies, 113 participants).

3. Anxiety severity

Three months after the traumatic event

Two studies provided data on anxiety severity as measured with the VAS-A at three months after the traumatic event (Carmi 2022; Zohar 2011). It is unclear whether hydrocortisone decreases the severity of anxiety symptoms as compared to placebo as these data are based on two small studies and the confidence interval is rather wide and includes the null effect (MD -0.82, 95% CI -4.09 to 2.45, scale range 0 to 10; I^2 = 90%; 2 studies, 93 participants; Analysis 2.11).

Study endpoint

Two studies provided data on anxiety severity as measured with the VAS-A at three months (Zohar 2011) and at 13 months (Carmi 2022) after the traumatic event. It is unclear whether hydrocortisone decreases the severity of anxiety symptoms as compared to placebo as these data are based on two small studies and the confidence interval is rather wide and includes the null effect (MD -1.04, 95% CI -3.83 to 1.76, scale range 0 to 10; I^2 = 87%; 2 studies, 113 participants; Analysis 2.12).

4. Functional disability

No study assessed functional disability in this comparison.

5. Quality of life

One study provided data on quality of life as measured with the SF-36 (Delahanty 2013). It is unclear whether hydrocortisone might improve quality of life as compared with placebo, as these data are based on a single, small trial and the confidence interval is very wide and includes the null effect (MD 19.70, 95% CI -1.10 to 40.50, scale range 0 to 100; 1 study, 43 participants; very low-certainty evidence; Analysis 2.13). We downgraded this outcome because of risk of attrition bias in the included study, and for imprecision as fewer than 400 participants were included, and the CI includes both appreciable benefit and harm.

6. Dropouts for any reason

Three months after the traumatic event

Three studies provided data on the number of participants leaving the study early for any reason (Carmi 2022; Delahanty 2013; Zohar 2011). It is unclear whether hydrocortisone increases or decreases the risk of leaving the study early, as these data are based on three small studies and the confidence interval is very wide and includes the null effect (RR 1.05, 95% CI 0.54 to 2.04; NNTH 56, 95% CI NNTB 6 to NNTH 3; I^2 = 54%; 3 studies, 207 participants; Analysis 2.14). When we excluded studies at overall high risk of bias (Delahanty 2013), we found similar results (RR 0.94, 95% CI 0.34 to 2.64; NNTB 42, 95% CI NNTB 4 to NNTH 2; I^2 = 55%; 2 studies, 143 participants).

Study endpoint

Three studies provided data on the number of participants leaving the study early for any reason (Carmi 2022; Delahanty 2013; Zohar 2011). It is unclear whether hydrocortisone increases or decreases the risk of leaving the study early, as these data are based on three small studies and the confidence interval is very wide and includes the null effect (RR 1.11, 95% CI 0.61 to 2.04; NNTH 38, 95% CI NNTB 11 to NNTH 4; I^2 = 29%; 3 studies, 207 participants; Analysis 2.15). When we excluded studies at overall high risk of bias (Delahanty 2013), we found similar results (RR 0.99, 95% CI 0.35 to 2.76; NNTB 453, 95% CI NNTB 7 to NNTH 3; I^2 = 45%; 2 studies, 143 participants).

Comparison 3: Oxytocin versus placebo

One study compared oxytocin and placebo (Van Zuiden 2017).

Primary outcomes

1. PTSD severity

Three months after the traumatic event

Van Zuiden 2017 assessed the severity of PTSD symptoms as measured with the CAPS at three months after the traumatic event. The evidence from this small study is inconclusive as to whether oxytocin reduces the severity of PTSD symptoms as compared to placebo, as the confidence interval is rather wide and includes the null effect (MD -4.27, 95% CI -10.85 to 2.31, scale range 0 to 136; 1 study, 107 participants; low-certainty evidence; Analysis 3.1). We downgraded this outcome to low-certainty because of serious imprecision as far fewer than 400 participants were included, and the CI includes both appreciable benefit and harm.

Study endpoint

Van Zuiden 2017 assessed the severity of PTSD symptoms as measured with the CAPS at six months after the traumatic event. The evidence from this small study is inconclusive as to whether oxytocin reduces the severity of PTSD symptoms as compared to placebo, as the confidence interval is rather wide and includes the null effect (MD -1.00, 95% CI -6.83 to 4.83, scale range 0 to 136; 1 study, 107 participants; Analysis 3.2).

2. Dropouts due to adverse events

No study provided data on the number of participants leaving the study early because of adverse events.

Secondary outcomes

1. PTSD rate

No study provided data on the number of participants with PTSD.

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2. Depression severity

Three months after the traumatic event

Van Zuiden 2017 assessed the severity of PTSD symptoms as measured with the HADS at three months after the traumatic event. It is unclear whether oxytocin reduces the severity of depression symptoms as compared to placebo, as these data are based on a relatively small study and the confidence interval includes the null effect (MD -0.56, 95% CI -2.53 to 1.41, scale range 0 to 21; 1 study, 107 participants; Analysis 3.3).

Study endpoint

Van Zuiden 2017 assessed the severity of PTSD symptoms as measured with the HADS at six months after the traumatic event. It is unclear whether oxytocin reduces the severity of depression symptoms as compared to placebo, as these data are based on a relatively small study and the confidence interval includes the null effect (MD -0.71, 95% CI -2.38 to 0.96, scale range 0 to 21; 1 study, 107 participants; Analysis 3.4).

3. Anxiety severity

Three months after the traumatic event

Van Zuiden 2017 assessed the severity of anxiety symptoms as measured with the HADS at three months after the traumatic event. It is unclear whether oxytocin reduces or increases the severity of depression symptoms as compared to placebo, as these data are based on only a relatively small study and the confidence interval includes the null effect (MD -0.31, 95% CI -2.10 to 1.48, scale range 0 to 21; 1 study, 107 participants; Analysis 3.5).

Study endpoint

Van Zuiden 2017 assessed the severity of anxiety symptoms as measured with the HADS at six months after the traumatic event. It is unclear whether oxytocin reduces or increases the severity of depression symptoms as compared to placebo, as these data are based on a relatively small study and the confidence interval includes the null effect (MD -0.47, 95% CI -2.00 to 1.06, scale range 0 to 21; 1 study, 107 participants; Analysis 3.6).

4. Functional disability

No study assessed this outcome.

5. Quality of life

No study assessed this outcome.

6. Dropouts for any reason

Three months after the traumatic event

Van Zuiden 2017 provided data on the number of participants leaving the study early for any reason at three months after the traumatic event. It is unclear whether oxytocin increases or decreases the risk of leaving the study early, as these data are based on one relatively small study and the confidence interval is rather wide and includes the null effect (RR 1.14, 95% CI 0.64 to 2.03; NNTH 28, 95% CI NNTB 11 to NNTH 4; 1 study, 120 participants; Analysis 3.7).

Study endpoint

Van Zuiden 2017 provided data on the number of participants leaving the study early for any reason at six months after the traumatic event. It is unclear whether oxytocin increases or decreases the risk of leaving the study early, as these data are based on one relatively small study and the confidence interval is rather wide and includes the null effect (RR 0.95, 95% CI 0.54 to 1.68; NNTB 69, 95% CI NNTB 7 to NNTH 5; 1 study, 120 participants; Analysis 3.8).

Comparison 4: Temazepam versus placebo

One study compared temazepam and placebo (Mellman 2002). As this study assessed the outcomes at up to six weeks after the traumatic event, we could not assess data for the review's primary time point of three months after the traumatic event.

Primary outcomes

1. PTSD severity at the study endpoint

Mellman 2002 assessed the severity of PTSD symptoms, as measured with the CAPS, at six weeks after the traumatic event. The evidence from this small study is inconclusive on whether temazepam increases the severity of PTSD symptoms as compared to placebo, as the confidence interval is very wide and includes the null effect (MD 9.20, 95% CI -9.91 to 28.31, scale range 0 to 136; 1 study, 22 participants; Analysis 4.1).

2. Dropout because of adverse events at the study endpoint

Mellman 2002 reported the number of participants leaving the study early because of adverse events at six weeks after the traumatic event. The evidence from this small study is inconclusive as to whether temazepam increases or decreases this risk as compared to placebo, as no event was recorded for either group in the context of a single, small trial (22 participants; Analysis 4.2).

Secondary outcomes

1. PTSD rate at the study endpoint

Mellman 2002 assessed the number of participants with PTSD, as measured with the CAPS, at six weeks after the traumatic event. The evidence is inconclusive as to whether temazepam increases the risk of experiencing PTSD as compared to placebo, as the data are based on a single, small study and the confidence interval is wide and includes the null effect (RR 2.00, 95% CI 0.66 to 6.04, scale range 0 to 136; NNTH 4, 95% CI NNTB 11 to NNTH 1; 1 study, 22 participants; Analysis 4.3). We conducted a sensitivity analysis exploring the effect of considering cases divided by the number of randomised participants instead of dividing by the number of analysed participants. As no participants left the study early, the sensitivity analysis is no different from the main analysis (RR 2.00, 95% CI 0.66 to 6.04; NNTH 4, 95% CI NNTB 11 to NNTH 1; 1 study, 22 participants; Analysis 4.4).

2. Depression severity at the study endpoint

No study assessed this outcome.

3. Anxiety severity at the study endpoint

No study assessed this outcome.

4. Functional disability at the study endpoint

No study assessed this outcome.

5. Quality of life at the study endpoint

No study assessed this outcome.

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6. Dropouts for any reason at the study endpoint

Mellman 2002 reported the number of participants leaving the study early for any reason at six weeks after the traumatic event. The evidence is inconclusive as to whether temazepam increases or decreases this risk as compared to placebo, as no event was recorded for either group, in the context of a single, small trial (22 participants; Analysis 4.5).

DISCUSSION

Summary of main results

During the review process, we identified eight studies comparing a medication to placebo for people experiencing acute stress symptoms. As we were expecting a multitude of different interventions, we planned a network meta-analysis. However, all the studies compared an active intervention against placebo and we deemed the resulting network plot unfit for an informative network meta-analysis. We had sufficient data to perform meta-analysis for two comparisons: escitalopram versus placebo and hydrocortisone versus placebo.

For escitalopram, we found no evidence of effectiveness for acute traumatic stress symptoms at three months after the traumatic event, or at the time of study endpoint, either in terms of severity of symptoms or in the rate of participants with PTSD. We also did not find any difference in terms of dropout rates.

For hydrocortisone, we found no evidence of effectiveness for acute traumatic stress symptoms at three months after the traumatic event, or at the time of study endpoint, either in terms of severity of symptoms or in the rate of participants with PTSD. We also did not find any difference in terms of dropout rates

The remaining two comparisons included only one study each. For both oxytocin and temazepam, we found no evidence of effectiveness for PTSD symptoms or prevention. Of note, the estimates for temazepam point towards a harmful effect, albeit these data lie on confidence intervals that include both harm and benefit.

Overall completeness and applicability of evidence

The body of evidence from RCTs on the prevention of PTSD by treating acute traumatic stress symptoms is very limited. We included eight studies, exploring four active interventions, and for only two comparisons was there enough data to perform a meta-analysis. Lack of direct comparisons prevented the possibility of conducting a network meta-analysis. Additionally, most of the trials had small sample sizes. Still, the quality of trial conduct and their reporting was generally good.

Many authors have reported difficulties in performing trials in people affected by traumatic events in the immediate aftermath of the event itself. All the included studies recruited participants from emergency departments or trauma centres. It has been reported that people might decline participation because of the desire to leave the emergency department as soon as possible, or denial of a possible mental health problem (Stein 2007). Additionally, embedding trial personnel in such a context can be difficult from an organisational perspective. In Zohar 2018, for example, trial personnel made phone calls to people previously admitted to emergency departments for traumatic events. More than 25,000 phone calls resulted in 353 recruited participants.

Criteria for defining acute stress symptoms to include participants varied, with most studies using modified criteria from either DSM-IV acute stress disorder (ASD) or PTSD. The variability in the criteria used may have led to different levels of psychological distress within the original samples.

All studies assessed the efficacy of the interventions in terms of PTSD symptoms, and almost all measured PTSD rates as well. However, most of the trials did not report figures for participants leaving the trials early due to adverse events, leaving dropout rates for any cause as the main negative outcome. High dropout rates are common in prevention trials and in psychiatric trials in general; the rates of dropout for any reason are thus marginally informative on intervention-associated negative events. Furthermore, many patients may have left the studies as they spontaneously improved, further complicating the interpretation of this outcome. Only a minority of the trials assessed quality of life or functional impairment, the ultimate goal of any intervention.

We considered data at a primary time point of three months after the traumatic event, a time point at which treatment could be initiated if PTSD had developed. However, only five out of eight trials assessed outcomes at three months, leaving a very small body of evidence for decision-making, as pooling data at different study endpoints limits the generalisability of the resulting evidence (study follow-up ranged from six weeks to 56 weeks or five years; see heterogeneity below).

The included trials considered two settings: emergency departments and trauma centres. Participants admitted to these settings were exposed to a range of traumatic events that included both intentional and unintentional harm. While two studies recruited participants mainly exposed to intentional harm (Suliman 2015; Zohar 2018), the majority of participants in the other trials experienced traumatic events of unintentional harm. Trials conducted in Israel included some participants exposed to terrorist attacks, but no trial considered exclusively large-scale events, such as acts of war or natural disasters.

The most common setting of the included trials was an emergency department of a high-income country. This could in theory limit the generalisability of the evidence to other contexts. However, hydrocortisone is currently listed in the World Health Organization (WHO) essential drug list, and thus it can be expected to also be available in low- and middle-income countries. Escitalopram is listed by the WHO as an alternative to fluoxetine and is usually a widely available drug. Temazepam and intranasal oxytocin are not on the WHO essential drug list, and intranasal oxytocin might not be readily available outside of research contexts.

Heterogeneity

Escitalopram versus placebo

Clinical heterogeneity was limited, as the trials had the same setting and two shared the same protocol. However, a considerable level of heterogeneity was introduced by a single trial for the outcome PTSD severity at the time of study endpoint (Suliman 2015). Considering the small number of participants included, this might be due to chance.

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Hydrocortisone versus placebo

As Zohar 2011 was the pilot study for Carmi 2022, the two studies share the same methodology and differ mainly in that Carmi 2022 assessed outcomes for a longer period. They used the same administration strategy of a body weight-determined single intravenous bolus administered within six hours of the traumatic event. Delahanty 2013 investigated a 16-day oral scheme of hydrocortisone, started within 12 hours. The statistical heterogeneity was substantial and mostly introduced by Carmi 2022, which is also the trial with the higher number of participants.

Other comparisons

As all of the other comparisons rely on single trials, heterogeneity could not be assessed.

Methodological certainty

We used the GRADE domains to assess the certainty of evidence for the review's primary time point of three months after the traumatic event. We downgraded all the outcomes for risk of bias, imprecision or both. The risk of bias mainly concerned trial attrition (detailed assessments can be found in the Characteristics of included studies; Figure 2 and Figure 3 provide a graphic summary). Attrition is a frequent phenomenon in RCTs concerning mental health and prevention. Large sample sizes could counterbalance this issue. However, the included trials could recruit only small sample sizes, resulting in the additional downgrading for imprecision. Overall, the certainty of the evidence ranged from low (further research is very likely to have an important impact on the estimate of effect and is likely to change it) to very low (the estimate of effect is very uncertain).

Potential biases in the review process

This review followed Cochrane guidelines. Two review authors independently screened search results, checked the full texts of studies marked for possible inclusion against inclusion criteria, extracted relevant data and assessed the risk of bias. We resolved disagreements through discussion or by involving a third review author. We followed Cochrane guidelines in performing the statistical analyses. Two review authors applied the GRADE tool to assess the certainty of the evidence in line with what is suggested by both Cochrane and GRADE. These methods should have minimised the risk of bias in the review process, although some possible issues remain.

We could not properly assess the risk of publication bias through funnel plots due to the low number of studies per comparison.

We found very limited information concerning adverse events. However, knowledge about the possible adverse effects of escitalopram, hydrocortisone and temazepam already exists, and this could mitigate this limitation of the review.

Agreements and disagreements with other studies or reviews

This Cochrane review and its parallel review (Bertolini 2022) are the first to consider separately indicated (i.e. treatments for people with at least some acute stress symptoms after a traumatic event) and universal prevention of PTSD. Previous systematic reviews have considered together the two approaches (Amos 2014; Astill Wright 2019; Bisson 2021), and thus a direct comparison is not possible. Despite this, and some other minor methodological differences, the results of this review are consistent with what has previously been reported. We did not find current evidence of efficacy for any intervention in the context of a very limited evidence base that prevents drawing definitive conclusions at the moment.

The results of this review are consistent with current guidance, which does not recommend routine use of pharmacological intervention for the indicated prevention of PTSD by treating acute stress symptoms. The UK National Institute for Health and Care Excellent (NICE) advises that drugs should not be offered to prevent PTSD (NICE 2018). The USA Department of Veteran Affairs and Department of Defense guidelines on PTSD found insufficient evidence to recommend pharmacotherapy for the indicated prevention of PTSD in people with acute stress disorder (ASD) (Veterans Affairs/Department of Defense 2017). Phoenix Australia guidelines do not list drugs as a possible preventive intervention but recognise a role for hydrocortisone in the research context (Phoenix Australia 2021). The International Society for Traumatic Stress Studies (ISTSS) guidelines list hydrocortisone as a universal intervention, with emerging evidence that it could be considered in people with severe physical illness or injury (ISTSS 2018), which is consistent with what we found for hydrocortisone in the review for universal prevention of PTSD (Bertolini 2022).

AUTHORS' CONCLUSIONS

Implications for practice

This review provides only uncertain evidence regarding the use of escitalopram, hydrocortisone, intranasal oxytocin and temazepam for the prevention of post-traumatic stress disorder (PTSD) in people experiencing acute stress symptoms. This evidence is limited by the very small number of participants included and by the fact that we could not properly assess tolerability. Hydrocortisone is a well-known drug, widely employed in other medical fields, for which several side effects are known, including psychiatric effects such as agitation and abnormally elevated mood. Acute stress symptoms are often self-limited in time, and a careful assessment of expected benefits against side effects is therefore required.

Implications for research

Future research might benefit from addressing the current limitations of the evidence base. Participant enrolment represents a major challenge for these trials. However, larger sample sizes are needed to yield stronger conclusions. This would also allow investigation of whether specific subgroups or trauma events might benefit more from the intervention (e.g. women rather than men, interpersonal trauma rather than non-interpersonal trauma). Criteria for defining acute stress symptoms for inclusion in the primary studies varied, which may have led to different levels of psychological distress within the original samples. Additionally, psychological distress has been assessed using a variety of tools. A common operative framework of criteria for inclusion and baseline assessment might help in better understanding who, if anyone, benefits from an intervention. As far as possible, assessment and reporting of reasons for dropout would better inform the understanding of tolerability, a key aspect for prevention trials. Specific high-risk populations, such as people exposed to major natural disasters, are not currently represented in the evidence

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base. For hydrocortisone, one of the most promising interventions, it is unclear whether the administration form (intravenous bolus or oral administration), timing after the traumatic event and length of treatment, or the phase of circadian rhythm influences the efficacy. This would have important repercussions in terms of practicality and feasibility and might explain the slightly conflicting results between randomised controlled trials.

Most of the investigated interventions have been thoroughly investigated in terms of side effects in other research fields. Nevertheless, future trials might consider better reporting of side effects in this specific context. We believe that both potential participants and clinicians need a robust assessment of possible benefits and harms in order to be confident in a pharmacological intervention for the prevention of PTSD.

Symptom severity by itself does not provide the full picture of the impact of exposure to trauma. Quality of life and functional impairment have been sparsely assessed. A more thorough assessment would provide a more comprehensive picture of the effects of the interventions.

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The following people conducted the editorial process for this article:

- **Sign-off Editor** (final editorial decision): Norio Watanabe, Department of Psychiatry, Soseikai General Hospital, Japan
- **Managing Editor** (edited the article, collated peer reviewer comments and provided editorial guidance to authors): Marwah Anas El-Wegoud, Cochrane Central Editorial Service
- **Editorial Assistant** (selected peer reviewers, conducted editorial policy checks and supported the editorial team): Sara Hales-Brittain, Cochrane Central Editorial Service
- **Copy Editor** (copy editing and production): Jenny Bellorini, Cochrane Central Production Service
- **Peer reviewers (provided comments and recommended an editorial decision)**: Emily Lowery-Gionta, PhD, Walter Reed Army Institute of Research, Center for Military Psychiatry and Neuroscience (**clinical review**); Marcelo Arancibia - Department of Psychiatry Universidad de Valparaíso (**clinical review**); Nuala Livingstone, Cochrane Evidence Production and Methods Directorate (**methods review**); Jo Platt, Central Editorial Information Specialist (**search review**); Brian Duncan (**consumer review**)

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REFERENCES

References to studies included in this review

Carmi 2022 *{published data only}*

Carmi L, Zohar J, Weissman T, Juven-Wetzler A, Bierer L, Yehuda R, et al. Hydrocortisone in the emergency department: a prospective, double-blind, randomized, controlled posttraumatic stress disorder study. Hydrocortisone during golden hours. *CNS Spectrums* 2022;**9**:1-7. [DOI: 10.1017/S1092852922000852] [PMID: 35678177]

Delahanty 2013 *{published data only}*

* Delahanty DL, Gabert-Quillen C, Ostrowski SA, Nugent NR, Fischer B, Morris A, et al. The efficacy of initial hydrocortisone administration at preventing posttraumatic distress in adult trauma patients: a randomized trial. CNS Spectrums 2013;**18**(2):103-11. [DOI: 10.1017/S1092852913000096)] [PMID: 23557627]

Delahanty DL, Ostrowski S, Nugent N, Gabert C, Fallon W. Hydrocortisone as a secondary intervention to prevent subsequent PTSD symptoms [conference abstract]. Psychosomatic Medicine [abstracts from the 69th Annual Meeting of the American Psychosomatic Society; 2011 Mar 9-12; San Antonio, TX United States] 2011;**73**(3):A107.

Mellman 2002 *{published data only}*

Mellman TA, Bustamante V, David D, Fins AI. Hypnotic medication in the aftermath of trauma. Journal of Clinical Psychiatry 2002;**63**(12):1183-4. [DOI: 10.4088/jcp.v63n1214h] [PMID: 12530420]

Shalev 2012 *{published data only}*

Galatzer-Levy IR, Ankri Y, Freedman S, Israeli-Shalev Y, Roitman P, Gilad M, et al. Early PTSD symptom trajectories: persistence, recovery, and response to treatment: results from the Jerusalem Trauma Outreach and Prevention Study (J-TOPS). PLOS One 2013;**8**(8):e70084. [DOI: 10.1371/journal.pone.0070084] [PMID: 23990895]

Shalev A Y, Ankri Y L, Peleg T, Israeli-Shalev Y, Freedman S. Barriers to receiving early care for PTSD: results from the Jerusalem trauma outreach and prevention study. *Psychiatric Services* 2011;**62**(7):765-73. [DOI: 10.1176/ps.62.7.pss6207_0765] [PMID: 21724790]

Shalev A Y, Ankri Y, Gilad M, Israeli-Shalev Y, Adessky R, Qian M, et al. Long-term outcome of early interventions to prevent posttraumatic stress disorder. *Journal of Clinical Psychiatry* 2016;**77**(5):e580-7. [DOI: 10.4088/JCP.15m09932] [PMID: 27135249]

Shalev AY, Ankri Y, Gilad M, Israeli- Shalev Y, Qian M, Galatzer-Levy I, et al. The differential effect of early and efficient interventions for acute PTSD declines with time [abstract]. In: Neuropsychopharmacology. A.Y. Shalev, New York University, New York, NY, United States, 2013:S365-6.

* Shalev AY, Ankri Y, Israeli-Shalev Y, Peleg T, Adessky R, Freedman S. Prevention of posttraumatic stress disorder by early treatment: results from the Jerusalem Trauma Outreach And Prevention study. Archives of General Psychiatry 2012;**69**(2):166-76. [DOI: 10.1001/archgenpsychiatry.2011.127] [PMID: 21969418]

Suliman 2015 *{published data only}*

Suliman S, Seedat S, Pingo J, Sutherland T, Zohar J, Stein DJ. Escitalopram in the prevention of posttraumatic stress disorder: a pilot randomized controlled trial. *BMC Psychiatry* 2015;**15**:24. [DOI: 10.1186/s12888-015-0391-3]

Van Zuiden 2017 *{published data only}*

Engel S, van Zuiden M, Frijling JL, Koch SBJ, Nawijn L, Schumacher S, et al. Patterns of recovery from early posttraumatic stress symptoms after a preventive intervention with oxytocin: hormonal contraception use is a prognostic factor. [References]. *Biological Psychiatry* 2019;**85**(12):e71-3. [DOI: 10.1016/j.biopsych.2019.01.014] [PMID: 30824111]

Engel S, van Zuiden M, Frijling JL, Koch SBJ, Nawijn L, Yildiz RLW, et al. Early posttraumatic autonomic and endocrine markers to predict posttraumatic stress symptoms after a preventive intervention with oxytocin. European Journal of Psychotraumatology 2020;**11**(1):1761622. [DOI: 10.1080/20008198.2020.1761622] [PMID: 32922686]

Frijling J, Van Zuiden M, Koch SBJ, Nawijn L, Veltman DJ, Olff M. Intranasal oxytocin attenuates amygdala functional connectivity after a trauma reminder in recently trauma-exposed individuals. *European Neuropsychopharmacology* 2015;**25**(Suppl 2):S560.

Frijling J, Van Zuiden M, Nawijn L, Koch S B J, Veltman D J, Olff M. Repeated intranasal oxytocin administration as early preventive intervention for PTSD: a randomized controlled trial. In: European Neuropsychopharmacology. Vol. 26. 2016:S129-30.

Frijling J, van Zuiden M, Koch S, Nawijn L, Veltman D, Olff M. Effects of intranasal oxytocin on amygdala reactivity to emotional faces in recently trauma-exposed individuals. *Social Cognitive and Affective Neuroscience* 2016;**11**(2):327-36. [DOI: 10.1093/scan/nsv116] [PMID: 26382634]

Frijling JL, Van Zuiden M, Koch SBJ, Nawijn L, Veltman DJ, Olff M. Intranasal oxytocin affects amygdala functional connectivity after trauma script-driven imagery in distressed recently trauma-exposed individuals. *Neuropsychopharmacology* 2016;**41**(5):1286-96.

Frijling JL, Van Zuiden M, Koch SBJ, Nawijn L, Veltman DJ, Olff M. Intranasal oxytocin modulates neural processing of emotional faces in recently traumatised individuals at increased risk for PTSD. In: European Neuropsychopharmacology. Vol. 27. 2014:S602. [DOI: 10.1016/S0924-977X(14)70965-4]

Frijling JL, Van Zuiden M, Nawijn L, Koch SBJ, Veltman DJ, Olff M. Repeated intranasal oxytocin administration AS early preventive intervention for PTSD: a randomized controlled trial. In: European Neuropsychopharmacology. 2016:S65-6.

Frijling JL, van Zuiden M, Koch SB, Nawijn L, Goslings JC, Luitse JS, et al. Efficacy of oxytocin administration early after psychotrauma in preventing the development of PTSD: study

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protocol of a randomized controlled trial. BMC Psychiatry 2014;**14**:92. [DOI: 10.1186/1471-244X-14-92] [PMID: 24679046]

Frijling JL. Preventing PTSD with oxytocin: effects of oxytocin administration on fear neurocircuitry and PTSD symptom development in recently trauma-exposed individuals. European Journal of Psychotraumatology 2017;**8**(1):1302652. [DOI: 10.1080/20008198.2017.1302652] [PMID: 28451068]

Olff M, Van Zuiden M, Nawijn L, Koch SBJ, Frijling JL, Veltman DJ. The effects of intranasal oxytocin after trauma. In: European Neuropsychopharmacology. Vol. 27. 2017:S527.

Van Zuiden M, Frijling JL, Nawijn L, Koch SBJ, Veltman DJ, Olff M. Prevention of PTSD by intranasal oxytocin administration and moderating effects of glucocorticoids. In: Biological Psychiatry. Vol. 1. 2016:68S.

* van Zuiden M, Frijling JL, Nawijn L, Koch SBJ, Goslings JC, Luitse JS, et al. Intranasal oxytocin to prevent posttraumatic stress disorder symptoms: a randomized controlled trial in emergency department patients. *Biological Psychiatry* 2017;**81**(12):1030-40. [1873-2402: (Electronic)]

Zohar 2011 *{published data only}*

* Zohar J, Yahalom H, Kozlovsky N, Cwikel-Hamzany S, Matar MA, Kaplan Z, et al. High dose hydrocortisone immediately after trauma may alter the trajectory of PTSD: interplay between clinical and animal studies. *European Neuropsychopharmacology* 2011;**21**(11):796-809.

Zohar J. High dose hydrocortisone immediately after trauma may alter the trajectory of posttraumatic stress disorder: Translational interplay between clinical and animal studies [abstract]. *Neuropsychopharmacology [abstracts of the 50th Annual Meeting of the American college of Neuropsychopharmacology, ACNP; 4-8 Dec 2011, Waikoloa, HI United States]* 2011;**36**:S24.

Zohar J. Hydrocortisone in the golden hours and PTSD trajectory-clinical and animal studies. *International Journal of Neuropsychopharmacology* 2012;**15**(Suppl 1):18.

Zohar J. Long-term effects of high-dose hydrocortisone immediately after trauma: a double blind, placebo-controlled prospective study. *Neuropsychopharmacology* 2017;**43**:S89-90.

Zohar J. New insights into secondary prevention in PTSD. *International Journal of Neuropsychopharmacology* 2014;**17**(Suppl 1):20. [DOI: 10.1017/S1461145714000741]

Zohar 2018 *{published data only}*

* Zohar J, Fostick L, Juven-Wetzler A, Kaplan Z, Shalev H, Schreiber G, et al. Secondary prevention of chronic PTSD by early and short-term administration of escitalopram: a prospective randomized, placebo-controlled, double-blind trial. *Journal of Clinical Psychiatry* 2018;**79**(2):48-54. [DOI: 10.4088/JCP.16m10730] [PMID: 28703951]

Zohar J. Golden hours in psychiatric disorders: focus on PTSD [abstract]. *Indian Journal of Psychiatry [Abstracts of the 64th Annual National Conference of the Indian Psychiatric Society, ANCIPS; 2012 Jan 19-22; Kochi, India]* 2012;**54**:S30-1.

References to studies excluded from this review

Bailly 2021 *{published data only}*

Bailly P, Egreteau PY, Ehrmann S, Thille AW, Guitton C, Grillet G, et al. Inased (inhaled sedation in ICU) trial protocol: a multicentre randomised open-label trial. *BMJ Open* 2021;**11**:e042284. [DOI: 10.1136/bmjopen-2020-042284] [PMID: 33608400]

Bartoszek 2023 *{published data only}*

Bartoszek M, McGuire JM, Wilson JT, Sorensen JS, Vice TFR, Hudson AJ. The effectiveness of dexmedetomidine as a prophylactic treatment for emergence delirium among combat veterans with high anxiety: a randomized placebo-controlled trial. *Military Medicine* 2023;**188**(1):e286-94. [DOI: 10.1093/milmed/usab212] [PMID: 34057183]

Beaudoin 2022 *{published data only}*

Beaudoin FL, Gaither R, DeLomba WC, McLean SA. Tolerability and efficacy of duloxetine for the prevention of persistent musculoskeletal pain after trauma and injury: a pilot three-group randomized controlled trial. *Pain* 2022;**15**:855-63. [DOI: 10.1097/j.pain.0000000000002782] [PMID: 36375173]

Blaha 1999 *{published data only}*

Blaha J, Svobodova K, Kapounkova Z. Therapeutical aspects of using citalopram in burns. *Acta Chirurgiae Plasticae* 1999;**41**(1):25-32.

Borrelli 2019 *{published data only}*

Borrelli J Jr, Starr A, Downs DL, North CS. Prospective study of the effectiveness of paroxetine on the onset of posttraumatic stress disorder, depression, and health and functional outcomes after trauma. Journal of Orthopaedic Trauma 2019;**33**(2):e58-63. [1531-2291: (Electronic)]

Denke 2008 *{published data only}*

Denke C, Deja M, Carstens S, Sprung CL, Annane D, Briegel J, et al. Effects of hydrocortisone on posttraumatic stress disorder after septic shock: results from the CORTICUS Berlin Study Group. *Critical Care* 2008;**12**(2):P421. [DOI: 10.1186/cc6642]

Sprung C L, Annane D, Keh D, Moreno R, Singer M, Freivogel K, et al. Hydrocortisone therapy for patients with septic shock. *New England Journal of Medicine* 2008;**358**(2):111-24. [DOI: 10.1056/NEJMoa071366] [PMID: 18184957]

EUCTR-004177-83-NL *{unpublished data only}*

EUCTR-004177-83-NL. Oxytocine en social support after a traumatic event. https://www.clinicaltrialsregister.eu/ctr-search/trial/2011-004177-83/NL 2011.

EUCTR2019-004537-16-FR *{published data only}*

EUCTR2019-004537-16-FR. Comparison of an inhaled sedation strategy to an intravenous sedation strategy in ICU patients treated with invasive mechanical ventilation. https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2019-004537-16-FR 2020.

Copyright © 2024 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

FDA 1999 *{published data only}*

FDA. Review and evaluation of clinical data. Drugs@fda [www.accessdata.fda.gov] | http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/19-839S026_Zoloft_Clinr_P1.pdf 1999.

Frankova 2017 *{published data only}*

Frankova I. Will early intervention with SSRI versus benzodiazepines reduce the risk of developing posttraumatic stress disorder? In: European Neuropsychopharmacology. Vol. 27. 2017:S998-9.

Gelpin 1996 *{published data only}*

Gelpin E, Bonne O, Peri T, Brandes D, Shalev AY. Treatment of recent trauma survivors with benzodiazepines: a prospective study. *Journal of Clinical Psychiatry* 1996;**57**(9):390-4.

Haywood 2021 *{published data only}*

Haywood K L, Ji C, Quinn T, Nolan JP, Deakin CD, Scomparin C, et al. Long term outcomes of participants in the PARAMEDIC2 randomised trial of adrenaline in out-of-hospital cardiac arrest. *Resuscitation* 2021;**160**:84-93. [DOI: 10.1016/j.resuscitation.2021.01.019] [PMID: 33861194]

Hicks 2009 *{published data only}*

Hicks P B, Adams M L, Litz B, Young K, Goldart J, Velez T, et al. Predictors of treatment response to fluoxetine in PTSD following a recent history of war zone stress exposure. In: CCMDCTR. 2009.

Hoge 2012 *{published data only}*

Hoge EA, Worthington JJ, Nagurney JT, Chang Y, Kay EB, Feterowski CM, et al. Effect of acute posttrauma propranolol on PTSD outcome and physiological responses during script-driven imagery. *CNS Neuroscience & Therapeutics* 2012;**18**(1):21-7. [DOI: 10.1111/j.1755-5949.2010.00227.x] [PMID: 22070357]

IRCT20190919044819N2 *{published data only}***20190919044819N**

IRCT20190919044819N2. The effect of propranolol on post-traumatic stress and clinical outcomes in burn patients. https://trialsearch.who.int/Trial2.aspx?TrialID=IRCT20190919044819N2 2020.

Kagan 2015 *{published data only}*

* Kagan I, Ben David I, Cohen J, Baniel I, Silva V, Grinev M, et al. SUN-PP054: Long term effects of EPA, GLA and antioxidant administration on post traumatic stress disorder (PTSD) following multiple trauma; a prospective randomized double blind study. *Clinical Nutrition* 2015;**34**(Suppl 1):S43. [DOI: 10.1016/S0261-5614(15)30205-3]

Kagan I, Cohen J, Stein M, Bendavid I, Pinsker D, Silva V, et al. Preemptive enteral nutrition enriched with eicosapentaenoic acid, gamma-linolenic acid and antioxidants in severe multiple trauma: a prospective, randomized, double-blind study. *Intensive Care Medicine* 2015;**41**(3):460-9. [DOI: 10.1007/s00134-015-3646-z] [PMID: 25672274]

Kaplan 2015 *{published data only}*

Kaplan BJ, Rucklidge JJ, Romijn AR, Dolph M. A randomised trial of nutrient supplements to minimise psychological stress after a natural disaster. *Psychiatry Research* 2015;**228**(3):373-9.

Kok 2016 *{published data only}*

Dieleman JM, Nierich AP, Rosseel PM, van der Maaten JM, Hofland J, Diephuis JC, et al. Intraoperative high-dose dexamethasone for cardiac surgery: a randomized controlled trial. *JAMA* 2012;**308**(17):1761-7. [DOI: 10.1001/jama.2012.14144] [PMID: 23117776]

Kok L, Hillegers M, Veldhuijzen D, Joels M, Van Dijk D. Individual susceptibility to stress-related psychopathology after cardiac surgery. *Psychoneuroendocrinology* 2015;**61**:24.

Kok L, Hillegers MH, Veldhuijzen DS, Boks MP, Dieleman JM, van Dijk D, et al. Genetic variation in the glucocorticoid receptor and psychopathology after dexamethasone administration in cardiac surgery patients. *Journal of Psychiatric Research* 2018;**103**:167-72. [DOI: 10.1016/j.jpsychires.2018.05.015] [PMID: 29879676]

* Kok L, Hillegers MH, Veldhuijzen DS, Cornelisse S, Nierich AP, van der Maaten JM, et al. The effect of dexamethasone on symptoms of posttraumatic stress disorder and depression after cardiac surgery and intensive care admission: longitudinal follow-up of a randomized controlled trial. *Critical Care Medicine* 2016;**44**(3):512-20. [DOI: 10.1097/CCM.0000000000001419] [PMID: 26540396]

Kok L, Hillegers MHJ, Veldhuijzen DS, Cornelisse S, Sep MSC, Peelen LM, et al. The effect of dexamethasone on symptoms of post-traumatic stress disorder and depression after cardiac surgery. *European Neuropsychopharmacology* 2015;**44**(3):S74-5. [DOI: 10.1097/CCM.0000000000001419]

Lijffijt 2019 *{published data only}*

Lijffijt M, Green CE, Balderston N, Iqbal T, Atkinson M, Vo-Le B, et al. A proof-of-mechanism study to test effects of the NMDA receptor antagonist lanicemine on behavioral sensitization in individuals with symptoms of PTSD. Frontiers in Psychiatry 2019;**10**:846. [DOI: 0.3389/fpsyt.2019.00846] [PMID: 31920733]

Lossada-Soto 2022 *{published data only}*

Lossada-Soto E, Pazik M, Horodyski M B, Vasilopoulos T, de Faria LB, Mathews C, et al. Can fluoxetine mitigate mental health decline in musculoskeletal trauma patients: a pilot single-center randomized clinical trial. *Pilot & Feasibility Studies* 2022;**8**(1):184. [DOI: 10.1186/s40814-022-01119-8] [PMID: 35978446]

Matsumura 2011 *{published data only}*

Matsumura K, Noguchi H, Nishi D, Matsuoka Y. The effect of omega-3 fatty acids on psychophysiological assessment for the secondary prevention of posttraumatic stress disorder: an open-label pilot study. *Global Journal of Health Science* 2012;**4**(1):3-9.

Matsuoka 2010 *{published data only}*

Matsuoka Y, Nishi D, Yonemoto N, Hamazaki K, Hamazaki T, Hashimoto K. Potential role of brain-derived neurotrophic factor in omega-3 fatty acid supplementation to prevent posttraumatic distress after accidental injury: An open-label pilot study. *Psychotherapy and Psychosomatics* 2011;**80**(5):310-2.

Copyright © 2024 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Matsuoka 2015 *{published data only}*

Matsumura K, Noguchi H, Nishi D, Hamazaki K, Hamazaki T, Matsuoka YJ. Effects of omega-3 polyunsaturated fatty acids on psychophysiological symptoms of post-traumatic stress disorder in accident survivors: a randomized, double-blind, placebo-controlled trial. *Journal of Affective Disorders* 2017;**224**:27-31. [DOI: 10.1016/j.jad.2016.05.054] [PMID: 27287561]

* Matsuoka Y, Nishi D, Hamazaki K, Yonemoto N, Matsumura K, Noguchi H, et al. Docosahexaenoic acid for selective prevention of posttraumatic stress disorder among severely injured patients: a randomized, placebo-controlled trial. *Journal of Clinical Psychiatry* 2015;**76**(8):e1015-22. [DOI: 10.4088/JCP.14m09260] [PMID: 26335087]

Matsuoka Y, Nishi D, Tanima Y, Itakura M, Kojima M, Hamazaki K, et al. Serum BDNF as a treatment biomarker for response to docosahexaenoic acid in traumatized people vulnerable to developing psychological distress: a randomized controlled trial. *Psychotherapy and Psychosomatics* 2015;**84**(Suppl 1):47. [DOI: 10.1159/000438780]

Matsuoka Y, Nishi D, Tanima Y, Itakura M, Kojima M, Hamazaki K, et al. Serum pro-BDNF/BDNF as a treatment biomarker for response to docosahexaenoic acid in traumatized people vulnerable to developing psychological distress: A randomized controlled trial. *Translational Psychiatry* 2015;**5**:e596. [DOI: 10.1038/tp.2015.89] [PMID: 26151924]

Matsuoka Y, Nishi D, Yonemoto N, Hamazaki K, Matsumura K, Noguchi H, et al. Tachikawa project for prevention of posttraumatic stress disorder with polyunsaturated fatty acid (TPOP): study protocol for a randomized controlled trial. *BMC Psychiatry* 2013;**13**:8. [DOI: 10.1186/1471-244X-13-8] [PMID: 23289548]

Matsuoka Y, Nishi D. Possible use of omega 3 polyunsaturated fatty acids for prevention of PTSD. Seishin Shinkeigaku Zasshi (Psychiatria et Neurologia Japonica) 2009;**111**(12):1527-30.

Noguchi H, Nishi D, Matsumura K, Hamazaki K, Hamazaki T, Matsuoka YJ. Limited effect of omega-3 fatty acids on the quality of life in survivors of traumatic injury: a randomized, placebo-controlled trial. *Prostaglandins, Leukotrienes, and Essential Fatty Acids* 2017;**127**:1-5. [10.1016/j.plefa.2017.09.018] [PMID: 29156152]

Noguchi H, Nishi Y, Matsumura K, Hamazaki K, Hamazaki T, Matsuoka Y. The effect of docosahexaenoic acid on quality of life among traumatized people: a randomized, placebo-controlled trial. *Psychotherapy and Psychosomatics* 2015;**84**(Suppl 1):52. [DOI: 10.1159/000438780]

McMullan 2021 *{published data only}*

McMullan J, Droege C, Strilka R, Hart K, Lindsell C. Intranasal ketamine as an adjunct to fentanyl for the prehospital treatment of acute traumatic pain: design and rationale of a randomized controlled trial. *Prehospital Emergency Care* 2021;**25**(4):519-29. [DOI: 10.1080/10903127.2020.1808746] [PMID: 32772873]

Mistraletti 2015 *{published data only}*

Mistraletti G, Umbrello M, Sabbatini G, Miori S, Taverna M, Cerri B, et al. Melatonin reduces the need for sedation in ICU patients: a randomized controlled trial. *Minerva Anestesiologica* 2015;**81**(12):1298-310. [PMID: 25969139]

Naylor 2013 *{published data only}*

Naylor JC, Dolber TR, Strauss JL, Kilts JD, Strauman TJ, Bradford DW, et al. A pilot randomized controlled trial with paroxetine for subthreshold PTSD in Operation Enduring Freedom/Operation Iraqi Freedom era veterans. Psychiatry Research 2013;**206**(2-3):318-20. [DOI: 10.1016/j.psychres.2012.11.008] [PMID: 23276723]

NCT00114374 *{unpublished data only}*

NCT00114374. SSRI administration to reduce acute stress disorder symptoms and prevent depression and PTSD in physical trauma victims. https://clinicaltrials.gov/ct2/show/NCT00114374 2005.

NCT00674570 *{published data only}*

Inslicht SS. Effects of hydrocortisone and D-cycloserine on fear extinction in veterans with posttraumatic stress disorder. http://clinicaltrials.gov/show/nct00674570 2008.

NCT02069366 *{published data only}*

Rabinak CA. Cannabinoid control of fear extinction neural circuits in post-traumatic stress disorder. https://clinicaltrials.gov/show/NCT02069366 2014. [clinicaltrials.gov/show/NCT02069366]

NCT02505984 *{unpublished data only}*

NCT02505984. Preventing postpartum depression with intranasal oxytocin (IN-OXT). https://clinicaltrials.gov/ct2/show/NCT02505984 2015.

NCT03724448 *{unpublished data only}*

Boukef R, Youssef R, Yaakoubi H, Trabelsi I, Sekma A, Ali KBH, Salah HB, Baccari A, Boukadida L, Zorgati A. Double-blind, randomized, placebo-controlled study to evaluate the efficacy of an early treatment with herbal supplement based in the prevention of post-traumatic stress disorder in emergency department (PHYTeS Study). medRxiv 2022;**13**.

NCT03724448. The efficacy of a herbal supplement in the prevention of PTSD (PHYTéS). https://clinicaltrials.gov/ct2/show/NCT03724448.

NCT04467086 *{published data only}*

NCT04467086. Propranolol as an anxiolytic to reduce the use of sedatives from critically-ill adults receiving mechanical ventilation. https://clinicaltrials.gov/show/NCT04467086 2020.

Nedergaard 2020 *{published data only}*

Nedergaard HK, Jensen HI, Stylsvig M, Olsen HT, Strom T, Toft P. Effect of non-sedation on post-traumatic stress and psychological health in survivors of critical illness-a substudy of the NONSEDA randomized trial. Acta Anaesthesiologica Scandinavica 2020;**64**(8):1136-43. [DOI: 10.1111/aas.13648] [PMID: 32470147]

Copyright © 2024 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Nishi 2012 *{published data only}*

JPRN-UMIN000005367. Omega-3 polyunsaturated fatty acids for secondary prevention of critical incident stress after Japan earthquake March 11 in disaster medical assistance team (DMAT) workers: a randomized controlled trial. https://rctportal.niph.go.jp/en/detail?trial_id=UMIN000005367 2011.

Matsuoka Y, Nishi D, Koido Y I, Nakaya N, Sone T, Noguchi H, et al. Fish oil for attenuating posttraumatic stress symptoms among rescue workers after the great east japan earthquake: a randomized controlled trial. *Psychosomatic Medicine* 2013;**75**(3):A-131.

Matsuoka Y, Nishi D, Nakaya N, Sone T, Hamazaki K, Hamazaki T, et al. Attenuating posttraumatic distress with omega-3 polyunsaturated fatty acids among disaster medical assistance team members after the Great East Japan Earthquake: the APOP randomized controlled trial. *BMC Psychiatry* 2011;**11**:132.

Nishi D, Koido Y, Nakaya N, Sone T, Noguchi H, Hamazaki K, et al. Fish oil for attenuating posttraumatic stress symptoms among rescue workers after the great east Japan earthquake: a randomized controlled trial. *Psychotherapy and Psychosomatics* 2012;**81**(5):315-7.

Nishi D, Matsuoka Y. Omega-3 fatty acids for attenuating posttraumatic stress symptoms after the earthquake: a randomized controlled trial. *Psychotherapy and Psychosomatics* 2013;**82**(Suppl 1):75.

Susukida R, Nishi D, Kawashima Y, Koido Y, Mojtabai R, Matsuoka YJ. Generalizability of findings from a randomized controlled trial of fish oil supplementation for attenuating posttraumatic stress symptoms among rescue workers in Japan. *Psychotherapy & Psychosomatics* 2018;**21**:21.

Orrey 2015 *{published data only}*

Orrey D, Bortsov A, Liberzon I, Shupp J W, Jones S, Hwang J, et al. Failure of propranolol to decrease anxiety and PTSD symptoms in a genotype-based RCT of patients with major thermal burn injury [abstract]. In: Biological Psychiatry [Abstracts of the 67th Annual Scientific Convention and Meeting of the Society of Biological Psychiatry; 2012 May 3-5; Philadelphia, PA United States]. Vol. 71. 2012:56S. [DOI: 10.1016/j.biopsych.2012.02.012]

Orrey D, Bortsov A, Shupp J, Jones S, Hwang J, Jordan M, et al. Individuals with elevated PTSD symptoms experience increased itch symptom morbidity after major burn injury [abstract]. *Biological Psychiatry [Abstracts of the 67th Annual Scientific Convention and Meeting of the Society of Biological Psychiatry; 2012 May 3-5; Philadelphia, PA United States]* 2012;**71**(8):242S. [DOI: 10.1016/j.biopsych.2012.02.014]

Orrey DC, Halawa OI, Bortsov AV, Shupp JW, Jones SW, Haith LR, et al. Results of a pilot multicenter genotype-based randomized placebo-controlled trial of propranolol to reduce pain after major thermal burn injury. *Clinical Journal of Pain* 2015;**31**(1):21-9. [DOI: 10.1097/Ajp.0000000000000086] [PMID: 25084070]

Pitman 2002 *{published data only}*

Pitman RK, Sanders KM, Zusman RM, Healy AR, Cheema F, Lasko NB, et al. Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. *Biological Psychiatry* 2002;**51**(2):189-92.

Rabinak 2020 *{published data only}*

Rabinak CA, Blanchette A, Zabik NL, Peters C, Marusak HA, Iadipaolo A, et al. Cannabinoid modulation of corticolimbic activation to threat in trauma-exposed adults: a preliminary study. *Psychopharmacology (Berl)* 2020;**237**(6):1813-26. [DOI: 10.1007/s00213-020-05499-8] [PMID: 32162103]

Rucklidge 2012 *{published data only}*

* Rucklidge JJ, Andridge R, Gorman B, Blampied N, Gordon H, Boggis A. Shaken but unstirred? Effects of micronutrients on stress and trauma after an earthquake: RCT evidence comparing formulas and doses. *Human Psychopharmacology* 2012;**27**(5):440-54. [DOI: 10.1002/hup.2246] [PMID: 22782571]

Rucklidge JJ, Blampied N, Gorman B, Gordon HA, Sole E. Psychological functioning 1 year after a brief intervention using micronutrients to treat stress and anxiety related to the 2011 Christchurch earthquakes: a naturalistic follow-up. *Human Psychopharmacology* 2014;**29**(3):230-43. [DOI: 10.1002/hup.2392] [PMID: 24554519]

Schelling 2001 *{published data only}*

Schelling G, Briegel J, Roozendaal B, Stoll C, Rothenhausler HB, Kapfhammer HP. The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder in survivors. *Biological Psychiatry* 2001;**50**(12):978-85. [DOI: 10.1016/s0006-3223(01)01270-7] [PMID: 11750894]

Schelling G, Stoll C, Wichmann A, Haller M, Schuffel W, Briegel J. The effect of hydrocortisone (HC) during septic shock on incidence and intensity of post-traumatic stress disorder (PTSD) in long term survivors. *Critical Care Medicine* 1998;**26**:131A.

Schelling 2004 *{published data only}*

Schelling G, Kilger E, Roozendaal B, de Quervain DJ, Briegel J, Dagge A, et al. Stress doses of hydrocortisone, traumatic memories, and symptoms of posttraumatic stress disorder in patients after cardiac surgery: a randomized study. *Biological Psychiatry* 2004;**55**(6):627-33. [PMID: 15013832]

Schelling G, Roozendaal B, De Quervain DJ. Can posttraumatic stress disorder be prevented with glucocorticoids? *Annals of the New York Academy of Sciences* 2004;**1032**:158-66.

Schelling G, Roozendaal B, Krauseneck T, Schmoelz M, DE Quervain D, Briegel J. Efficacy of hydrocortisone in preventing posttraumatic stress disorder following critical illness and major surgery. *Annals of the New York Academy of Sciences* 2006;**1071**:46-53.

Shaked 2019 *{published data only}*

Shaked G, Shaked D, Sebbag G, Czeiger D. The effect of steroid treatment on whiplash associated syndrome: a controlled randomized prospective trial. *European Journal of Trauma and Emergency Surgery* 2019;**6**:1115-22. [DOI: 10.1007/s00068-019-01282-3] [PMID: 31811333]

Copyright © 2024 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Stein 2007 *{published data only}*

Stein M B, Kerridge C, Dimsdale JE, Hoyt DB. Pharmacotherapy to prevent PTSD: results from a randomized controlled proof-of-concept trial in physically injured patients. *Journal of Traumatic Stress* 2007;**20**(6):923-32. [DOI: 10.1002/jts.20270] [PMID: 18157888]

Stoddard 2011 *{published data only}*

Stoddard Jr, Fj, Luthra R, Sorrentino EA, Saxe GN, Drake J, et al. A randomized controlled trial of sertraline to prevent posttraumatic stress disorder in burned children. *Journal of Child and Adolescent Psychopharmacology* 2011;**21**(5):469-77.

Takehiro 2014 *{published data only}*

Takehiro N, Shen G, Shin T, Satomi T, Yasutake M, Soichiro K, et al. Treatment of posttraumatic stress disorder using the traditional Japanese herbal medicine Saikokeishikankyoto: a randomized, observer-blinded, controlled trial in survivors of the Great East Japan Earthquake and Tsunami. *Evidence-based Complementary and Alternative Medicine* 2014;**2014**:683293. [DOI: 10.1155/2014/683293] [PMID: 24790634]

Tincu 2016 *{published data only}*

Tincu R, Cobilinschi C, Tomescu D, Ghiorghiu Z, Macovei R. Can 5-hydroxytriptophan prevent post-traumatic stress disorder in critically ill patients? *Critical Care. Conference: 36th International Symposium on Intensive Care and Emergency Medicine. Brussels Belgium.* 2016;**20**:119.

Treggiari 2009 *{published data only}*

Treggiari MM, Rom, AJ, Yanez ND, Deem SA, Goldberg J, et al. Randomized trial of light versus deep sedation on mental health after critical illness. *Critical Care Medicine* 2009;**37**(9):2527-34.

Truppman Lattie 2020 *{published data only}*

Truppman Lattie D, Nehoff H, Neehoff S, Gray A, Glue P. Anxiolytic effects of acute and maintenance ketamine, as assessed by the Fear Questionnaire subscales and the Spielberger State Anxiety Rating Scale. Journal of Psychopharmacology 2020 Sep 9 [Epub ahead of print]:137-41. [DOI: 10.1177/0269881120953991] [PMID: 32900266]

Weis 2006 *{published data only}*

Weis F, Kilger E, Roozendaal B, de Quervain DJ, Lamm P, Schmidt M, et al. Stress doses of hydrocortisone reduce chronic stress symptoms and improve health-related quality of life in high-risk patients after cardiac surgery: a randomized study. *Journal of Thoracic and Cardiovascular Surgery* 2006;**131**(2):277-82. [DOI: 10.1016/j.jtcvs.2005.07.063] [PMID: 16434254]

Yang 2011 *{published data only}*

Yang H T, Xiong Y, Zhou F. Immunoprotection of dexmedetomidine from acute psychological stress. *Journal of Dalian Medical University* 2011;**33**(5):479-82.

Zhong 2022 *{published data only}*

ChiCTR2100050202. Effect of general anesthetics on post-traumatic stress disorder after emergency surgery in trauma patients. https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR2100050202 2021.

Zhong J, Li Y, Fang L, Han D, Gong C, Hu S, et al. Effects of sevoflurane and propofol on posttraumatic stress disorder after emergency trauma: a double-blind randomized controlled trial. *Frontiers in Psychiatry Frontiers Research Foundation* 2022;**13**:853795. [DOI: 10.3389/fpsyt.2022.853795] [PMID: 35280171]

Zoellner 2001 *{published data only}*

Zoellner LA, Foa EB, Feeny NC, Meadows EA, Hembree EA. Prevention of chronic PTSD in recent asault victims. In: 17th Annual Meeting, International Society for Traumatic Stress Studies, December 6-9, New Orleans, LA. 2001.

References to ongoing studies

EUCTR-000088-12-DE *{unpublished data only}*

EUCTR-000088-12-DE. A prospective, single-blinded (rater-blinded), randomized, parallel group study of the efficacy of quetiapine XR in the treatment of patients with acute stress disorder (DSM-VI 308.3) - QSR-ASD. https://www.clinicaltrialsregister.eu/ctr-search/trial/2007-000088-12/DE 2009.

McMullan 2020 *{published data only}*

McMullan J, Droege C, Strilka R, Hart K, Lindsell C. Intranasal ketamine as an adjunct to fentanyl for the prehospital treatment of acute traumatic pain: design and rationale of a randomized controlled trial. Prehospital Emergency Care 2020:1-11. [DOI: 10.1080/10903127.2020.1808746] [PMID: 32772873]

NCT01039766 *{published data only}*

NCT01039766. The efficacy of a single dose of intranasal oxytocin in the prevention of post traumatic stress disorder (PTSD). http://clinicaltrials.gov/show/NCT01039766 2009.

NCT03997864 *{unpublished data only}*

NCT03997864. Administration of prazosin to prevent PTSD in adult women after sexual assault. https://clinicaltrials.gov/show/NCT03997864 2019.

NCT04071600 *{unpublished data only}*

NCT04071600. Intranasal neuropeptide Y in clinical trial in level two trauma patients for PTSD and acute stress disorder. https://clinicaltrials.gov/ct2/show/NCT04071600.

NCT04274361 *{published data only}*

NCT04274361. Ketamine in severe traumatic injury. https://clinicaltrials.gov/show/NCT04274361 2020.

NCT04924166 *{published data only}*

NCT04924166. PTSD prevention using oral hydrocortisone. https://clinicaltrials.gov/show/NCT04924166 2021.

Additional references

Amos 2014

Amos T, Stein DJ, Ipser JC. Pharmacological interventions for preventing post-traumatic stress disorder (PTSD). *Cochrane Database of Systematic Reviews* 2014, Issue 7. Art. No:

Copyright © 2024 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

CD006239. [DOI: 10.1002/14651858.CD006239.pub2] [PMID: 25001071]

APA 2000

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (4th edition, text revision). Washington, DC: American Psychiatric Association, 2000.

APA 2013

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Washington, DC: American Psychiatric Association, 2013.

Astill Wright 2019

Astill Wright L, Sijbrandij M, Sinnerton R, Lewis C, Roberts NP, Bisson JI. Pharmacological prevention and early treatment of post-traumatic stress disorder and acute stress disorder: a systematic review and meta-analysis. Translational Psychiatry 2019;**9**(1):334. [DOI: 10.1038/s41398-019-0673-5] [PMID: 31819037]

Barbee 1993

Barbee JG. Memory, benzodiazepines, and anxiety: integration of theoretical and clinical perspectives. *Journal of Clinical Psychiatry* 1993;**54 Suppl**:86-97; discussion 98-101. [PMID: 8262893]

Beck 1961

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Archives of General Psychiatry* 1961;**4**:561-71. [PMID: 13688369]

Beck 1988

Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *Journal of Consulting and Clinical Psychology* 1988;**56**(6):893-7. [PMID: 3204199]

Bertolini 2022

Bertolini F, Robertson L, Bisson JL, Meader N, Churchill R, Ostuzzi G, et al. Early pharmacological interventions for universal prevention of post-traumatic stress disorder (PTSD). *Cochrane Database of Systematic Reviews* 2022, Issue 2. Art. No: CD013443. [DOI: 10.1002/14651858.CD013443.pub2]

Besnard 2012

Besnard A, Caboche J, Laroche S. Reconsolidation of memory: a decade of debate. *Progress in Neurobiology* 2012;**99**(1):61-80. [PMID: 22877586]

Bisson 2021

Bisson JI, Wright LA, Jones KA, Lewis C, Phelps AJ, Sijbrandij M, et al. Preventing the onset of post traumatic stress disorder. *Clinical Psychology Review* 2021;**86**:102004. [DOI: j.cpr.2021.102004] [PMID: 33857763]

Blake 1995

Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, et al. The development of a Clinician-Administered PTSD Scale. *Journal of Traumatic Stress* 1995;**8**(1):75-90. [PMID: 7712061]

Bogic 2015

Bogic M, Njoku A, Priebe S. Long-term mental health of war-refugees: a systematic literature review. *BMC International Health and Human Rights* 2015;**15**:29. [PMID: 26510473]

Boissel 1999

Boissel JP, Cucherat M, Li W, Chatellier G, Gueyffier F, Buyse M, et al. The problem of therapeutic efficacy indices. 3. Comparison of the indices and their use [Apercu sur la problematique des indices d'efficacite therapeutique, 3: comparaison des indices et utilisation. Groupe d'Etude des Indices D'efficacite]. *Therapie* 1999;**54**(4):405-11. [PMID: 10667106]

Breslau 2012

Breslau N. Epidemiology of posttraumatic stress disorder in adults. In: Beck JG, Sloan DM, editors(s). The Oxford Handbook of Traumatic Stress Disorders. Oxford: Oxford University Press, 2012:84-97.

Bryant 2007

Bryant RA. Early intervention for post-traumatic stress disorder. *Early Intervention in Psychiatry* 2007;**1**(1):19-26. [DOI: 10.1111/j.1751-7893.2007.00006.x] [PMID: 21352105]

Bryant 2009

Bryant RA, Creamer M, O'Donnell M, Silove D, McFarlane AC. A study of the protective function of acute morphine administration on subsequent posttraumatic stress disorder. *Biological Psychiatry* 2009;**65**(5):438-40. [PMID: 19058787]

Bryant 2011

Bryant RA. Acute stress disorder as a predictor of posttraumatic stress disorder: a systematic review. *Journal of Clinical Psychiatry* 2011;**72**(2):233-9. [PMID: 21208593]

Cahill 1994

Cahill L, Prins B, Weber M, McGaugh JL. Beta-adrenergic activation and memory for emotional events. *Nature* 1994;**371**(6499):702-4.

CINeMA 2007 [Computer program]

CINeMA: Confidence in Network Meta-Analysis. Bern: Institute of Social and Preventive Medicine, University of Bern, accessed prior to 17 September 2019.

Cohen 2008

Cohen H, Matar MA, Buskila D, Kaplan Z, Zohar J. Early post-stressor intervention with high-dose corticosterone attenuates posttraumatic stress response in an animal model of posttraumatic stress disorder. *Biological Psychiatry* 2008;**64**(8):708-17. [DOI: 10.1016/j.biopsych.2008.05.025] [PMID: 18635156]

Cohen 2010

Cohen H, Kaplan Z, Kozlovsky N, Gidron Y, Matar M A, Zohar J. Hippocampal microinfusion of oxytocin attenuates the behavioural response to stress by means of dynamic interplay with the glucocorticoid-catecholamine responses. *Journal of Neuroendocrinology* 2010;**22**(8):889-904. [DOI: 10.1111/j.1365-2826.2010.02003.x] [PMID: 20403087]

Copyright © 2024 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Covi 1984

Covi L, Lipman RS. Primary depression or primary anxiety. A possible psychometric approach to a diagnostic dilemma. *Clinical Neuropharmacology* 1984;**7**(Suppl 1):S502–3.

de Vries 2009

de Vries GJ, Olff M. The lifetime prevalence of traumatic events and posttraumatic stress disorder in the Netherlands. *Journal of Traumatic Stress* 2009;**22**(4):259-67. [PMID: 19645050]

Deeks 2002

Deeks JJ. Issues in the selection of a summary statistic for meta-analysis of clinical trials with binary outcomes. *Statistics in Medicine* 2002;**21**(11):1575-600. [PMID: 12111921]

Deeks 2011

Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/handbook/archive/v5.1/.

Delahanty 2000

Delahanty DL, Raimonde AJ, Spoonster E. Initial posttraumatic urinary cortisol levels predict subsequent PTSD symptoms in motor vehicle accident victims. *Biological Psychiatry* 2000;**48**(9):940-7. [DOI: 10.1016/s0006-3223(00)00896-9] [PMID: 11074232]

Dias 2010

Dias S, Welton NJ, Marinho VCC, Salanti G, Higgins JPT, Ades AE. Estimation and adjustment of bias in randomized evidence by using mixed treatment comparison meta-analysis. *Journal of the Royal Statistical Society (A)* 2010;**173**:613-29. [DOI: 10.1111/j.1467-985X.2010.00639.x]

Dias 2013

Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Medical Decision Making* 2013;**33**(5):607-17. [DOI: 10.1177/0272989X12458724] [PMID: 23104435]

Dias 2013a

Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. *Medical Decision Making* 2013;**33**(5):641-56. [DOI: 10.1177/0272989X12455847] [PMID: 23804508]

Duru 2008

Duru G, Fantino B. The clinical relevance of changes in the Montgomery-Asberg Depression Rating Scale using the minimum clinically important difference approach. *Current Medical Research and Opinion* 2008;**24**(5):1329-35. [DOI: 10.1185/030079908x291958] [PMID: 18377706]

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical Research Ed.)* 1997;**315**(7109):629-34. [PMID: 9310563]

EndNote [Computer program]

EndNote. Philadelphia: Clarvariate Analytics, 2019.

Furukawa 2006

Furukawa TA, Barbui C, Cipriani A, Brambilla P, Watanabe N. Imputing missing standard deviations in meta-analyses can provide accurate results. *Journal of Clinical Epidemiology* 2006;**59**(1):7-10. [PMID: 16360555]

Galatzer-Levy 2014

Galatzer-Levy IR, Karstoft KI, Statnikov A, Shalev AY. Quantitative forecasting of PTSD from early trauma responses: a Machine Learning application. *Journal of Pscyhiatric Research* 2014;**59**:68-76.

GRADEpro GDT 2015 [Computer program]

GRADEpro GDT. Hamilton (ON): McMaster University (developed by Evidence Prime), accessed prior to 17 September 2019. Available at gradepro.org.

Hamilton 1959

Hamilton M. The assessment of anxiety states by rating. *British Journal of Medical Psychology* 1959;**32**(1):50-5. [DOI: 10.1111/j.2044-8341.1959.tb00467.x] [PMID: 13638508]

Hamilton 1960

Hamilton M. A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry* 1960;**23**(1):56-62. [PMID: 14399272]

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from training.cochrane.org/handbook/archive/v5.1/.

Higgins 2011a

Higgins JP, Deeks JJ. Chapter 7: Selecting studies and collecting data. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/handbook/archive/v5.1/.

Higgins 2011b

Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/handbook/archive/v5.1/.

Higgins 2011c

Higgins JPT, Deeks JJ, Altman DG (editors). Chapter 16: Special topics in statistics. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011.

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Available from training.cochrane.org/handbook/archive/v5.1/
Available from handbook-5-1.cochrane.org.

Holbrook 2010

Holbrook TL, Galarneau MR, Dye JL, Quinn K, Dougherty AL. Morphine use after combat injury in Iraq and post-traumatic stress disorder. *New England Journal of Medicine* 2010;**362**(2):110-7. [PMID: 20071700]

Howlett 2016

Howlett JR, Stein MB. Prevention of trauma and stressor-related disorders: a review. *Neuropsychopharmacology* 2016;**41**(1):357-69.

Hruska 2014

Hruska B, Cullen PK, Delahanty DL. Pharmacological modulation of acute trauma memories to prevent PTSD: considerations from a developmental perspective. *Neurobiology of Learning and Memory* 2014;**112**:122-9. [DOI: 10.1016/j.nlm.2014.02.001] [PMID: 24513176]

ISTSS 2018

International Society for Traumatic Stress Studies. Posttraumatic Stress Disorder Prevention and Treatment Guidelines. International Society for Traumatic Stress Studies, 2018.

Karam 2014

Karam EG, Friedman MJ, Hill ED, Kessler RC, McLaughlin KA, Petukhova M, et al. Cumulative traumas and risk thresholds: 12-month PTSD in the World Mental Health (WMH) surveys. *Depression and Anxiety* 2014;**31**(2):130-42. [DOI: 10.1002/da.22169] [PMID: 23983056]

Karstoft 2015

Karstoft KI, Galatzer-Levy IR, Statnikov A, Li Z, Shalev AY. Bridging a translational gap: using machine learning to improve the prediction of PTSD. *BMC Psychiatry* 2015;**15**:30. [PMID: 25886446]

Kearns 2012

Kearns MC, Ressler KJ, Zatzick D, Rothbaum BO. Early interventions for PTSD: a review. *Depression and Anxiety* 2012;**29**(10):833-42. [DOI: 10.1002/da.21997] [PMID: 22941845]

Kelmendi 2016

Kelmendi B, Adams TG, Yarnell S, Southwick S, Abdallah CG, Krystal JH. PTSD: from neurobiology to pharmacological treatments. *European Journal of Psychotraumatology* 2016;**7**:31858. [PMID: 27837583]

Kessler 2014

Kessler R, Rose C, Koenen S, Karam KC, Stang EG, Stein PE et al. How well can post-traumatic stress disorder be predicted from pre-trauma risk factors? An exploratory study in the WHO World Mental Health Surveys. *World Psychiatry* 2014;**13**(3):265-74.

Koch 2014

Koch SB, van Zuiden M, Nawijn L, Frijling JL, Veltman DJ, Olff M. Intranasal oxytocin as strategy for medication-enhanced psychotherapy of PTSD: salience processing and fear inhibition processes. *Psychoneuroendocrinology* 2014;**40**:242-56. [PMID: 24485496]

Koenen 2017

Koenen KC, Ratanatharathorn A, Ng L, McLaughlin KA, Bromet EJ, Stein DJ, et al. Posttraumatic stress disorder in the World Mental Health Surveys. *Psychological Medicine* 2017;**47**(3):2260–74. [DOI: 10.1017/S0033291717000708] [PMID: 28385165]

Lee 2016

Lee DJ, Schnitzlein CW, Wolf JP, Vythilingam M, Rasmusson AM, Hoge CW. Psychotherapy versus pharmacotherapy for posttraumatic stress disorder: systemic review and meta-analyses to determine first-line treatments. *Depression and Anxiety* 2016;**33**(9):792-806. [PMID: 27126398]

Leonard 2000

Leonard BE, Richelson E. Synaptic effects of antidepressants. In: Buckley PF, Waddington JL, editors(s). Schizophrenia and Mood Disorders: The New Drug Therapies in Clinical Practice. Boston: Butterworth-Heinemann, 2000:67–84.

Licznerski 2013

Licznerski P, Duman RS. Remodeling of axo-spinous synapses in the pathophysiology and treatment of depression. *Neuroscience* 2013;**251**:33-50. [DOI: 10.1016/j.neuroscience.2012.09.057] [PMID: 23036622]

Lydiard 2003

Lydiard RB. The role of GABA in anxiety disorders. *Journal of Clinical Psychiatry* 2003;**64**(Suppl 3):21-7. [PMID: 12662130]

Masson 2013

Masson SC, Tejani AM. Minimum clinically important differences identified for commonly used depression rating scales. *Journal of Clinical Epidemiology* 2013;**66**(7):805-7. [DOI: 10.1016/j.jclinepi.2013.01.010] [PMID: 23618794]

Matsuoka 2011

Matsuoka Y. Clearance of fear memory from the hippocampus through neurogenesis by omega-3 fatty acids: a novel preventive strategy for posttraumatic stress disorder? *BioPsychoSocial Medicine* 2011;**5**:3. [PMID: 21303552]

McFarlane 1997

McFarlane AC, Atchison M, Yehuda R. The acute stress response following motor vehicle accidents and its relation to PTSD. *Annals of the New York Academy of Sciences* 1997;**821**:437-41. [PMID: 9238224]

McNally 2003

McNally GP, Westbrook RF. Temporally graded, context-specific retrograde amnesia and its alleviation by context preexposure: effects of postconditioning exposures to morphine in the rat. *Journal of Experimental Psychology* 2003;**29**(2):130-42. [PMID: 12735277]

Meyerhoff 2014

Meyerhoff DJ, Mon A, Metzler T, Neylan TC. Cortical gamma-aminobutyric acid and glutamate in posttraumatic stress

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disorder and their relationships to self-reported sleep quality. *Sleep* 2014;**37**(5):893-900. [PMID: 24790267]

Montgomery 1979

Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *British Journal of Psychiatry* 1979;**134**:382-9. [DOI: 10.1192/bjp.134.4.382]

Mouthaan 2015

Mouthaan J, Sijbrandij M, Reitsma JB, Luitse JS, Goslings JC, Gersons BP, et al. The role of early pharmacotherapy in the development of posttraumatic stress disorder symptoms after traumatic injury: an observational cohort study in consecutive patients. *General Hospital Psychiatry* 2015;**37**(3):230-5. [PMID: 25805128]

NICE 2018

National Institute for Health and Care Excellence. Post-traumatic stress disorder: management (NG116). www.nice.org.uk/guidance/ng116 2018.

Nickerson 2013

Nickerson A, Aderka IM, Bryant RA, Hofmann SG. The role of attribution of trauma responsibility in posttraumatic stress disorder following motor vehicle accidents. *Depression and Anxiety* 2013;**30**(5):483-8. [PMID: 23090752]

Olff 2010

Olff M, Langeland W, Witteveen A, Denys D. A psychobiological rationale for oxytocin in the treatment of posttraumatic stress disorder. *CNS Spectrums* 2010;**15**(8):522-30. [PMID: 20703199]

Phoenix Australia 2021

Phoenix Australia. The Australian Guidelines for the Prevention and Treatment of Acute Stress Disorder (ASD), Posttraumatic Stress Disorder (PTSD) and Complex PTSD. Available at https://www.phoenixaustralia.org/australian-guidelines-for-ptsd/ 2021.

Pitman 1989

Pitman RK. Post-traumatic stress disorder, hormones, and memory. Biological Psychiatry 1989;**26**(3):221-3. [PMID: 2545287]

Pitman 2012

Pitman RK, Rasmusson AM, Koenen KC, Shin LM, Orr SP, Gilbertson MW, et al. Biological studies of post-traumatic stress disorder. *Nature Reviews. Neuroscience* 2012;**13**(11):769-87. [PMID: 23047775]

Qi 2016

Qi W, Gevonden M, Shalev A. Prevention of post-traumatic stress disorder after trauma: current evidence and future directions. *Current Psychiatry Reports* 2016;**18**(2):20. [PMID: 26800995]

R 2017 [Computer program]

R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2017.

Reist 2001

Reist C, Duffy JG, Fujimoto K, Cahill L. beta-Adrenergic blockade and emotional memory in PTSD. *International Journal of Neuropsychopharmacology* 2001;**4**(4):377-83.

Ressler 2020

Ressler KJ. Translating across circuits and genetics toward progress in fear- and anxiety-related disorders. *American Journal of Psychiatry* 2020;**177**(3):214-22. [DOI: 10.1176/appi.ajp.2020.20010055] [PMID: 32114783]

Review Manager 2014 [Computer program]

Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Roberts 2019

Roberts NP, Kitchiner NJ, Kenardy J, Robertson L, Lewis C, Bisson JI. Multiple session early psychological interventions for the prevention of post-traumatic stress disorder. *Cochrane Database of Systematic Reviews* 2019, Issue 8. Art. No: CD006869. [DOI: 10.1002/14651858.CD006869.pub3] [PMID: 31425615]

Salanti 2014

Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP. Evaluating the quality of evidence from a network meta-analysis. *PLOS One* 2014;**9**(7):e99682. [DOI: 10.1371/journal.pone.0099682] [PMID: 24992266]

Santarelli 2003

Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, et al. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* 2003 ;**301**(5634):805-9. [DOI: 10.1126/science.1083328] [PMID: 12907793]

Schünemann 2011

Schünemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/handbook/archive/v5.1/.

Sheehan 1996

Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. *International Clinical Psychopharmacology* 1996;**11**(Suppl 3):89-95. [PMID: 8923116]

Sijbrandij 2015

Sijbrandij M, Kleiboer A, Bisson JI, Barbui C, Cuijpers P. Pharmacological prevention of post-traumatic stress disorder and acute stress disorder: a systematic review and meta-analysis. *Lancet Psychiatry* 2015;**2**(5):413-21. [PMID: 26360285]

Southwick 1999

Southwick SM, Bremner JD, Rasmusson A, Morgan CA 3rd, Arnsten A, Charney DS. Role of norepinephrine in the pathophysiology and treatment of posttraumatic stress disorder. *Biological Psychiatry* 1999;**46**(9):1192-204. [PMID: 10560025]

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Spielberger 1970

Spielberger CD, Gorsuch RL, Lushene RE. Manual for the Stait-Trait Anxiety Inventory. Palo Alto, California: Consulting Psychologists Press, 1970.

Steel 2009

Steel Z, Chey T, Silove D, Marnane C, Bryant RA, van Ommeren M. Association of torture and other potentially traumatic events with mental health outcomes among populations exposed to mass conflict and displacement: a systematic review and meta-analysis. *JAMA* 2009;**302**(5):537-49. [PMID: 19654388]

Stein 2006

Stein DJ, Ipser JC, Seedat S. Pharmacotherapy for post traumatic stress disorder (PTSD). *Cochrane Database of Systematic Reviews* 2006, Issue 1. Art. No: CD002795. [DOI: 10.1002/14651858.CD002795.pub2] [PMID: 16437445]

Turrini 2017

Turrini G, Purgato M, Ballette F, Nose M, Ostuzzi G, Barbui C. Common mental disorders in asylum seekers and refugees: umbrella review of prevalence and intervention studies. *International Journal of Mental Health Systems* 2017;**11**:51. [PMID: 28855963]

Van Ameringen 2004

Van Ameringen M, Mancini C, Pipe B, Bennett M. Antiepileptic drugs in the treatment of anxiety disorders: role in therapy. *Drugs* 2004;**64**(19):2199-220. [PMID: 15456335]

van Valkenhoef 2016

van Valkenhoef G, Dias S, Ades AE, Welton NJ. Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. *Research Synthesis Methods* 2016;**7**(1):80-93. [DOI: 10.1002/jrsm.1167] [PMID: 26461181]

van Zuiden 2017

van Zuiden M, Frijling JL, Nawijn L, Koch SBJ, Goslings JC, Luitse JS, et al. Intranasal oxytocin to prevent posttraumatic stress disorder symptoms: a randomized controlled trial in emergency department patients. *Biological Psychiatry* 2017;**81**(12):1030-40. [PMID: 28087128]

Veterans Affairs/Department of Defense 2017

Veterans Affairs/Department of Defense. VA/DoD Clinical Practice Guidelines: Management of Posttraumatic Stress Disorder and Acute Stress Reaction. Available at https://www.healthquality.va.gov/guidelines/MH/ptsd/VADoDPTSDCPGFinal012418.pdf 2017.

Ware 1992

Ware JE, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36): I. Conceptual framework and item selection. *Medical Care* 1992;**30**:473-81. [PMID: 1593914]

Weathers 2001

Weathers FW, Keane TM, Davidson JR. Clinician-administered PTSD scale: a review of the first ten years of research. Depression and Anxiety 2001;**13**(3):132-56. [1091-4269: (Print)]

WHO 1997

World Health Organization. Composite International Diagnostic Interview (CIDI) 2.1. Geneva, Switzerland: World Health Organization, 1997.

WHO 2017

World Health Organization. The selection and use of essential medicines: report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization, 2017.

WHO 2018

WHO Collaborating Centre for Drug Statistics Methodology. ATC classification index with DDDs, 2019. Oslo, Norway: WHO Collaborating Centre for Drug Statistics Methodology, 2018. Available at www.whocc.no/atc_ddd_index.

WHO 2019

World Health Organization. International Statistical Classification of Diseases and Related Health Problems, Eleventh Revision (ICD-11). https://icd.who.int/browse11. World Health Organization, 2019.

WinBUGS 2000

Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS — a Bayesian modelling framework: concepts, structure, and extensibility. Statistics and Computing 2000;**10**(4):325-37.

Yepes-Nunez 2019

Yepes-Nunez JJ, Li SA, Guyatt G, Jack SM, Brozek JL, Beyene J, et al. Development of the summary of findings table for network meta-analysis. *Journal of Clinical Epidemiology* 2019;**115**:1-13. [DOI: 10.1016/j.jclinepi.2019.04.018] [PMID: 31055177]

Zatzick 1997

Zatzick DF, Marmar CR, Weiss DS, Browner WS, Metzler TJ, Golding JM, et al. Posttraumatic stress disorder and functioning and quality of life outcomes in a nationally representative sample of male Vietnam veterans. *American Journal of Psychiatry* 1997;**154**(12):1690-5. [PMID: 9396947]

References to other published versions of this review

Bertolini 2020

Bertolini F, Robertson L, Ostuzzi G, Meader N, Bisson JI, Churchill R, et al. Early pharmacological interventions for acute traumatic stress symptoms: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2020, Issue 5. Art. No: CD013613. [DOI: 10.1002/14651858.CD013613]

* Indicates the major publication for the study

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CHARACTERISTICS OF STUDIES

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

Carmi 2022

Study characteristics	
Methods	**Study design:** RCT, parallel groups, double-blind, placebo-controlled **Number of centres:** 1 **Location:** Israel **Number of arms:** 2 (hydrocortisone versus placebo) **Follow-up time points:** 1, 3, 8 and 13 months after the traumatic event **Imputation strategy:** no imputation for missing values **Original study outcomes (name, measure, time points):** PTSD rate and symptoms severity (CAPS), anxiety (visual analogue scale for anxiety (VAS-A)) and depression (visual analogue scale for depression (VAS-D)), at 2 weeks, 1, 3, 8 and 13 months after the traumatic event
Participants	**Sample size:** 118 **Baseline characteristics** Hydrocortisone • *Participants with a history of previous trauma*: not reported • *Type of traumatic event*: motor vehicle accident: 45, work accident: 4, violent attack: 2, rocket attacks: 0 • *Sex (F/M) and mean age (SD)*: 27/24, 38.1 (12.5) • *Baseline acute traumatic stress symptoms (assessed before intervention administration):* VAS Distress: 3.22 (2.99), VAS anxiety: 3.39 (3.10) Placebo • *Participants with a history of previous trauma*: not reported • *Type of traumatic event*: motor vehicle accident: 39, work accident: 3, violent attack: 2, rocket attacks: 1 • *Sex (F/M) and mean age (SD)*: 23/22, 40.4 (12.6) • *Baseline acute traumatic stress symptoms (assessed before intervention administration):* VAS Distress: 3.45 (2.91), VAS anxiety: 3.62 (3.08) **Baseline group differences:** no baseline group imbalances **Inclusion criteria:** admission to the emergency department of Chaim Sheba Medical Center, exposure to a traumatic event **Acute traumatic stress symptoms criteria:** modified DSM-IV acute stress response criteria: exposure to traumatic events, presenting at least 2 of the 5 dissociative symptoms, presence of anxiety or arousal, and significant distress **Exclusion criteria:** 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, hypersensitivity to hydrocortisone, pregnancy, treatment for asthma, medical (including psychiatric) conditions that may represent contraindications for hydrocortisone administration
Interventions	**Setting:** emergency department **Intervention characteristics**

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Carmi 2022 *(Continued)*

	Hydrocortisone • *Number of randomised participants*: 60 • *Time from traumatic event to first intervention administration*: within 6 hours from the traumatic event • *Intervention regimen*: single intravenous bolus at a dose based on body weight: 100 mg for weights of 60 to 69 kg, 120 mg for weights of 70 to 89 kg, and 140 mg for weights of 90 to 99 kg Placebo • *Number of randomised participants*: 58 • *Time from traumatic event to first intervention administration*: within 6 hours from the traumatic event • *Intervention regimen*: equivalent placebo scheme
Outcomes	PTSD severity • **Outcome type:** continuous outcome • **Reporting:** fully reported • **Scale:** CAPS • **Time points:** 3 and 13 months post-traumatic event Dropout due to adverse events • **Outcome type**: dichotomous outcome • **Reporting**: fully reported • **Time points**: 3 months from the traumatic event PTSD rate • **Outcome type:** dichotomous outcome • **Reporting:** fully reported • **Scale:** CAPS (over 49 points) • **Time points:** 3 and 13 months post-traumatic event Depression severity • **Outcome type:** continuous outcome • **Reporting:** fully reported • **Scale:** VAS-D (3 months) and MADRS (13 months) • **Time points:** 3 and 13 months post-traumatic event Anxiety severity • **Outcome type:** continuous outcome • **Reporting:** fully reported • **Scale:** VAS-A • **Time points:** 3 and 13 months post-traumatic event Dropout for any reason • **Outcome type:** dichotomous outcome • **Reporting:** fully reported • **Time points:** 3 and 13 months post-traumatic event
Identification	**Sponsorship source:** the National Institutes of Health (NIH; Grant No. RO1 NCT00855270) **Country:** Israel **Author's name:** Joseph Zohar **Institution:** Post Trauma Center, Chaim Sheba Medical Center, Ramat Gan, Israel

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Carmi 2022 *(Continued)*

	Email: Joseph.Zohar@sheba.health.gov.il **Address:** Anxiety and Stress Research Unit, Ministry of Health, Mental Health Center, Faculty of Health Sciences, Ben-Gurion University of the Negev, P.O. Box 4600, Beer Sheva 84170, Israel
Declarations of interest among primary researchers	Authors report no financial affiliation or other relationship relevant to the study
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The participants were randomized by a computerized program" (p2).
Allocation concealment (selection bias)	Low risk	Most likely done, due to the fact that this trial is based on a previous pilot trial included in this review (Zohar 2011), where allocation concealment by means of randomisation by a predetermined program was confirmed in a different Cochrane review (Amos 2014).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial is reported as double-blind; although the blinding strategy is not reported, blinding was most likely done, due to the fact that this trial is based on a previous pilot trial included in this review (Zohar 2011), for which information on procedures was available in deeper detail.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All assessments were performed by expert investigators who were blind to the treatment condition" (p2).
Incomplete outcome data (attrition bias) All outcomes	High risk	At the review primary time point of 3 months after the traumatic event, about 60% of the placebo arm and 70% of the hydrocortisone arm were analysed.
Selective reporting (reporting bias)	Low risk	The registration entry on clinicaltrials.gov (NCT00855270) reports only the CAPS outcome, without mention of the other outcomes reported in the paper. This trial follows a published pilot trial, against which it is consistent.
Other bias	Low risk	No other sources of bias were found.

Delahanty 2013

Study characteristics

Methods	**Study design:** RCT, parallel groups, double-blind, placebo-controlled **Number of centres:** 1 **Location:** "Midwestern Level-1 Trauma Unit" **Number of arms:** 2 (hydrocortisone versus placebo) **Follow-up time points:** 1 and 3 months after the traumatic event **Imputation strategy:** none

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Delahanty 2013 *(Continued)*

	Original study outcomes (name, measure, time points): PTSD rate and PTSD symptoms severity (Clinician-Administered PTSD Scale (CAPS)), Depressive symptoms (Center for Epidemiological Studies-Depression Scale (CES-D, self-reported)) and quality of life (SF-36, self-reported), all at 1 and 3 months post-injury
Participants	**Sample size:** 64 **Baseline characteristics** Hydrocortisone • *Participants with a history of previous trauma*: not reported; 17 participants sought mental health treatment previously for the traumatic event • *Type of traumatic event*: motor vehicle accident: 20, fall: 5, assault: 4, other: 2 • *Sex (F/M) and mean age (SD)*: 10/21, 27.2 (8.0) • *Baseline acute traumatic stress symptoms (assessed within 12 hours from the traumatic event):* Peritraumatic Distress Inventory (PDI) mean score (SD): 2.3 (0.88); Peritraumatic Dissociative Experiences Questionnaire Self-Report Version (PDEQ) mean score (SD): 36.5 (5.6) Placebo • *Participants with a history of previous trauma*: not reported; 12 sought mental health treatment previously for the traumatic event • *Type of traumatic event*: motor vehicle accident: 17, fall: 7, assault: 7, other: 2 • *Sex (F/M) and mean age (SD)*: 12/21 33.8 (12.0) • *Baseline acute traumatic stress symptoms (assessed within 12 hours from the traumatic event):* Peritraumatic Distress Inventory (PDI) mean score (SD): 2.3 (0.97); Peritraumatic Dissociative Experiences Questionnaire Self-Report Version (PDEQ) mean score (SD): 34.5 (5.2) **Baseline group differences:** placebo receivers were on average younger (33.8 ± 12.0 versus 27.2 ± 8.0); more hydrocortisone receivers had sought prior mental health treatment ($Chi^2 = 3.61$, P = 0.06) compared to placebo receivers **Inclusion criteria:** injury victims admitted as inpatients to trauma unit **Acute traumatic stress symptoms criterion:** score of at least 27 (mean score of 2.7 per item) on the 10-item Peritraumatic Dissociative Experiences Questionnaire Self-Report Version (PDEQ) **Exclusion criteria:** 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 breastfeeding; 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
Interventions	**Setting:** level 1 trauma unit **Intervention characteristics** Hydrocortisone • *Number of randomised participants*: 31 • *Time from traumatic event to first intervention administration*: within 12 hours • *Intervention regimen*: 20 mg every 12 hours (twice a day) for 10 days, followed by a 6-day taper period (dose halved every 2 days) Placebo • *Number of randomised participants*: 33 • *Time from traumatic event to first intervention administration*: within 12 hours

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Delahanty 2013 *(Continued)*

	• *Intervention regimen*: placebo tablets
Outcomes	PTSD severity • **Outcome type**: continuous outcome • **Reporting**: fully reported • **Scale**: CAPS • **Time points**: 3 months from the traumatic event Dropout due to adverse events • **Outcome type**: dichotomous outcome • **Reporting**: fully reported • **Time points**: 3 months from the traumatic event PTSD rate • **Outcome type**: dichotomous outcome • **Reporting**: fully reported • **Scale**: CAPS • **Time points**: 3 months from the traumatic event Depression severity • **Outcome type**: continuous outcome • **Reporting**: fully reported • **Scale**: CES-D • **Time points**: 3 months from the traumatic event Quality of life • **Outcome type**: continuous outcome • **Reporting**: fully reported • **Scale**: SF-36 (general health) • **Time points**: 3 months from the traumatic event Dropout for any reason • **Outcome type**: dichotomous outcome • **Reporting**: fully reported • **Time points**: 3 months from the traumatic event
Identification	**Sponsorship source:** study founded by the National Institute of Mental Health (R34 MH73014) and the Ohio Board of Regents **Country:** USA **Author's name:** Douglas L. Delahanty **Institution:** Kent State University, Department of Psychology, Kent, Ohio, USA and Department of Trauma Services, Akron, Ohio, USA **Email:** ddelahan@kent.edu **Address:** Douglas Delahanty, Department of Psychology, 144 Kent Hall, Kent, OH 44242, USA
Declarations of interest among primary researchers	One of the authors discloses speaker's honoraria (John Bon: The Medicine Company, speaker's bureau, honoraria; Merck & Co., speaker's bureau, honoraria); all the remaining authors, including the leading researcher, report none.

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Delahanty 2013 *(Continued)*

Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation according to a random number table was confirmed in a different Cochrane review (Amos 2014).
Allocation concealment (selection bias)	Unclear risk	No details are provided regarding allocation concealment. Slight imbalances in baseline characteristics between randomisation groups are still compatible with effective randomisation, considering the limited sample size.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Although the blinding strategy is not reported in the published paper, blinding procedures were confirmed in a different Cochrane review (identical pills/blister packs prepared by the hospital's pharmacist, only co-author unblinded for safety reasons) (Amos 2014).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trial is reported as double-blind. Most of the outcomes are from a self-administered scale and there is no suggestion that the personnel administering the CAPS were aware of allocation (see also comment on blinding of participants and personnel).
Incomplete outcome data (attrition bias) All outcomes	High risk	Less than 70% of the randomised participants were analysed.
Selective reporting (reporting bias)	Unclear risk	A protocol or a trial registration entry is not available for this trial.
Other bias	Low risk	One of the authors disclosed speaker's honoraria (John Bon: The Medicine Company, speaker's bureau, honoraria; Merck & Co., speaker's bureau, honoraria), but most of the authors, including the leading researcher, report none. No other sources of bias were found.

Mellman 2002

Study characteristics

Methods	**Study design:** RCT, parallel groups, double-blind, placebo-controlled **Number of centres:** 1 **Location:** USA **Number of arms:** 2 (temazepam versus placebo) **Follow-up time points:** 1 day post intervention start, 1 week post-treatment, 6 weeks after initial assessment **Imputation strategy:** none **Original study outcomes (name, measure, time points):** total sleep hours and number of awakenings after first night of intervention and 1 week post-treatment; PTSD rate and symptoms severity (CAPS) at 1 week post-treatment and 6 weeks after initial assessment or just prior to initiating a non-study medication
Participants	**Sample size:** 22

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Mellman 2002 *(Continued)*

	Baseline characteristics Overall • *Participants with a history of previous trauma*: not reported • *Type of traumatic event*: motor vehicle accidents: 15, industrial accidents: 2, interpersonal assault: 5 • *Sex (F/M) and mean age (SD)*: 8/14, 36.1 (11.4) • *Baseline acute traumatic stress symptoms (exact assessment timing not specified):* full criteria for at least 2 DSM-IV PTSD symptom clusters (7 participants met full ASD criteria) **Baseline group differences:** not reported **Inclusion criteria:** admission to a level 1 trauma centre following life-threatening incidents; having recall of the incident and endorsing at least moderate impairment of sleep initiation or maintenance **Acute traumatic stress symptoms criterion:** meeting full criteria for at least 2 PTSD symptom clusters (DSM-IV criteria) **Exclusion criteria:** being intoxicated at the time of the incident; brain injury and pre-existing active psychiatric disorders; inability or unwillingness to provide informed consent
Interventions	**Setting:** level 1 trauma centre **Intervention characteristics** Temazepam • *Number of randomised participants*: 11 • *Time from traumatic event to first intervention administration*: study medication initiated when medical/surgical stabilisation was achieved, a mean of 14.3 ± 10.0 days after the traumatic incident • *Intervention regimen*: 30 mg at bedtime for 5 nights followed by 15 mg for 2 nights Placebo • *Number of randomised participants*: 11 • *Time from traumatic event to first intervention administration*: study medication initiated when medical/surgical stabilisation was achieved, a mean of 14.3 ± 10.0 days after the traumatic incident • *Intervention regimen*: equivalent placebo scheme
Outcomes	PTSD severity • **Outcome type**: continuous outcome • **Reporting**: fully reported • **Scale**: CAPS • **Time points**: 6 weeks after initial assessment or just prior to initiating a non-study medication Dropout due to adverse events • **Outcome type**: dichotomous outcome • **Reporting**: fully reported • **Time points**: 6 weeks after initial assessment or just prior to initiating a non-study medication PTSD rate • **Outcome type**: dichotomous outcome • **Reporting**: fully reported • **Scale**: CAPS • **Time points**: 6 weeks after initial assessment or just prior to initiating a non-study medication Dropout for any reason

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Mellman 2002 *(Continued)*

- **Outcome type**: dichotomous outcome
- **Reporting**: fully reported
- **Time points**: 6 weeks after initial assessment or just prior to initiating a non-study medication

Identification	**Sponsorship source:** Grant MH54006 from the National Institute of Mental Health to Dr. Mellman **Country:** USA **Author's name:** Thomas A. Mellman **Institution:** Dartmouth Medical School Hanover, New Hampshire
Declarations of interest among primary researchers	Authors report no financial affiliation or other relationship relevant to the study
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation according to a predetermined randomisation schedule was confirmed in a different Cochrane review (Amos 2014).
Allocation concealment (selection bias)	Low risk	A personal communication to one member of the review team on the occasion of a previous meta-analysis reports that the medication schedule was known only to the research pharmacist.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Although the blinding strategy is not reported in the published paper, blinding procedures were confirmed in a different Cochrane review (medication placed in identical capsules) (Amos 2014).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information is provided regarding blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All of the randomised participants were analysed.
Selective reporting (reporting bias)	Unclear risk	A protocol or trial registration entry is not available for this trial.
Other bias	High risk	The only source of information available for this trial is a short 'letter to the editor'.

Shalev 2012

Study characteristics

Methods	**Study design:** RCT, parallel groups. This study had 5 arms, of which only the SSRI and placebo ones are of interest for this review. For these 2 arms, the design was 'triple-blind' (participant, carer, assessor). **Number of centres:** 1

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Shalev 2012 *(Continued)*

	Location: Jerusalem, Israel **Number of arms:** 5: escitalopram versus placebo, plus 3 non-pharmacological arms (prolonged exposure (PE), cognitive therapy (CT), waiting list (WL)) **Follow-up time points:** 5 months, 9 months, 3 years after the traumatic event **Imputation strategy:** none for the outcomes of interest **Original study outcomes (name, measure, time points):** PTSD symptoms and PTSD prevalence assessed by CAPS, depression severity (Beck Depression Inventory (BDI)), DSM-IV axis I disorder other than PTSD (The Structured Clinical Interview for DSM-IV (SCID-IV)) and functional disability (Global Assessment of Functioning (GAF)); all of them at 5, 9 months and 3 years post-trauma
Participants	**Sample size:** sample size of escitalopram/placebo arms: 46 (sample size including non-pharmacological arms: 242) **Baseline characteristics** Escitalopram • *Participants with a history of previous trauma*: not reported • *Type of traumatic event*: motor vehicle accident: 21, terrorist attack: 0; other: 2 • *Sex (F/M) and mean age (SD)*: 13/10, 39.83 (11.74) • *Baseline acute traumatic stress symptoms (assessment took place at mean 19.8 days (SD 5.2) after the traumatic event):* CAPS score at baseline (SD) 79.83 (15.60) Placebo • *Participants with a history of previous trauma*: not reported • *Type of traumatic event*: motor vehicle accident: 20, terrorist attack: 2; other: 1 • *Sex (F/M) and mean age (SD)*: 10/13, 36.26 (12.39) • *Baseline acute traumatic stress symptoms (assessment took place at mean 19.8 days (SD 5.2) after the traumatic event):* CAPS score at baseline (SD) 74.91 (14.69) **Baseline group differences:** none reported **Inclusion criteria:** adult traumatic event (DSM-IV PTSD criterion A) survivors admitted to Hadassah University Hospital's emergency services; resided within a 1-hour drive from Jerusalem (could attend treatment) **Acute traumatic stress symptoms criterion:** meeting DSM-IV PTSD (save the 1-month duration) criteria either fully or partially (2 out of 3 PTSD symptom criteria (B, C, and D)) **Exclusion criteria:** injury requiring more than 7 days of hospital stay, unconscious on admission to emergency services, medical or surgical conditions that interfered with their ability to participate or provide informed consent, not fluent enough in Hebrew, Arabic or English; current or past psychosis or bipolar disorder, current substance abuse problem, other conditions requiring urgent attention (e.g. suicidal ideations or acute grief) or chronic PTSD; started treatment elsewhere
Interventions	**Setting:** post hospital emergency department admission **Intervention characteristics** Escitalopram • *Number of randomised participants*: 23 • *Time from traumatic event to first intervention administration (SD)*: 29.35 (4.91) days • *Intervention regimen*: 10 mg tablets: 1 tablet daily for 2 weeks, then 2 tablets daily for 10 weeks Placebo • *Number of randomised participants*: 23

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Shalev 2012 *(Continued)*

- *Time from traumatic event to first intervention administration (SD)*: 28.91 (5.71) days
- *Intervention regimen*: equivalent placebo scheme

Outcomes	PTSD severity • **Outcome type**: continuous outcome • **Reporting**: fully reported • **Scale**: CAPS • **Time points**: 3 years after the traumatic event PTSD rate • **Outcome type**: dichotomous outcome • **Reporting**: fully reported • **Scale**: CAPS • **Time points**: 3 years after the traumatic event Depression severity • **Outcome type**: continuous outcome • **Reporting**: fully reported • **Scale**: BDI • **Time points**: 3 years after the traumatic event Functional disability • **Outcome type**: continuous outcome • **Reporting**: fully reported • **Scale**: SCID IV GAF (higher is better) • **Time points**: 3 years after the traumatic event Dropout for any reason • **Outcome type**: dichotomous outcome • **Reporting**: fully reported • **Time points:** 3 years after the traumatic event
Identification	**Sponsorship source:** The study was sponsored by the Jerry Lee Foundation in Philadelphia, Pennsylvania, USA, Jewish Federation of New York, research grant MH071651 from the National Institute of Mental Health, and an investigator-initiated research grant from Lundbeck Pharmaceuticals Ltd (Denmark). **Author's name:** Arieh Y. Shalev **Institution:** Center for Traumatic Stress Studies, Department of Psychiatry, Hadassah University Hospital, Jerusalem, Israel **Email:** arieh.shalev@nyumc.org **Address:** Arieh Y. Shalev, MD, Department of Psychiatry, Hadassah University Hospital, PO Box 12000, Kiriat Hadassah–Ein Kerem, Jerusalem 91120, Israel
Declarations of interest among primary researchers	Dr Shalev received an investigator-initiated grant from Lundbeck Pharmaceuticals Ltd for this study and for an ongoing collaborative study (Joseph Zohar, MD, principal investigator) entitled “Prevention of PTSD by Escitalopram.” No conflicts of interest to declare from the other co-authors.
Notes	This trial has 5 arms; only the escitalopram/placebo arms have been considered in this review.
Risk of bias	

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Shalev 2012 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Equipoise stratified randomization was used to allocate eligible and consenting survivors" (p167).
Allocation concealment (selection bias)	Unclear risk	Allocation concealment strategy is not clearly specified.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "To separate the pharmacological effect of an SSRI from that of receiving medication and psychiatric care, this blinded group includes both the active agent and placebo. Concealed tablets of either 10 mg of escitalopram or placebo were prepared and coded by Lundbeck Pharmaceuticals" (p168).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The clinical assessments were made by clinical psychology interns. [...] They remained blind to treatment attendance and adherence" (p167).
Incomplete outcome data (attrition bias) All outcomes	High risk	About 50% of randomised participants had been analysed at 5 years.
Selective reporting (reporting bias)	Low risk	Different time points for outcome assessment are found when comparing the outcome reported in the study report (Shalev 2016) with the trial registration on clinicaltrials.gov (NCT00146900). However, this difference is most likely related to how the study was carried out, rather than to selective reporting.
Other bias	Low risk	The study received funding from several sources, including Lundbeck Pharmaceuticals. Quote: "The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication." (Shalev 2016, p e586)

Suliman 2015

Study characteristics	
Methods	**Study design:** RCT, double-blind, parallel groups, placebo-controlled pilot study **Number of centres:** 1 (University of Cape Town affiliated hospitals) **Primary location:** Cape Town, South Africa **Number of arms:** 2 (escitalopram versus placebo) **Follow-up time points:** every 2 weeks until visit 8 and thereafter every 4 weeks **Imputation strategy:** none **Original study outcomes (name, measure, time points):** Primary: CAPS score and CAPS determined PTSD rate. Secondary: Clinical Global Impression - Severity and Improvement scales (CGI), Mini International Neuropsychiatric Interview (MINI 5.0.0), Montgomery-Asberg Depression Rating Scale (MADRS), Visual Analogue Scale for Depression (VAS-D), Visual Analogue Scale for Anxiety (VAS-A), Sheehan Disability Scale (SDS). All of them at weeks 0, 4, 12, 24, 32, 40, 48 and 56 (visits 2, 4, 8, 11, 13, 15, 17, 19)
Participants	**Sample size:** 31 **Baseline characteristics**

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Suliman 2015 *(Continued)*

(Baseline characteristics were provided only for the 29 participants that completed the trial)

Escitalopram

- *Participants with a history of previous trauma*: not reported
- *Type of traumatic event*: assault (physical/sexual): 10, other (MVA/witnessing event): 2
- *Sex (F/M) and mean age (SD)*: 5/7, 31.33 (7.85)
- *Baseline acute traumatic stress symptoms (exact timing of assessment not reported):* baseline CAPS score (SD): 45.33 (21.43), all 12 meeting full ASD criteria

Placebo

- *Participants with a history of previous trauma*: not reported
- *Type of traumatic event*: assault (physical/sexual): 10, other (MVA/witnessing event): 7
- *Sex (F/M) and mean age (SD)*: 5/12, 28.24 (8.38)
- *Baseline acute traumatic stress symptoms (exact timing of assessment not reported):* baseline CAPS score (SD): 62.00 (22.98); 15 meeting full ASD criteria, 2 meeting partial ASD criteria

Baseline group differences: ethnicity: no coloured/mixed race participants in escitalopram group

Inclusion criteria: experience of a traumatic event, such as a vehicle collision or other accident, physical or sexual assault within the previous 4 weeks; between 18 and 65 years of age; sufficient knowledge of English in order to read, understand and sign the Informed Consent form as well as study procedures and assessment instruments

Acute traumatic stress symptoms criterion: presence of either full DSM-IV criteria or intrusion and hyper-arousal criteria for ASD

Exclusion criteria: refusal of any medication therapy; serious physical injury (Abbreviated Injury Scale (AIS) score of 3 or more); concomitant medications not allowed in the study (monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase A (RIMAs), mood stabilisers, antipsychotics or psychoactive herbal remedies within the 3 weeks prior to screening, anxiolytics or serotonergic agonists within the 2 weeks prior to screening, treatment with any anticonvulsant drug); lifetime DSM-IV-TR criteria for mania or bipolar disorder, schizophrenia, any personality disorder, mental retardation or pervasive developmental disorder, or cognitive disorder; significant suicide risk and/or a score of = 5 on item 10 of the Montgomery Asberg Depression Rating Scale (MADRS) scale; history of severe suicide attempt; electroconvulsive therapy within the last year; currently serving in the South African security forces.; history of drug allergy or hypersensitivity to escitalopram or citalopram; illness severe enough to prevent participation in the study (including liver or renal insufficiency; cardiovascular, pulmonary, gastrointestinal, endocrine (including uncontrolled thyroid), neurological (including epilepsy), infectious, neoplastic or metabolic disturbances; pregnant or breastfeeding; refusal of adequate contraceptive use (if female)

Interventions	**Setting:** emergency department **Intervention characteristics** Escitalopram • *Number of randomised participants*: 13 • *Time from traumatic event to first intervention administration*: not reported • *Intervention regimen*: 10 mg daily for 4 weeks, then 20 mg daily for 20 weeks. Down-titration for intolerable side effects allowed. Placebo • *Number of randomised participants*: 18 • *Time from traumatic event to first intervention administration*: not reported • *Intervention regimen*: equivalent placebo scheme
Outcomes	PTSD severity

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Suliman 2015 *(Continued)*

- **Outcome type**: continuous outcome
- **Reporting**: personal communication and paper reported data
- **Scale**: CAPS
- **Time points**: 12 and 24 weeks

Dropout due to adverse events

- **Outcome type**: dichotomous outcome
- **Reporting**: personal communication
- **Time points**: 12 and 56 weeks

PTSD rate

- **Outcome type**: dichotomous outcome
- **Reporting**: personal communication and paper reported data
- **Scale**: CAPS
- **Time points**: 12 and 56 weeks

Depression severity

- **Outcome type**: continuous outcome
- **Reporting**: personal communication
- **Scale**: MADRS
- **Time points**: 12 and 56 weeks

Anxiety severity

- **Outcome type**: continuous outcome
- **Reporting**: personal communication
- **Scale**: VAS-A
- **Time points**: 12 and 56 weeks

Dropout for any reason

- **Outcome type**: dichotomous outcome
- **Reporting**: personal communication
- **Time points**: 12 and 56 weeks

Identification	**Sponsorship source:** Lundbeck A/S **Country:** South Africa **Author's name:** Sharain Suliman **Institution:** MRC Anxiety Disorders Unit, Department of Psychiatry, Stellenbosch University, Cape Town, South Africa **Email:** sharain@sun.ac.za
Declarations of interest among primary researchers	S Suliman has received research grants from the Stellenbosch University Faculty of Health Sciences, Hendrik Vrouwes Research Scholarship, and South African National Research Foundation (Thuthuka). DJ Stein has received research grants and/or consultancy honoraria from Abbott, Astrazeneca, Eli-Lilly, GlaxoSmithKline, Jazz Pharmaceuticals, Johnson & Johnson, Lundbeck, Orion, Pfizer, Pharmacia, Roche, Servier, Solvay, Sumitomo, Takeda, Tikvah, and Wyeth. S Seedat is supported by South African Research Chairs Initiative (SARChI) hosted by the Department of Science and Technology and the National Research Foundation, South Africa.
Notes	—
Risk of bias	

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Suliman 2015 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated randomization list" (p3).
Allocation concealment (selection bias)	Low risk	Quote: "Randomization numbers were assigned consecutively. [...] Wallet cards were identified by visit (i.e., visit 2, visit 3, etc.) with the escitalopram and placebo packed by the study pharmacist in sequentially numbered identical blister packs. Participants and investigators were blinded to treatment allocation and there were no instances of un-blinding" (p3).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Wallet cards were identified by visit (i.e., visit 2, visit 3, etc.) with the escitalopram and placebo packed by the study pharmacist in sequentially numbered identical blister packs. Participants and investigators were blinded to treatment allocation and there were no instances of un-blinding" (p3).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See quote above.
Incomplete outcome data (attrition bias) All outcomes	High risk	Less than 80% of randomised participants were available for the outcomes of interest.
Selective reporting (reporting bias)	Low risk	Outcomes listed in the trial registration entry at clinicaltrials.gov are reported in the paper. The protocol for this trial was shared by another research group. All of the pre-specified outcomes in the methods section are reported.
Other bias	Low risk	The study was funded by a grant from Lundbeck A/S. The sponsor had no role in the conduct of the trial.

Van Zuiden 2017

Study characteristics	
Methods	**Study design:** RCT, double-blind, parallel groups, placebo-controlled **Number of centres:** 3 emergency departments in Amsterdam, the Netherlands (academic level 1 trauma centres: Academic Medical Center, VU University Medical Center; level 2 trauma centre: Onze Lieve Vrouwe Gasthuis Hospital West) **Number of arms:** 2 (oxytocin and placebo) **Follow-up time points:** 1.5, 3 and 6 months post-trauma **Imputation strategy:** pooled results of 40 generated datasets using multiple imputation for missing outcome data for the CAPS and HADS scores using as auxiliary variables the intervention, demographic, trauma and baseline clinical characteristics **Original study outcomes (name, measure, time points):** Primary: PTSD symptoms severity (CAPS) at 1.5 months post-trauma. Secondary: PTSD symptoms severity (CAPS) at 3 and 6 months post-trauma; self-reported PTSD symptoms severity (IES-R), depression and anxiety (Hospital Anxiety and Depression Scale (HADS)) at 1.5, 3 and 6 months post-trauma
Participants	**Sample size:** 120 **Baseline characteristics**

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Van Zuiden 2017 *(Continued)*

	(Baseline characteristics were provided for the 107 participants who started the assigned intervention; 2 of the non-starters had exclusion criteria that emerged after the randomisation). Oxytocin • *Participants with a history of previous trauma*: not reported • *Type of traumatic event*: accidental: 43, assault: 10 • *Sex (F/M) and mean age (SD)*: 27/26, 35.00 (13.13) • *Baseline acute traumatic stress symptoms (assessed within 10 days from the traumatic event):* CAPS (SD): 42.83 (16.93) Placebo • *Participants with a history of previous trauma*: not reported • *Type of traumatic event*: accidental: 48, assault: 6 • *Sex (F/M) and mean age (SD)*: 26/28, 35.91 (13.30) • *Baseline acute traumatic stress symptoms (assessed within 10 days from the traumatic event):* CAPS (SD): 41.28 (20.96) **Baseline group differences:** no baseline imbalances **Inclusion criteria:** admission to emergency department after experiencing a traumatic event, 18 to 65 years of age **Acute traumatic stress symptoms criterion:** scoring ≥ 5 on the Trauma Screening Questionnaire (TSQ) and ≥ 17 on the Peritraumatic Distress Inventory (PDI) screening questionnaire **Exclusion criteria:** current PTSD or depression; psychotic, bipolar, substance-related and personality disorder; severe/chronic systemic disease; mental retardation; neurological/endocrine disorder; ongoing traumatisation; medications potentially interfering with oxytocin administration (e.g. systemic glucocorticoids or psychotropic medications); oxytocin allergy; persistent impaired consciousness or amnesia; pregnancy; and breastfeeding
Interventions	**Setting:** emergency department **Intervention characteristics** Oxytocin • *Number of randomised participants*: 58 • *Time from traumatic event to first intervention administration*: overall for both interventions, mean of 8.94 (1.80) days, within 12 days from trauma • *Intervention regimen*: intranasal administration: 5 puffs of 4 IU per nostril twice a day, for 8 days Placebo • *Number of randomised participants*: 62 • *Time from traumatic event to first intervention administration*: overall for both interventions, mean of 8.94 (1.80) days, within 12 days from trauma • *Intervention regimen*: equivalent scheme with 0.9% NaCl solution
Outcomes	PTSD severity • **Outcome type**: continuous outcome • **Reporting**: fully reported • **Scale**: CAPS • **Time points**: 3 and 6 months post-traumatic event Depression severity • **Outcome type**: continuous outcome

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Van Zuiden 2017 *(Continued)*

- **Reporting**: fully reported
- **Scale**: Hospital Anxiety and Depression Scale (HADS)
- **Time points**: 3 and 6 months post-traumatic event

Anxiety severity

- **Outcome type**: continuous outcome
- **Reporting**: fully reported
- **Scale**: Hospital Anxiety and Depression Scale (HADS)
- **Time points**: 3 and 6 months post-traumatic event

Dropout for any reason

- **Outcome type**: dichotomous outcome
- **Reporting**: fully reported
- **Time points**: 3 and 6 months post-traumatic event

Identification	**Sponsorship source:** Supported by grants from the Netherlands Organisation for Health Research and Development (Grant No. 91210041) and from the Academic Medical Center Research Council (Grant No. 110614). **Country:** the Netherlands **Author's name:** Mirjam van Zuiden **Institution:** Department of Psychiatry, Academic Medical Center, University of Amsterdam, VU University Medical Center, Amsterdam **Email:** m.vanzuiden@amc.nl
Declarations of interest among primary researchers	Authors report no biomedical financial interests or potential conflicts of interest.
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "We used a block randomization method (block size 4: 2 oxytocin, 2 placebo) and randomization was stratified for sex and participation in a fMRI substudy" (Supplementary Methods, p2).
Allocation concealment (selection bias)	Low risk	Quote: "Intervention allocation was concealed using a code provided by Oracle Clinical, which was sent to the trial pharmacy" (Supplementary Methods, p2).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial is described as double-blind; the active and placebo loaded pump-activated devices were both labelled by the Slotervaart Hospital Pharmacy.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The intervention allocation was disclosed to one member of the research team (MvZ) at two moments: after the first 30 participants finished the first follow-up assessment to assess safety (1.5 month posttrauma follow up) and after 50% of the required participants finished the first follow-up assessment in order to conduct pre-planned interim analyses [...] Disclosed researchers did not perform any follow-up measurements after disclosure. The

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Van Zuiden 2017 *(Continued)*

		other researchers and all participants remained blinded for intervention allocation." (Supplementary Methods, p2).
Incomplete outcome data (attrition bias) All outcomes	Low risk	107 participants were analysed out of the 120 randomised.
Selective reporting (reporting bias)	Low risk	The outcomes stated in the trial registration on the Netherlands Trial Registry ("Boosting Oxytocin After Trauma" - NL3042) are all reported within the primary and secondary publications of the study.
Other bias	Low risk	No other sources of bias were found.

Zohar 2011

Study characteristics	
Methods	**Study design:** RCT, parallel groups, double-blind, placebo-controlled pilot study **Number of centres:** 1 **Location:** Israel **Number of arms:** 2 (hydrocortisone and placebo) **Follow-up time points:** 2 weeks, 1 and 3 months post-trauma **Imputation strategy:** none **Original study outcomes (name, measure, time points):** PTSD rate and symptoms severity (CAPS), anxiety (Visual Analogue Scale for Anxiety (VAS-A)) and depression (Visual Analogue Scale for Depression (VAS-D)), at 2 weeks, 1 and 3 months post-trauma
Participants	**Sample size:** 25 **Baseline characteristics** Hydrocortisone • *Participants with a history of previous trauma*: not reported • *Type of traumatic event*: work accident: 1, motor vehicle accident: 7, snake bite: 1 • *Sex (F/M) and mean age (SD)*: 6/3, 36.1 (15.9) • *Baseline acute traumatic stress symptoms (assessed before intervention administration):* VAS anxiety: 4.3 (3.2) Placebo • *Participants with a history of previous trauma*: not reported • *Type of traumatic event*: work accident: 3, motor vehicle accident: 5, snake bite: 0 • *Sex (F/M) and mean age (SD)*: 2/6, 34.4 (12.1) • *Baseline acute traumatic stress symptoms (assessed before intervention administration):* VAS anxiety: 5.1 (4.6) **Baseline group differences:** no baseline group imbalances **Inclusion criteria:** admission to the emergency department of Chaim Sheba Medical Center, exposure to a traumatic event

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Zohar 2011 *(Continued)*

	Acute traumatic stress symptoms criteria: experience of either acute stress reaction or sub-threshold acute stress reaction, meeting 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) **Exclusion criteria:** 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. Hypersensitivity to hydrocortisone, pregnancy, or treatment for asthma.
Interventions	**Setting:** emergency department **Intervention characteristics** Hydrocortisone • *Number of randomised participants*: 15 • *Time from traumatic event to first intervention administration*: between 1.5 and 5.5 hours from the traumatic event • *Intervention regimen*: single intravenous bolus at a dose based on body weight: 100 mg for weights of 60 to 69 kg, 120 mg for weights of 70 to 89 kg and 140 mg for weights of 90 to 99 kg Placebo • *Number of randomised participants*: 10 • *Time from traumatic event to first intervention administration*: between 1.5 and 5.5 hours from the traumatic event • *Intervention regimen*: equivalent placebo scheme
Outcomes	PTSD severity • **Outcome type**: continuous outcome • **Reporting**: data reported in figure, extracted by plot digitiser • **Scale**: CAPS • **Time points**: 3 months post-traumatic event PTSD rate • **Outcome type**: dichotomous outcome • **Reporting**: fully reported • **Scale**: CAPS • **Time points**: 3 months post-traumatic event Depression severity • **Outcome type**: continuous outcome • **Reporting**: data reported in figure, extracted by plot digitiser • **Scale**: VAS-D • **Time points**: 3 months post-traumatic event Anxiety severity • **Outcome type**: continuous outcome • **Reporting**: data reported in figure, extracted by plot digitiser • **Scale**: VAS-A • **Time points**: 3 months post-traumatic event Dropout for any reason • **Outcome type**: dichotomous outcome

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Zohar 2011 *(Continued)*

- **Reporting**: fully reported
- **Time points**: 3 months post-traumatic event

Identification	**Sponsorship source:** The National Institute for Psychobiology in Israel, funded by Charles E. Smith Family, The Israel Academy of Science and Humanities (grant #416/09) and the Ministry of Health (grant #3-0000-6086) **Country:** Israel **Author's name:** Joseph Zohar **Institution:** Division of Psychiatry, The State of Israel Ministry of Health, The Chaim Sheba Medical Center, Sackler Medical School, Tel-Aviv University, Tel Hashomer **Email:** hagitc@bgu.ac.il **Address:** Anxiety and Stress Research Unit, Ministry of Health, Mental Health Center, Faculty of Health Sciences, Ben-Gurion University of the Negev, P.O. Box 4600, Beer Sheva 84170, Israel
Declarations of interest among primary researchers	Authors report no financial affiliation or other relationship relevant to the study.
Notes	This is a pilot trial for Carmi 2022.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The participants were randomized by a predetermined program" (p798).
Allocation concealment (selection bias)	Low risk	Although the publication does not report the allocation concealment strategy in detail, allocation concealment through randomisation with a predetermined program was confirmed in a different Cochrane review (Amos 2014).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Although the publication does not report the allocation concealment strategy in detail, the procedures were confirmed in a different Cochrane review (intravenous bags identical in appearance prepared by a separate physician) (Amos 2014).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	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" (p798).
Incomplete outcome data (attrition bias) All outcomes	High risk	15 out of 25 randomised participants were analysed (60%).
Selective reporting (reporting bias)	Low risk	The trial registration entry on clinicaltrials.gov (NCT00855270) reports only the CAPS outcome, without mention of the other outcomes reported in the paper.
Other bias	Low risk	No other sources of bias were found.

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Zohar 2018

Study characteristics	
Methods	**Study design:** RCT, parallel groups, double-blind, placebo-controlled **Number of centres:** 5 **Locations:** 5 medical centres in Israel and 1 medical centre in South Africa **Number of arms:** 2 (escitalopram versus placebo) **Follow-up time points:** at end of treatment phase (12 to 24 weeks - most of the sample (91%) concluded 24 weeks of treatment) and after 56 weeks **Imputation strategy:** none **Original study outcomes (name, measure, time points):** Primary outcome: CAPS score difference from baseline to follow-up; secondary outcomes: PTSD symptoms scale self-rated (PSS-SR), Pittsburgh Sleep Quality Index (PSQI), Montgomery-Asberg Depression Rating Scale (MADRS), Clinical Global Impressions Severity of Illness scale (CGI-S) and Improvement scale (CGI-I), self-report visual analogue scale (VAS) for depression and anxiety. Outcomes measured at end of treatment (12 to 24 weeks - most of the sample (91%) concluded 24 weeks of treatment) and at 56 weeks.
Participants	**Sample size:** 353 **Baseline characteristics** (Baseline characteristics were provided for completers only). Escitalopram (102) • *Participants with a history of previous trauma*: not reported • *Type of traumatic event*: intentional: 78, unintentional: 24 • *Sex (F/M) and mean age (SD)*: 42/60, 39.6 (13.2) • *Baseline acute traumatic stress symptoms (SD) (exact timing of assessment not reported):* CAPS: 71.9 (22.1) Placebo (96) • *Participants with a history of previous trauma*: not reported • *Type of traumatic event*: intentional: 70, unintentional: 26 • *Sex (F/M) and mean age (SD)*: 55/41, 39.1 (12.2) • *Baseline acute traumatic stress symptoms (SD) (exact timing of assessment not reported):* CAPS: 72.8 (21.8) **Baseline group differences:** the escitalopram group had significantly more men than the placebo group **Inclusion criteria:** exposure to a traumatic event within the prior month; between the ages of 18 and 65 years **Acute traumatic stress symptoms criterion:** met at least 2 DSM-IV criteria for acute stress disorder (re-experiencing and hyperarousal) **Exclusion criteria:** serious injury (Abbreviated Injury Scale score ≥ 3); diagnosis (DSM-IV) of bipolar disorder, schizophrenia or personality disorder; a history of alcohol or drug abuse, mental retardation, or dementia; having significant suicide risk or a past serious suicide attempt, as evaluated by the Mini-International Neuropsychiatric Interview (MINI); therapy with psychiatric medications, (medications for depression, psychosis, or relapse prevention (mood stabilisers)); participation in psychotherapy; electroconvulsive treatment within the previous year; sensitivity to citalopram or escitalopram; any major physical illness; being pregnant or lactating; and being of childbearing age and not using contraceptives

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Zohar 2018 *(Continued)*

Interventions	**Setting:** emergency department **Intervention characteristics** Escitalopram • *Number of randomised participants*: 176 • *Time from traumatic event to first intervention administration*: within 1 month from the traumatic event • *Intervention regimen*: flexible length: no less than 12 weeks, up to 24 weeks; starting dose of 10 mg/day and then gradual titration to 20 mg/day during the first 4 weeks Placebo • *Number of randomised participants*: 177 • *Time from traumatic event to first intervention administration*: within 1 month from the traumatic event • *Intervention regimen*: equivalent placebo scheme
Outcomes	PTSD severity • **Outcome type**: continuous outcome • **Reporting**: data reported in figure, extracted by plot digitiser • **Scale**: CAPS • **Time points**: 56 weeks post-traumatic event Depression severity • **Outcome type**: continuous outcome • **Reporting**: not reported in enough detail to meta-analyse • **Scale**: MADRS Anxiety severity • **Outcome type**: continuous outcome • **Reporting**: not reported in enough detail to meta-analyse • **Scale**: VAS-A Dropout for any reason • **Outcome type**: dichotomous outcome • **Reporting**: fully reported • **Time points**: 56 weeks post-traumatic event
Identification	**Sponsorship source:** Lundbeck A/S **Country:** Israel, South Africa **Author's name:** Joseph Zohar **Institution:** Department of Psychiatry, Chaim Sheba Medical Center, Tel Hashomer, Israel **Email:** jzohar@post.tau.ac.il **Address:** Joseph Zohar, MD, Department of Psychiatry, Chaim Sheba Medical Center, Tel Hashomer, Israel 52621
Declarations of interest among primary researchers	Dr Zohar has received grant/research support from Lundbeck, Servier, and Pfizer; has served as a consultant or on advisory boards for Servier, Pfizer, Abbott, Lilly, Actelion, AstraZeneca, and Roche; and has served on speakers' bureaus for Lundbeck, Roche, and Abbott. Dr Juven-Wetzler has served on speakers' bureaus for Pfizer. Dr H. Shalev served on speakers' bureaus for Eli Lilly and Unifarm between 2008 and 2011. In the past 3 years, Dr Stein has received research grants and/or consultancy honoraria from Biocodex, Lundbeck, Novartis, Servier, and Sun Lifetime; has received research grants and/or con-

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	sultancy honoraria from Abbott, Astrazeneca, Biocodex, Eli Lilly, GlaxoSmithKline, Jazz, Johnson & Johnson, Lundbeck, Novartis, Orion, Pfizer, Pharmacia, Roche, Servier, Solvay, Sumitomo, Sun, Takeda, Tikvah, and Wyeth. Dr Suliman has received research grants from the Stellenbosch University Faculty of Health Sciences, Hendrik Vrouwes Research Scholarship, and South African National Research Foundation (Thuthuka). Drs Fostick, Kaplan, Schreiber, Miroshnik, A. Y. Shalev, Seedat, and Klein have no financial interests or other conflicts to disclose.
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization was conducted by Trialog Clinical Trials, Ltd, an independent company that was not involved in the study except for the randomization procedure" (p50).
Allocation concealment (selection bias)	Low risk	Quote: "Each center received the medications (escitalopram and placebo) directly from Trialog with participant numbers marked on them" (p.50).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial is reported as double-blind and, although not explicitly stated, it is likely that blinding of participants and personnel was ensured by the external company.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above.
Incomplete outcome data (attrition bias) All outcomes	High risk	About 56% of randomised participants were analysed.
Selective reporting (reporting bias)	Low risk	Outcomes listed in the trial registration entry on clinicaltrials.gov are reported in the paper.
Other bias	Low risk	The study was funded by a grant from Lundbeck A/S. The sponsor had no role in the conduct of the trial.

ASD: acute stress disorder; BDI: Beck Depression Inventory; CAPS: Clinician-Administered PTSD Scale; CES-D: Center for Epidemiological Studies - Depression Scale; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, text revision; GAF: Global Assessment of Functioning; HADS: Hospital Anxiety and Depression Scale; IES-R: Impact of Event Scale – Revised; MADRS: Montgomery-Asberg Depression Rating Scale; MINI: Mini-International Neuropsychiatric Interview ; MVA: motor vehicle accident; PDI: Peritraumatic Distress Inventory; PTSD: post-traumatic stress disorder; RCT: randomised controlled trial; SCID IV GAF: Structured Clinical Interview for DSM-IV Global Assessment of Functioning; SD: standard deviation; SSRI: selective serotonin reuptake inhibitor; VAS-A: Visual Analogue Scale - Anxiety; VAS-D: Visual Analogue Scale - Depression; VAS: visual analogue scale

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

Study	Reason for exclusion
Bailly 2021	Ongoing trial not selecting participants on the basis of experiencing acute traumatic stress symptoms

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Study	Reason for exclusion
Bartoszek 2023	Participants were veterans, previously exposed to combat experience, undergoing elective surgery and selected for high anxiety levels before the surgery
Beaudoin 2022	Wrong condition: trial recruiting individuals with acute musculoskeletal pain; about half of the sample due to events not eligible as psychological traumatic events
Blaha 1999	Ineligible study design
Borrelli 2019	Trial on universal prevention of PTSD (interventions provided to trauma-exposed individuals regardless of the presence or not of acute traumatic stress symptoms)
Denke 2008	Trial on universal prevention of PTSD (interventions provided to trauma-exposed individuals regardless of the presence or not of acute traumatic stress symptoms)
EUCTR-004177-83-NL	Prematurely ended
EUCTR2019-004537-16-FR	Ongoing trial not selecting participants on the basis of experiencing acute traumatic stress symptoms
FDA 1999	Intervention started after 3 months from the traumatic experience
Frankova 2017	Study was withdrawn shortly after initiation (14 randomised participants out of 120 expected) due to lack of funding (personal communication to FB)
Gelpin 1996	Ineligible study design
Haywood 2021	Trial on universal prevention of PTSD (interventions provided to trauma-exposed individuals regardless of the presence or not of acute traumatic stress symptoms)
Hicks 2009	Not a prevention trial
Hoge 2012	Trial on universal prevention of PTSD (interventions provided to trauma-exposed individuals regardless of the presence or not of acute traumatic stress symptoms)
IRCT20190919044819N2	Ongoing trial. No placebo or medication control group (intervention group receives propranolol and standard burn care, control group receives standard burn care only).
Kagan 2015	Trial on universal prevention of PTSD (interventions provided to trauma-exposed individuals regardless of the presence or not of acute traumatic stress symptoms)
Kaplan 2015	Intervention started after 3 months from the traumatic experience
Kok 2016	Trial on universal prevention of PTSD (interventions provided to trauma-exposed individuals regardless of the presence or not of acute traumatic stress symptoms)
Lijffijt 2019	Not a prevention trial
Lossada-Soto 2022	Trial on universal prevention of PTSD (interventions provided to trauma-exposed individuals regardless of the presence or not of acute traumatic stress symptoms)
Matsumura 2011	No control arm
Matsuoka 2010	No control arm
Matsuoka 2015	Trial on universal prevention of PTSD (interventions provided to trauma-exposed individuals regardless of the presence or not of acute traumatic stress symptoms)

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Study	Reason for exclusion
McMullan 2021	Trial on universal prevention of PTSD (interventions provided to trauma-exposed individuals regardless of the presence or not of acute traumatic stress symptoms)
Mistraletti 2015	Ineligible study design. Secondary outcomes related to mental health were not systematically assessed despite what was originally planned.
Naylor 2013	Not a prevention trial
NCT00114374	Terminated before completion
NCT00674570	Not a prevention trial
NCT02069366	Ineligible study design
NCT02505984	Wrong condition
NCT03724448	Trial on a herbal product, not a WHO ATC-listed drug
NCT04467086	Ongoing trial. No placebo or medication control group (intervention group receives propranolol and sedation, control group receives sedation only).
Nedergaard 2020	Wrong interventions: participants randomised to being sedated or not during mechanical ventilation (not a drug vs another/placebo)
Nishi 2012	No placebo or medication control group
Orrey 2015	Trial on universal prevention of PTSD (interventions provided to trauma-exposed individuals regardless of the presence or not of acute traumatic stress symptoms)
Pitman 2002	Trial on universal prevention of PTSD (interventions provided to trauma-exposed individuals regardless of the presence or not of acute traumatic stress symptoms)
Rabinak 2020	Not a prevention trial
Rucklidge 2012	More than 3 months between the traumatic event and the trial
Schelling 2001	Trial on universal prevention of PTSD (interventions provided to trauma-exposed individuals regardless of the presence or not of acute traumatic stress symptoms)
Schelling 2004	No placebo or medication control group (control group is "standard treatment", which is also administered to the hydrocortisone group)
Shaked 2019	Trial on universal prevention of PTSD (interventions provided to trauma-exposed individuals regardless of the presence or not of acute traumatic stress symptoms)
Stein 2007	Trial on universal prevention of PTSD (interventions provided to trauma-exposed individuals regardless of the presence or not of acute traumatic stress symptoms)
Stoddard 2011	Participants too young (< 18 years old)
Takehiro 2014	Not a prevention trial
Tincu 2016	Trial on universal prevention of PTSD (interventions provided to trauma-exposed individuals regardless of the presence or not of acute traumatic stress symptoms)
Treggiari 2009	Wrong intervention (“deep” vs “light” sedation, apparently both accomplished with midazolam)

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Study	Reason for exclusion
Truppman Lattie 2020	Not a prevention trial
Weis 2006	Trial on universal prevention of PTSD (interventions provided to trauma-exposed individuals regardless of the presence or not of acute traumatic stress symptoms)
Yang 2011	No placebo or medication control group
Zhong 2022	Trial on universal prevention of PTSD (interventions provided to trauma-exposed individuals regardless of the presence or not of acute traumatic stress symptoms)
Zoellner 2001	Wrong intervention

PTSD: post-traumatic stress disorder; WHO: World Health Organization

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

EUCTR-000088-12-DE

Study name	A prospective, single-blinded (rater-blinded), randomized, parallel group study of the efficacy of Quetiapine XR in the treatment of patients with Acute Stress Disorder (DSM-VI 308.3)
Methods	Randomised controlled trial, parallel-group, single-blind
Participants	Adults with DSM-IV defined acute stress disorder
Interventions	Quetiapine extended-release, mirtazapine
Outcomes	Primary: improvement of ASD 'key symptoms' (unspecified scale and time point) Secondary: risk of transition from ASD to PTSD (unspecified scale and time point); Clinical Global Impression (unspecified time point); psychosocial functioning, quality of sleep, length of disability (unspecified scale and time point)
Starting date	6 August 2009 (registration date)
Contact information	—
Notes	Apparently completed but never published

McMullan 2020

Study name	Intranasal ketamine as an adjunct to fentanyl for the prehospital treatment of acute traumatic pain
Methods	Randomised, triple-blind (participant, care provider, investigator)
Participants	Participants experiencing pain due to acute trauma (i.e. extremity deformity, tourniquet placement or severe burns)
Interventions	Ketamine IN, placebo IN
Outcomes	Primary: pain reduction on a verbal numeric rating scale after 30 minutes from administration Secondary outcomes: pain at emergency department arrival, adverse event incidence, oppiate requiments prior to ED arrival and in the first 3 hours of ED care, chronic pain (Brief Pain Inventory) at

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McMullan 2020 *(Continued)*

	90 days after injury, PTSD (PTSD checklist for DSM-5) 90 days after injury, overall satisfaction with life (Satisfaction With Life Scale) 90 days after injury
Starting date	3 October 2017
Contact information	Jason McMullan, University of Cincinnati
Notes	—

NCT01039766

Study name	The efficacy of a single dose of intranasal oxytocin in the prevention of post traumatic stress disorder (PTSD)
Methods	Double-blind, parallel assignment, placebo-controlled trial
Participants	Quote: "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 Analog Scales. 2. The traumatic event occured up to six hour 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. Exclusion Criteria: 1. Physical injury that would contraindicate participation or interfere with a subject's ability to give informed consent or cooperate with the screening or collection of initial measures. Examples include severe burn injury, life-threatening medical or surgical condition, condition requiring surgical intervention under general anesthesia, as indicated by Abbreviated Injury Scale (AIS), or by clinical judgment; 2. Head injury involving confusion, loss of consciousness, or amnesia; 3. Medical conditions in which oxytocin administration might cause harm to the patient such as patients with a cardiovascular disease or intracranial mass. 4. Weight below 45 or above 100 kg. 5. Pregnancy (in suggestive cases, a pregnancy test will be performed); 6. Traumatic exposure that reflects ongoing victimization (e.g., domestic violence) to which the subject is likely to be re-exposed during the study period. 7. Overt psychopathology, intoxication, or under the influence of substances. 8. Evidence or history of schizophrenia, bipolar, other psychotic condition, autism; 9. Prior history of PTSD; 10. Current or past history of dementia, amnesia, or other cognitive disorder predating trauma exposure; 11.Assessed serious suicide risk."
Interventions	Oxytocin: single intranasal administration of 40 IU of oxytocin up to 6 hours after a traumatic event Placebo: saline nasal spray, single intranasal administration of saline up to 6 hours after a traumatic event
Outcomes	Primary: DSM-IV diagnosis of PTSD at the end of the trial (13 months) Secondary: PTSD severity as measured by the Clinician Administered PTSD Scale (CAPS), at the end of the trial (13 months)
Starting date	February 2010
Contact information	Joseph Zohar: jzohar@post.tau.ac.il
Notes	—

NCT03997864

Study name	Administration of prazosin to prevent PTSD in adult women after sexual assault

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NCT03997864 *(Continued)*

Methods	RCT, parallel-group, quadruple masking (participant, care provider, investigator, outcomes assessor)
Participants	Adult women treated at the University of Colorado Hospital after an alleged sexual assault
Interventions	Prazosin (flexible dosing up to 15 mg per day), placebo
Outcomes	Primary: CAPS score (PTSD severity) at 1 and 3 months post-traumatic event Secondary: Pittsburgh Sleep Quality Index (PSQI) and Pittsburgh Sleep Quality Index - Trauma Addendum (sleep quality), at 3 months post-traumatic event; Patient Health Questionnaire (PHQ-9) (depression severity and prevalence (cut-off = 10)), at 3 months post-traumatic event
Starting date	23 February 2020
Contact information	Steven J Berkowitz, MD, steven.berkowitz@ucdenver.edu
Notes	—

NCT04071600

Study name	Intranasal neuropeptide Y in clinical trial in level two trauma patients for PTSD and acute stress disorder
Methods	RCT, parallel-group, quadruple masking (participant, care provider, investigator, outcomes assessor)
Participants	Level 2 trauma patients admitted to Westchester Medical Center
Interventions	Intranasal neuropeptide Y, intranasal placebo
Outcomes	Primary: safety and tolerability (dose escalation until treatment emergent adverse effect); PSS-I-5 score, at least 60 days after the traumatic event; National Stressful Events Survey Acute Stress Disorder Short Form (NSESS) score, 3 to 7 days and 14 to 30 days after the traumatic event Secondary: Beck Anxiety Inventory (BAI) at 2 to 3 years after the traumatic event
Starting date	1 November 2019
Contact information	Esther Sabban, New York Medical College
Notes	Estimated primary completion date: 31 October 2022

NCT04274361

Study name	Ketamine for pain control after severe traumatic injury
Methods	RCT, open-label, parallel-group
Participants	Acutely injured adult trauma hospital inpatients with an ISS > 15
Interventions	Ketamine, placebo

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NCT04274361 *(Continued)*

Outcomes	Cumulative opioid morphine equivalent dose after 24 hours
Starting date	4 January 2021
Contact information	Margo Mantz-Wichman, BS, RN, mmantzwichman@mcw.edu
Notes	The study is currently ongoing. Effect of pain on future risk of PTSD development is mentioned in the 'detail description' but the only outcome currently listed is "Cumulative opioid morphine equivalent dose [Time Frame: The first 24 hours]". It is unclear if the study will consider PTSD or focus on pain only.

NCT04924166

Study name	PTSD prevention using oral hydrocortisone
Methods	Double-blind, randomised, placebo-controlled
Participants	Participants who present to the emergency department at Mount Sinai Hospital in New York City, US and at the Tel Hashomer Hospital, Israel, following trauma exposure and report high distress, panic, anxiety or dissociation
Interventions	Single dose of hydrocortisone versus placebo
Outcomes	Primary: CAPS score at 7 months Secondary: Structured Clinical Interview for DSM-5 (SCID), Pittsburgh Sleep Quality Index (PSQI), Sheehan Disability Scale (SDS), change in the Clinical Global Impression - Severity (CGI-S), change in the Clinical Global Impression - Improvement (CGI-I), Montgomery-Asberg Depression Rating Scale (MADRS), all up to 7 months
Starting date	June 2021
Contact information	Rachel Yehuda, Icahn School of Medicine at Mount Sinai
Notes	—

ASD: acute stress disorder; CAPS: Clinician-Administered PTSD Scale; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ED: emergency department; IN: intranasal; ISS: Injury Severity Score; PTSD: post-traumatic stress disorder; RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Escitalopram versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 PTSD severity at three months	1	23	Mean Difference (IV, Random, 95% CI)	-11.35 [-24.56, 1.86]
1.2 PTSD severity at study endpoint	3	255	Mean Difference (IV, Random, 95% CI)	3.34 [-10.72, 17.39]

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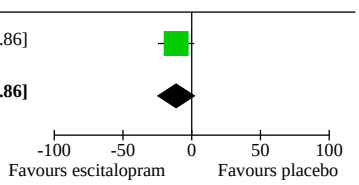
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Dropouts due to adverse events at three months	1	31	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.4 Dropouts due to adverse events at study endpoint	1	31	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.5 PTSD rate at three months	1	23	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.03, 13.08]
1.6 Sensitivity analysis: PTSD rate at three months (cases out of randomised)	1	31	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.02, 10.30]
1.7 PTSD rate at study endpoint	2	47	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.49, 2.71]
1.8 Sensitivity analysis: PTSD rate at study endpoint (cases out of randomised)	2	77	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.38, 2.65]
1.9 Depression severity at three months	1	23	Mean Difference (IV, Random, 95% CI)	-5.07 [-9.75, -0.39]
1.10 Depression severity at study endpoint	2	47	Std. Mean Difference (IV, Random, 95% CI)	-0.50 [-1.09, 0.09]
1.11 Anxiety severity at three months	1	23	Mean Difference (IV, Random, 95% CI)	-1.02 [-2.39, 0.35]
1.12 Anxiety severity at study endpoint	1	19	Mean Difference (IV, Random, 95% CI)	-0.13 [-1.65, 1.39]
1.13 Functional disability at study endpoint	1	28	Mean Difference (IV, Random, 95% CI)	1.06 [-7.16, 9.28]
1.14 Dropout for any reason at three months	1	31	Risk Ratio (M-H, Random, 95% CI)	2.31 [0.67, 7.98]
1.15 Dropout for any reason at study endpoint	3	430	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.78, 1.20]

Analysis 1.1. Comparison 1: Escitalopram versus placebo, Outcome 1: PTSD severity at three months

Study or Subgroup	Escitalopram Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Suliman 2015	12.38	10.74	8	23.73	21.56	15	100.0%	-11.35 [-24.56 , 1.86]
Total (95% CI)			**8**			**15**	**100.0%**	**-11.35 [-24.56 , 1.86]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.68 (P = 0.09)
Test for subgroup differences: Not applicable



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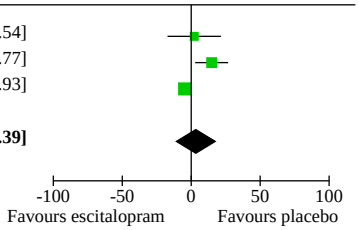
Analysis 1.2. Comparison 1: Escitalopram versus placebo, Outcome 2: PTSD severity at study endpoint

Study or Subgroup	Escitalopram Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Shalev 2012	34.31	29.36	13	32.13	21.64	15	23.8%	2.18 [-17.18 , 21.54]
Suliman 2015	-29.29	16.4891	12	-44.11	15.709	17	33.0%	14.82 [2.87 , 26.77]
Zohar 2018	-45.05	3.22	102	-40.26	2.98	96	43.2%	-4.79 [-5.65 , -3.93]
Total (95% CI)			**127**			**128**	**100.0%**	**3.34 [-10.72 , 17.39]**

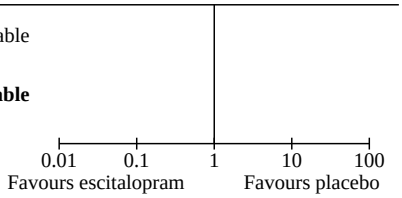
Heterogeneity: Tau² = 118.75; Chi² = 10.77, df = 2 (P = 0.005); I² = 81%
Test for overall effect: Z = 0.47 (P = 0.64)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Escitalopram versus placebo, Outcome 3: Dropouts due to adverse events at three months

Study or Subgroup	Escitalopram Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Suliman 2015	0	13	0	18		Not estimable
Total (95% CI)		**13**		**18**		**Not estimable**
Total events:	0		0			

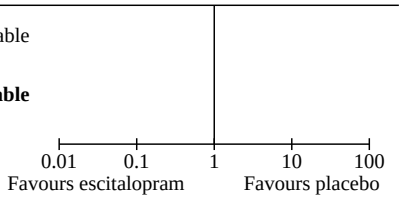
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Escitalopram versus placebo, Outcome 4: Dropouts due to adverse events at study endpoint

Study or Subgroup	Escitalopram Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Suliman 2015	0	13	0	18		Not estimable
Total (95% CI)		**13**		**18**		**Not estimable**
Total events:	0		0			

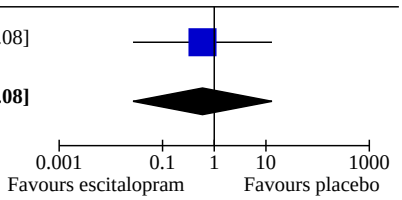
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Escitalopram versus placebo, Outcome 5: PTSD rate at three months

Study or Subgroup	Escitalopram Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Suliman 2015	0	8	1	15	100.0%	0.59 [0.03 , 13.08]
Total (95% CI)		**8**		**15**	**100.0%**	**0.59 [0.03 , 13.08]**
Total events:	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Not applicable



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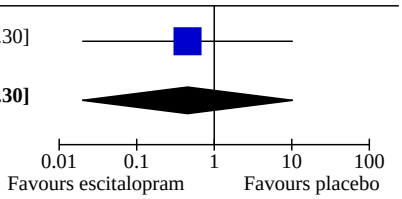
Analysis 1.6. Comparison 1: Escitalopram versus placebo, Outcome 6: Sensitivity analysis: PTSD rate at three months (cases out of randomised)

Study or Subgroup	Escitalopram Events	Escitalopram Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Suliman 2015	0	13	1	18	100.0%	0.45 [0.02 , 10.30]
Total (95% CI)		**13**		**18**	**100.0%**	**0.45 [0.02 , 10.30]**
Total events:	0		1			

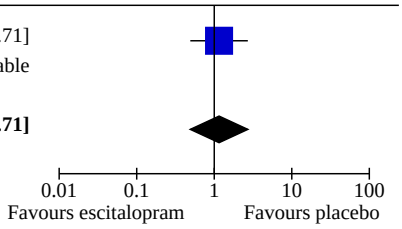
Heterogeneity: Not applicable
Test for overall effect: Z = 0.50 (P = 0.62)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Escitalopram versus placebo, Outcome 7: PTSD rate at study endpoint

Study or Subgroup	Escitalopram Events	Escitalopram Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Shalev 2012	6	13	6	15	100.0%	1.15 [0.49 , 2.71]
Suliman 2015	0	7	0	12		Not estimable
Total (95% CI)		**20**		**27**	**100.0%**	**1.15 [0.49 , 2.71]**
Total events:	6		6			

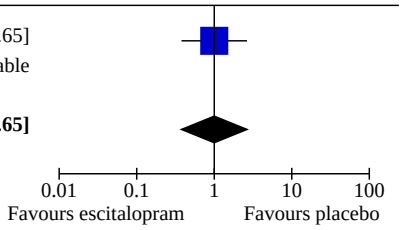
Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: Escitalopram versus placebo, Outcome 8: Sensitivity analysis: PTSD rate at study endpoint (cases out of randomised)

Study or Subgroup	Escitalopram Events	Escitalopram Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Shalev 2012	6	23	6	23	100.0%	1.00 [0.38 , 2.65]
Suliman 2015	0	13	0	18		Not estimable
Total (95% CI)		**36**		**41**	**100.0%**	**1.00 [0.38 , 2.65]**
Total events:	6		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



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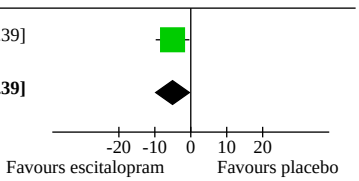
Analysis 1.9. Comparison 1: Escitalopram versus placebo, Outcome 9: Depression severity at three months

Study or Subgroup	Escitalopram Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Suliman 2015	1.13	1.64	8	6.2	8.98	15	100.0%	-5.07 [-9.75 , -0.39]
Total (95% CI)			**8**			**15**	**100.0%**	**-5.07 [-9.75 , -0.39]**

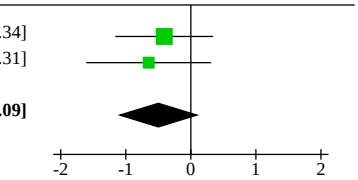
Heterogeneity: Not applicable
Test for overall effect: Z = 2.12 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: Escitalopram versus placebo, Outcome 10: Depression severity at study endpoint

Study or Subgroup	Escitalopram Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Shalev 2012	10.08	9.71	13	14.8	12.33	15	62.0%	-0.41 [-1.16 , 0.34]
Suliman 2015	0.71	1.89	7	2.5	2.97	12	38.0%	-0.65 [-1.61 , 0.31]
Total (95% CI)			**20**			**27**	**100.0%**	**-0.50 [-1.09 , 0.09]**

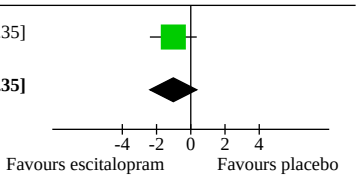
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 1.66 (P = 0.10)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: Escitalopram versus placebo, Outcome 11: Anxiety severity at three months

Study or Subgroup	Escitalopram Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Suliman 2015	1.88	0.99	8	2.9	2.34	15	100.0%	-1.02 [-2.39 , 0.35]
Total (95% CI)			**8**			**15**	**100.0%**	**-1.02 [-2.39 , 0.35]**

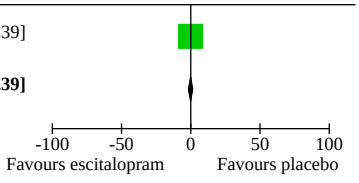
Heterogeneity: Not applicable
Test for overall effect: Z = 1.46 (P = 0.14)
Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1: Escitalopram versus placebo, Outcome 12: Anxiety severity at study endpoint

Study or Subgroup	Escitalopram Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Suliman 2015	1.29	1.76	7	1.42	1.38	12	100.0%	-0.13 [-1.65 , 1.39]
Total (95% CI)			**7**			**12**	**100.0%**	**-0.13 [-1.65 , 1.39]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.17 (P = 0.87)
Test for subgroup differences: Not applicable



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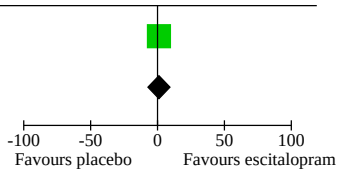
Analysis 1.13. Comparison 1: Escitalopram versus placebo, Outcome 13: Functional disability at study endpoint

Study or Subgroup	Escitalopram Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Shalev 2012	71.33	11.56	13	70.27	10.46	15	100.0%	1.06 [-7.16 , 9.28]
Total (95% CI)			**13**			**15**	**100.0%**	**1.06 [-7.16 , 9.28]**

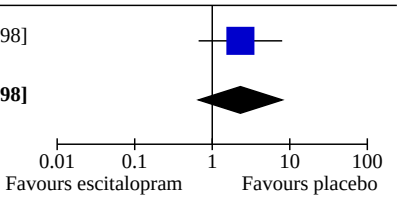
Heterogeneity: Not applicable
Test for overall effect: Z = 0.25 (P = 0.80)
Test for subgroup differences: Not applicable



Analysis 1.14. Comparison 1: Escitalopram versus placebo, Outcome 14: Dropout for any reason at three months

Study or Subgroup	Escitalopram Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Suliman 2015	5	13	3	18	100.0%	2.31 [0.67 , 7.98]
Total (95% CI)		**13**		**18**	**100.0%**	**2.31 [0.67 , 7.98]**
Total events:	5		3			

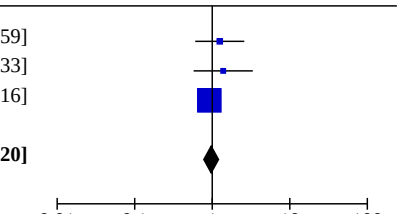
Heterogeneity: Not applicable
Test for overall effect: Z = 1.32 (P = 0.19)
Test for subgroup differences: Not applicable



Analysis 1.15. Comparison 1: Escitalopram versus placebo, Outcome 15: Dropout for any reason at study endpoint

Study or Subgroup	Escitalopram Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Shalev 2012	10	23	8	23	8.9%	1.25 [0.60 , 2.59]
Suliman 2015	6	13	6	18	6.1%	1.38 [0.58 , 3.33]
Zohar 2018	74	176	81	177	84.9%	0.92 [0.73 , 1.16]
Total (95% CI)		**212**		**218**	**100.0%**	**0.97 [0.78 , 1.20]**
Total events:	90		95			

Heterogeneity: Tau² = 0.00; Chi² = 1.30, df = 2 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.29 (P = 0.77)
Test for subgroup differences: Not applicable



Comparison 2. Hydrocortisone versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 PTSD severity at three months	3	136	Mean Difference (IV, Random, 95% CI)	-7.53 [-25.20, 10.13]
2.2 PTSD severity at study endpoint	3	156	Mean Difference (IV, Random, 95% CI)	-9.69 [-21.91, 2.53]
2.3 Dropouts due to adverse events at three months	2	182	Risk Ratio (M-H, Random, 95% CI)	3.19 [0.13, 75.43]

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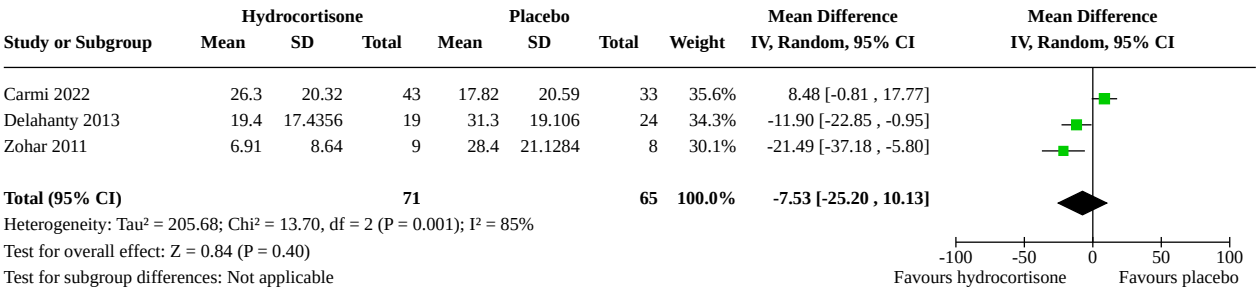
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.4 Dropouts due to adverse events at study endpoint	2	182	Risk Ratio (M-H, Random, 95% CI)	3.19 [0.13, 75.43]
2.5 PTSD rate at three months	3	136	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.09, 2.38]
2.6 Sensitivity analysis: PTSD rate at three months (cases out of randomised)	3	207	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.05, 3.02]
2.7 PTSD rate at study endpoint	3	156	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.14, 1.63]
2.8 Sensitivity analysis: PTSD rate at study endpoint (cases out of randomised)	3	207	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.08, 1.83]
2.9 Depression severity at three months	3	136	Std. Mean Difference (IV, Random, 95% CI)	-0.49 [-1.40, 0.42]
2.10 Depression severity at study endpoint	3	156	Std. Mean Difference (IV, Random, 95% CI)	-0.51 [-1.38, 0.36]
2.11 Anxiety severity at three months	2	93	Mean Difference (IV, Random, 95% CI)	-0.82 [-4.09, 2.45]
2.12 Anxiety severity at study endpoint	2	113	Mean Difference (IV, Random, 95% CI)	-1.04 [-3.83, 1.76]
2.13 Quality of life at three months	1	43	Mean Difference (IV, Random, 95% CI)	19.70 [-1.10, 40.50]
2.14 Dropout for any reason at three months	3	207	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.54, 2.04]
2.15 Dropout for any reason at study endpoint	3	207	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.61, 2.04]

Analysis 2.1. Comparison 2: Hydrocortisone versus placebo, Outcome 1: PTSD severity at three months



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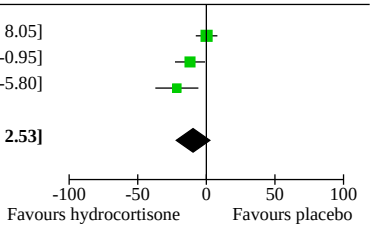
Analysis 2.2. Comparison 2: Hydrocortisone versus placebo, Outcome 2: PTSD severity at study endpoint

Study or Subgroup	Hydrocortisone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Carmi 2022	16.67	17.95	51	16.49	21.01	45	39.4%	0.18 [-7.69 , 8.05]
Delahanty 2013	19.4	17.4356	19	31.3	19.106	24	34.1%	-11.90 [-22.85 , -0.95]
Zohar 2011	6.91	8.64	9	28.4	21.1284	8	26.5%	-21.49 [-37.18 , -5.80]
Total (95% CI)			**79**			**77**	**100.0%**	**-9.69 [-21.91 , 2.53]**

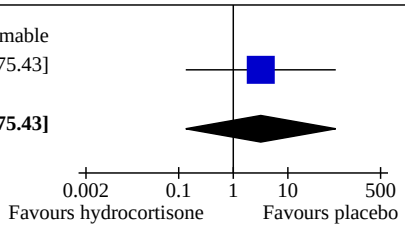
Heterogeneity: Tau² = 82.64; Chi² = 7.21, df = 2 (P = 0.03); I² = 72%
Test for overall effect: Z = 1.55 (P = 0.12)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Hydrocortisone versus placebo, Outcome 3: Dropouts due to adverse events at three months

Study or Subgroup	Hydrocortisone Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Carmi 2022	0	60	0	58		Not estimable
Delahanty 2013	1	31	0	33	100.0%	3.19 [0.13 , 75.43]
Total (95% CI)		**91**		**91**	**100.0%**	**3.19 [0.13 , 75.43]**
Total events:	1		0			

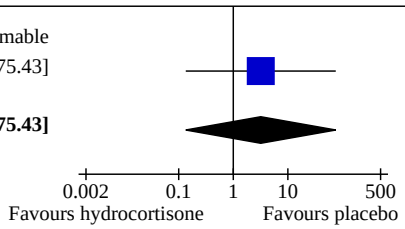
Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Hydrocortisone versus placebo, Outcome 4: Dropouts due to adverse events at study endpoint

Study or Subgroup	Hydrocortisone Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Carmi 2022	0	60	0	58		Not estimable
Delahanty 2013	1	31	0	33	100.0%	3.19 [0.13 , 75.43]
Total (95% CI)		**91**		**91**	**100.0%**	**3.19 [0.13 , 75.43]**
Total events:	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)
Test for subgroup differences: Not applicable



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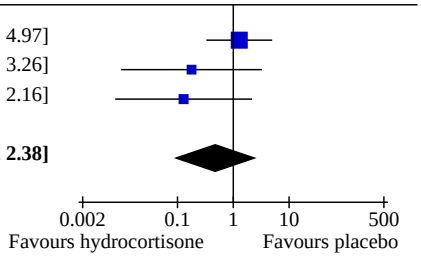
Analysis 2.5. Comparison 2: Hydrocortisone versus placebo, Outcome 5: PTSD rate at three months

Study or Subgroup	Hydrocortisone Events	Hydrocortisone Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Carmi 2022	5	43	3	33	53.6%	1.28 [0.33 , 4.97]
Delahanty 2013	0	19	3	24	22.7%	0.18 [0.01 , 3.26]
Zohar 2011	0	9	3	8	23.7%	0.13 [0.01 , 2.16]
Total (95% CI)		**71**		**65**	**100.0%**	**0.47 [0.09 , 2.38]**
Total events:	5		9			

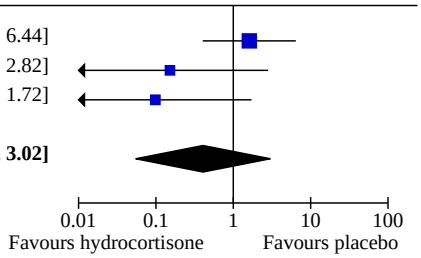
Heterogeneity: Tau² = 0.79; Chi² = 3.13, df = 2 (P = 0.21); I² = 36%
Test for overall effect: Z = 0.91 (P = 0.36)
Test for subgroup differences: Not applicable



Analysis 2.6. Comparison 2: Hydrocortisone versus placebo, Outcome 6: Sensitivity analysis: PTSD rate at three months (cases out of randomised)

Study or Subgroup	Hydrocortisone Events	Hydrocortisone Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Carmi 2022	5	60	3	58	46.6%	1.61 [0.40 , 6.44]
Delahanty 2013	0	31	3	33	26.4%	0.15 [0.01 , 2.82]
Zohar 2011	0	15	3	10	27.0%	0.10 [0.01 , 1.72]
Total (95% CI)		**106**		**101**	**100.0%**	**0.41 [0.05 , 3.02]**
Total events:	5		9			

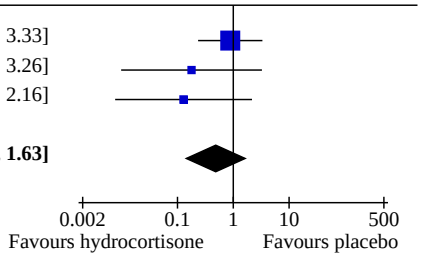
Heterogeneity: Tau² = 1.74; Chi² = 4.45, df = 2 (P = 0.11); I² = 55%
Test for overall effect: Z = 0.88 (P = 0.38)
Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2: Hydrocortisone versus placebo, Outcome 7: PTSD rate at study endpoint

Study or Subgroup	Hydrocortisone Events	Hydrocortisone Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Carmi 2022	4	51	4	45	66.1%	0.88 [0.23 , 3.33]
Delahanty 2013	0	19	3	24	16.5%	0.18 [0.01 , 3.26]
Zohar 2011	0	9	3	8	17.4%	0.13 [0.01 , 2.16]
Total (95% CI)		**79**		**77**	**100.0%**	**0.48 [0.14 , 1.63]**
Total events:	4		10			

Heterogeneity: Tau² = 0.12; Chi² = 2.17, df = 2 (P = 0.34); I² = 8%
Test for overall effect: Z = 1.17 (P = 0.24)
Test for subgroup differences: Not applicable



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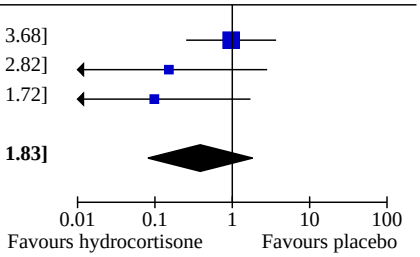
Analysis 2.8. Comparison 2: Hydrocortisone versus placebo, Outcome 8: Sensitivity analysis: PTSD rate at study endpoint (cases out of randomised)

Study or Subgroup	Hydrocortisone Events	Hydrocortisone Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Carmi 2022	4	60	4	58	55.6%	0.97 [0.25 , 3.68]
Delahanty 2013	0	31	3	33	21.8%	0.15 [0.01 , 2.82]
Zohar 2011	0	15	3	10	22.5%	0.10 [0.01 , 1.72]
Total (95% CI)		**106**		**101**	**100.0%**	**0.39 [0.08 , 1.83]**
Total events:	4		10			

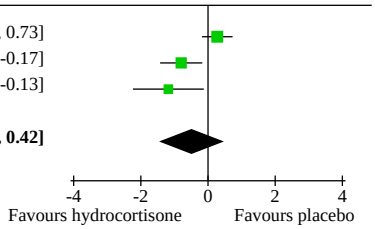
Heterogeneity: Tau² = 0.67; Chi² = 2.95, df = 2 (P = 0.23); I² = 32%
Test for overall effect: Z = 1.20 (P = 0.23)
Test for subgroup differences: Not applicable



Analysis 2.9. Comparison 2: Hydrocortisone versus placebo, Outcome 9: Depression severity at three months

Study or Subgroup	Hydrocortisone Mean	Hydrocortisone SD	Hydrocortisone Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Carmi 2022	3	3.01	43	2.24	2.32	33	38.1%	0.28 [-0.18 , 0.73]
Delahanty 2013	32.7	11.769	19	42.5	12.2474	24	35.1%	-0.80 [-1.43 , -0.17]
Zohar 2011	0.52	2.2479	9	3.83	3.0646	8	26.9%	-1.18 [-2.24 , -0.13]
Total (95% CI)			**71**			**65**	**100.0%**	**-0.49 [-1.40 , 0.42]**

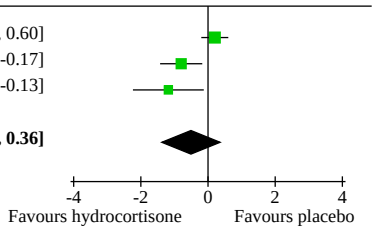
Heterogeneity: Tau² = 0.51; Chi² = 10.99, df = 2 (P = 0.004); I² = 82%
Test for overall effect: Z = 1.06 (P = 0.29)
Test for subgroup differences: Not applicable



Analysis 2.10. Comparison 2: Hydrocortisone versus placebo, Outcome 10: Depression severity at study endpoint

Study or Subgroup	Hydrocortisone Mean	Hydrocortisone SD	Hydrocortisone Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Carmi 2022	5.85	7.73	51	4.44	5.91	45	39.0%	0.20 [-0.20 , 0.60]
Delahanty 2013	32.7	11.769	19	42.5	12.2474	24	34.8%	-0.80 [-1.43 , -0.17]
Zohar 2011	0.52	2.2479	9	3.83	3.0646	8	26.1%	-1.18 [-2.24 , -0.13]
Total (95% CI)			**79**			**77**	**100.0%**	**-0.51 [-1.38 , 0.36]**

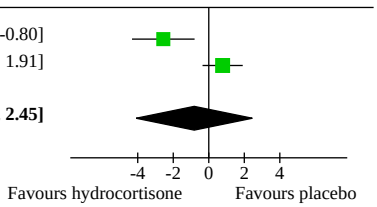
Heterogeneity: Tau² = 0.46; Chi² = 10.66, df = 2 (P = 0.005); I² = 81%
Test for overall effect: Z = 1.15 (P = 0.25)
Test for subgroup differences: Not applicable



Analysis 2.11. Comparison 2: Hydrocortisone versus placebo, Outcome 11: Anxiety severity at three months

Study or Subgroup	Hydrocortisone Mean	Hydrocortisone SD	Hydrocortisone Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Zohar 2011	0.61	1.629	9	3.17	2.0252	8	47.9%	-2.56 [-4.32 , -0.80]
Carmi 2022	2.88	2.79	43	2.1	2.24	33	52.1%	0.78 [-0.35 , 1.91]
Total (95% CI)			**52**			**41**	**100.0%**	**-0.82 [-4.09 , 2.45]**

Heterogeneity: Tau² = 5.01; Chi² = 9.78, df = 1 (P = 0.002); I² = 90%
Test for overall effect: Z = 0.49 (P = 0.62)
Test for subgroup differences: Not applicable



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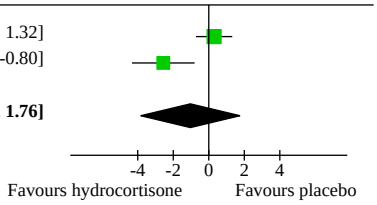
Analysis 2.12. Comparison 2: Hydrocortisone versus placebo, Outcome 12: Anxiety severity at study endpoint

Study or Subgroup	Hydrocortisone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Carmi 2022	1.91	2.73	51	1.61	2.38	45	53.3%	0.30 [-0.72 , 1.32]
Zohar 2011	0.61	1.629	9	3.17	2.0252	8	46.7%	-2.56 [-4.32 , -0.80]
Total (95% CI)			**60**			**53**	**100.0%**	**-1.04 [-3.83 , 1.76]**

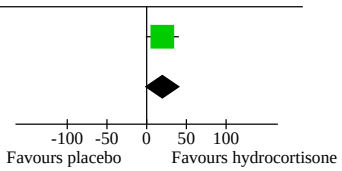
Heterogeneity: Tau² = 3.55; Chi² = 7.58, df = 1 (P = 0.006); I² = 87%
Test for overall effect: Z = 0.73 (P = 0.47)
Test for subgroup differences: Not applicable



Analysis 2.13. Comparison 2: Hydrocortisone versus placebo, Outcome 13: Quality of life at three months

Study or Subgroup	Hydrocortisone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Delahanty 2013	48	33.5635	19	28.3	35.7626	24	100.0%	19.70 [-1.10 , 40.50]
Total (95% CI)			**19**			**24**	**100.0%**	**19.70 [-1.10 , 40.50]**

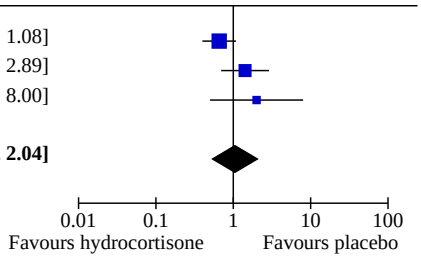
Heterogeneity: Not applicable
Test for overall effect: Z = 1.86 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 2.14. Comparison 2: Hydrocortisone versus placebo, Outcome 14: Dropout for any reason at three months

Study or Subgroup	Hydrocortisone Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Carmi 2022	17	60	25	58	46.5%	0.66 [0.40 , 1.08]
Delahanty 2013	12	31	9	33	36.6%	1.42 [0.70 , 2.89]
Zohar 2011	6	15	2	10	16.9%	2.00 [0.50 , 8.00]
Total (95% CI)		**106**		**101**	**100.0%**	**1.05 [0.54 , 2.04]**
Total events:	35		36			

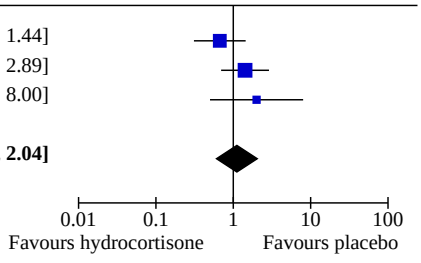
Heterogeneity: Tau² = 0.18; Chi² = 4.38, df = 2 (P = 0.11); I² = 54%
Test for overall effect: Z = 0.15 (P = 0.88)
Test for subgroup differences: Not applicable



Analysis 2.15. Comparison 2: Hydrocortisone versus placebo, Outcome 15: Dropout for any reason at study endpoint

Study or Subgroup	Hydrocortisone Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Carmi 2022	9	60	13	58	39.8%	0.67 [0.31 , 1.44]
Delahanty 2013	12	31	9	33	43.9%	1.42 [0.70 , 2.89]
Zohar 2011	6	15	2	10	16.3%	2.00 [0.50 , 8.00]
Total (95% CI)		**106**		**101**	**100.0%**	**1.11 [0.61 , 2.04]**
Total events:	27		24			

Heterogeneity: Tau² = 0.08; Chi² = 2.82, df = 2 (P = 0.24); I² = 29%
Test for overall effect: Z = 0.35 (P = 0.73)
Test for subgroup differences: Not applicable



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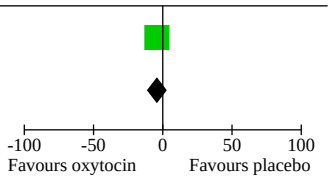
Comparison 3. Oxytocin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 PTSD severity at three months	1	107	Mean Difference (IV, Random, 95% CI)	-4.27 [-10.85, 2.31]
3.2 PTSD severity at study endpoint	1	107	Mean Difference (IV, Random, 95% CI)	-1.00 [-6.83, 4.83]
3.3 Depression severity at three months	1	107	Mean Difference (IV, Random, 95% CI)	-0.56 [-2.53, 1.41]
3.4 Depression severity at study endpoint	1	107	Mean Difference (IV, Random, 95% CI)	-0.71 [-2.38, 0.96]
3.5 Anxiety severity at three months	1	107	Mean Difference (IV, Random, 95% CI)	-0.31 [-2.10, 1.48]
3.6 Anxiety severity at study endpoint	1	107	Mean Difference (IV, Random, 95% CI)	-0.47 [-2.00, 1.06]
3.7 Dropout for any reason at three months	1	120	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.64, 2.03]
3.8 Dropout for any reason at study endpoint	1	120	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.54, 1.68]

Analysis 3.1. Comparison 3: Oxytocin versus placebo, Outcome 1: PTSD severity at three months

	Oxytocin			Placebo				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Van Zuiden 2017	16.97	16.22	53	21.24	18.43	54	100.0%	-4.27 [-10.85 , 2.31]	
Total (95% CI)			**53**			**54**	**100.0%**	**-4.27 [-10.85 , 2.31]**	

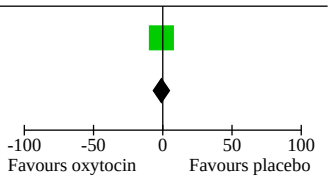
Heterogeneity: Not applicable
Test for overall effect: Z = 1.27 (P = 0.20)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Oxytocin versus placebo, Outcome 2: PTSD severity at study endpoint

	Oxytocin			Placebo				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Van Zuiden 2017	12.78	12.69	53	13.78	17.7	54	100.0%	-1.00 [-6.83 , 4.83]	
Total (95% CI)			**53**			**54**	**100.0%**	**-1.00 [-6.83 , 4.83]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.74)
Test for subgroup differences: Not applicable



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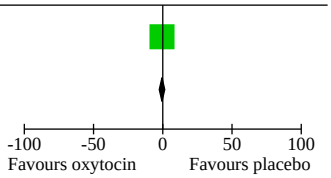
Analysis 3.3. Comparison 3: Oxytocin versus placebo, Outcome 3: Depression severity at three months

Study or Subgroup	Oxytocin Mean	Oxytocin SD	Oxytocin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Van Zuiden 2017	4.03	5.5	53	4.59	4.88	54	100.0%	-0.56 [-2.53 , 1.41]
Total (95% CI)			**53**			**54**	**100.0%**	**-0.56 [-2.53 , 1.41]**

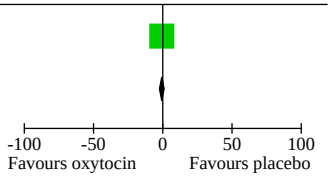
Heterogeneity: Not applicable
Test for overall effect: Z = 0.56 (P = 0.58)
Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3: Oxytocin versus placebo, Outcome 4: Depression severity at study endpoint

Study or Subgroup	Oxytocin Mean	Oxytocin SD	Oxytocin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Van Zuiden 2017	3.21	4.45	53	3.92	4.35	54	100.0%	-0.71 [-2.38 , 0.96]
Total (95% CI)			**53**			**54**	**100.0%**	**-0.71 [-2.38 , 0.96]**

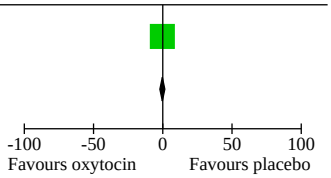
Heterogeneity: Not applicable
Test for overall effect: Z = 0.83 (P = 0.40)
Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3: Oxytocin versus placebo, Outcome 5: Anxiety severity at three months

Study or Subgroup	Oxytocin Mean	Oxytocin SD	Oxytocin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Van Zuiden 2017	4.78	5.04	53	5.09	4.35	54	100.0%	-0.31 [-2.10 , 1.48]
Total (95% CI)			**53**			**54**	**100.0%**	**-0.31 [-2.10 , 1.48]**

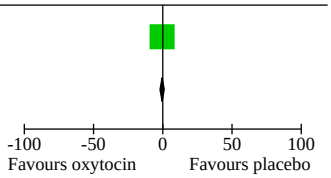
Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.73)
Test for subgroup differences: Not applicable



Analysis 3.6. Comparison 3: Oxytocin versus placebo, Outcome 6: Anxiety severity at study endpoint

Study or Subgroup	Oxytocin Mean	Oxytocin SD	Oxytocin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Van Zuiden 2017	4.41	4.03	53	4.88	4.03	54	100.0%	-0.47 [-2.00 , 1.06]
Total (95% CI)			**53**			**54**	**100.0%**	**-0.47 [-2.00 , 1.06]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.60 (P = 0.55)
Test for subgroup differences: Not applicable



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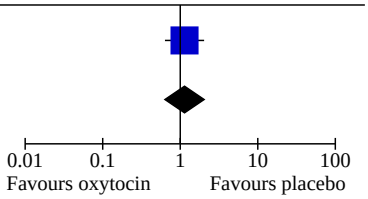
Analysis 3.7. Comparison 3: Oxytocin versus placebo, Outcome 7: Dropout for any reason at three months

Study or Subgroup	Oxytocin Events	Oxytocin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Van Zuiden 2017	17	58	16	62	100.0%	1.14 [0.64 , 2.03]
Total (95% CI)		**58**		**62**	**100.0%**	**1.14 [0.64 , 2.03]**
Total events:	17		16			

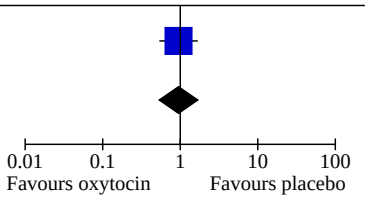
Heterogeneity: Not applicable
Test for overall effect: Z = 0.43 (P = 0.67)
Test for subgroup differences: Not applicable



Analysis 3.8. Comparison 3: Oxytocin versus placebo, Outcome 8: Dropout for any reason at study endpoint

Study or Subgroup	Oxytocin Events	Oxytocin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Van Zuiden 2017	16	58	18	62	100.0%	0.95 [0.54 , 1.68]
Total (95% CI)		**58**		**62**	**100.0%**	**0.95 [0.54 , 1.68]**
Total events:	16		18			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.18 (P = 0.86)
Test for subgroup differences: Not applicable



Comparison 4. Temazepam versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 PTSD severity at study endpoint	1	22	Mean Difference (IV, Random, 95% CI)	9.20 [-9.91, 28.31]
4.2 Dropouts due to adverse events at study endpoint	1	22	Risk Ratio (M-H, Random, 95% CI)	Not estimable
4.3 PTSD rate at study endpoint	1	22	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.66, 6.04]
4.4 Sensitivity analysis: PTSD rate at study endpoint (cases out of randomised)	1	22	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.66, 6.04]
4.5 Dropout for any reason at study endpoint	1	22	Risk Ratio (M-H, Random, 95% CI)	Not estimable

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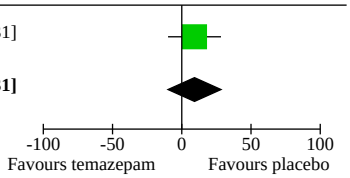
Analysis 4.1. Comparison 4: Temazepam versus placebo, Outcome 1: PTSD severity at study endpoint

Study or Subgroup	Temazepam Mean	Temazepam SD	Temazepam Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Mellman 2002	53.3	19.1	11	44.1	26.1	11	100.0%	9.20 [-9.91 , 28.31]
Total (95% CI)			**11**			**11**	**100.0%**	**9.20 [-9.91 , 28.31]**

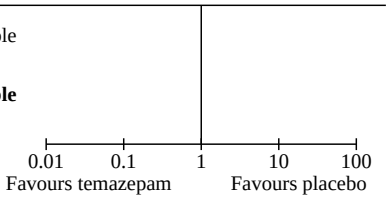
Heterogeneity: Not applicable
Test for overall effect: Z = 0.94 (P = 0.35)
Test for subgroup differences: Not applicable



Analysis 4.2. Comparison 4: Temazepam versus placebo, Outcome 2: Dropouts due to adverse events at study endpoint

Study or Subgroup	Temazepam Events	Temazepam Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Mellman 2002	0	11	0	11		Not estimable
Total (95% CI)		**11**		**11**		**Not estimable**
Total events:	0		0			

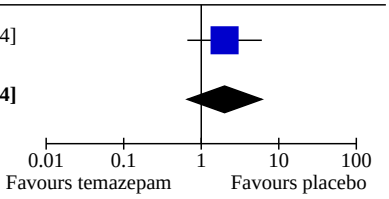
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 4.3. Comparison 4: Temazepam versus placebo, Outcome 3: PTSD rate at study endpoint

Study or Subgroup	Temazepam Events	Temazepam Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Mellman 2002	6	11	3	11	100.0%	2.00 [0.66 , 6.04]
Total (95% CI)		**11**		**11**	**100.0%**	**2.00 [0.66 , 6.04]**
Total events:	6		3			

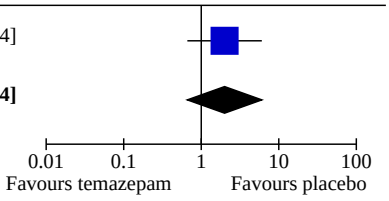
Heterogeneity: Not applicable
Test for overall effect: Z = 1.23 (P = 0.22)
Test for subgroup differences: Not applicable



Analysis 4.4. Comparison 4: Temazepam versus placebo, Outcome 4: Sensitivity analysis: PTSD rate at study endpoint (cases out of randomised)

Study or Subgroup	Temazepam Events	Temazepam Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Mellman 2002	6	11	3	11	100.0%	2.00 [0.66 , 6.04]
Total (95% CI)		**11**		**11**	**100.0%**	**2.00 [0.66 , 6.04]**
Total events:	6		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.23 (P = 0.22)
Test for subgroup differences: Not applicable



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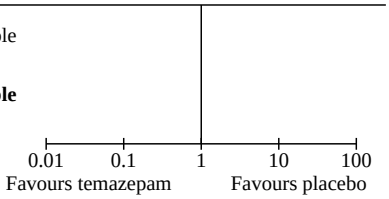
Analysis 4.5. Comparison 4: Temazepam versus placebo, Outcome 5: Dropout for any reason at study endpoint

Study or Subgroup	Temazepam Events	Temazepam Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Mellman 2002	0	11	0	11		Not estimable
Total (95% CI)		**11**		**11**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Oxytocin compared to placebo for prevention of PTSD in individuals experiencing acute traumatic stress symptoms

Patient or population: adults experiencing acute traumatic stress symptoms
Setting: emergency department patients
Intervention: oxytocin
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with oxytocin				
PTSD severity at 3 months	The mean PTSD severity at 3 months was 21.24 on the CAPS	MD 4.27 lower on the CAPS (10.85 lower to 2.31 higher)	-	107 (1 RCT)	⊕⊕⊖⊖ Low[a]	-
Dropout due to adverse events at 3 months - not measured	-	-	-	-	-	-
PTSD rate at 3 months - not measured	-	-	-	-	-	-
Functional disability at 3 months - not measured	-	-	-	-	-	-
Quality of life at 3 months - not measured	-	-	-	-	-	-

*__The risk in the intervention group__ (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; **MD**: mean difference; **PTSD**: post-traumatic stress disorder; **RCT**: randomised controlled trial

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

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Table 1. Oxytocin compared to placebo for prevention of PTSD in individuals experiencing acute traumatic stress symptoms *(Continued)*

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded two levels for imprecision as far fewer than 400 participants have been included, and the CI includes both appreciable benefit and harm.

Table 2. Temazepam compared to placebo for prevention of PTSD in individuals experiencing acute traumatic stress symptoms

Patient or population: adults experiencing acute traumatic stress symptoms
Setting: trauma centre patients
Intervention: temazepam
Comparison: placebo

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
PTSD severity at 3 months - not measured	No study reported this outcome	-	-
Dropout due to adverse events at 3 months - not measured	No study reported this outcome	-	-
PTSD rate at 3 months - not measured	No study reported this outcome	-	-
Functional disability at 3 months - not measured	No study reported this outcome	-	-
Quality of life at 3 months - not measured	No study reported this outcome	-	-

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

PTSD: post-traumatic stress disorder

APPENDICES

Appendix 1. CCMDCTR (core MEDLINE search)

Core search strategy used to inform Specialised Register: OVID MEDLINE (1946 to June 2016)

A weekly search alert based on condition + RCT filter only

1. [MeSH Headings]:

eating disorders/ or anorexia nervosa/ or binge-eating disorder/ or bulimia nervosa/ or female athlete triad syndrome/ or pica/ or hyperphagia/ or bulimia/ or self-injurious behavior/ or self mutilation/ or suicide/ or suicidal ideation/ or suicide, attempted/ or mood disorders/ or affective disorders, psychotic/ or bipolar disorder/ or cyclothymic disorder/ or depressive disorder/ or depression,

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postpartum/ or depressive disorder, major/ or depressive disorder, treatment-resistant/ or dysthymic disorder/ or seasonal affective disorder/ or neurotic disorders/ or depression/ or adjustment disorders/ or exp antidepressive agents/ or anxiety disorders/ or agoraphobia/ or neurocirculatory asthenia/ or obsessive-compulsive disorder/ or obsessive hoarding/ or panic disorder/ or phobic disorders/ or stress disorders, traumatic/ or combat disorders/ or stress disorders, post-traumatic/ or stress disorders, traumatic, acute/ or anxiety/ or anxiety, castration/ or koro/ or anxiety, separation/ or panic/ or exp anti-anxiety agents/ or somatoform disorders/ or body dysmorphic disorders/ or conversion disorder/ or hypochondriasis/ or neurasthenia/ or hysteria/ or munchausen syndrome by proxy/ or munchausen syndrome/ or fatigue syndrome, chronic/ or obsessive behavior/ or compulsive behavior/ or behavior, addictive/ or impulse control disorders/ or firesetting behavior/ or gambling/ or trichotillomania/ or stress, psychological/ or burnout, professional/ or sexual dysfunctions, psychological/ or vaginismus/ or Anhedonia/ or Affective Symptoms/ or *Mental Disorders/2.

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

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

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

Appendix 2. CCMD Editorial Base search strategy (2014 to 2020)

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

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

Inclusion criteria were as follows.

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

Exclusion criteria were as follows.

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

The following databases were searched: CENTRAL, MEDLINE, Embase, PsycINFO, PILOTS.

1. Cochrane Central Register of Controlled Trials (CENTRAL)

Host: Wiley interfaceDate Last Searched: 13 November 2020ID Search #1 MeSH descriptor: [Stress Disorders, Post-Traumatic] this term only #2 (PTSD or ((posttrauma* or post-trauma* or post trauma*) near/3 (stress* or disorder* or psych* or symptom*)) or acute stress disorder*

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or combat disorder* or war neuros*) #3 (((acute or traumatic) near/1 stress*) and (expos* or psyc*)) #4 (traumatised near/1 (victim* or survivor*)) #5 (traumatized near/1 (victim* or survivor*)) #6 (trauma* near/2 (event* or memor* or flashback* or nightmare*)) #7 ((trauma* or posttrauma* or post-trauma* or victim* or survivor*) and (exposure near/3 (therap* or psychotherap* or training or counsel*))) #8 MeSH descriptor: [Crisis Intervention] this term only #9 (critical incident near/1 (stress or debrief* or de-brief*)) #10 (debriefing or de-briefing) #11 (crisis intervention* or CISD) #12 ((stress or group* or psychological or crisis) near/3 (debrief* or de-brief*)) #13 (trauma* near/2 (event* or memor* or flashback* or nightmare*)) #14 (EMDR or (eye movement desensitization and reprocessing)) #15 (EMDR or (eye movement desensitisation and reprocessing)) #16 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14

2. Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to present

Host: OVID
Date last searched: 13 November 2020

#	Searches
1	Stress Disorders, Post-Traumatic/
2	(PTSD or ((posttrauma* or post-trauma* or post trauma*) adj3 (stress* or disorder* or psych* or symptom?)) or acute stress disorder* or combat disorder* or war neuros*).ti,ab,kf,kw,id.
3	(((acute or traumatic) adj stress*) and (expos* or psyc*)).ti,ab,kf,kw,id.
4	(traumati#ed adj (victim? or survivor?)).ti,ab,kf,kw,id.
5	(trauma* adj2 (event? or memor* or flashback* or nightmare?)).ti,ab,kf,kw,id.
6	((trauma* or posttrauma* or post-trauma* or victim* or survivor?) and (exposure adj3 (therap* or psychotherap* or training or counsel*))).ti,ab,kf,kw,id,hw.
7	Crisis Intervention/
8	(critical incident adj (stress or debrief* or de-brief*)).ti,ab,kf,kw,id.
9	(debriefing or de-briefing).ti,kf,kw,id.
10	(crisis intervention? or CISD).ti,ab,kf,kw,id.
11	((stress or group? or psychological or crisis) adj3 (debrief* or de-brief*)).ti,ab,kf,kw,id.
12	(trauma* adj2 (event? or memor* or flashback* or nightmare?)).ti,kf,kw,id.
13	(EMDR or (eye movement desensiti#ation and reprocessing)).ti,ab,kf,kw,id,sh.
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15	randomized controlled trial.pt.
16	controlled clinical trial.pt.
17	randomized.ab.
18	placebo.ab.
19	clinical trials as topic.sh.
20	randomly.ab.

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(Continued)

21	trial.ti.
22	15 or 16 or 17 or 18 or 19 or 20 or 21
23	14 and 22

3. Embase

Host: OVID

Date last searched: 13 November 2020

Search strategy:

#	Searches
1	posttraumatic stress disorder/
2	"trauma and stressor related disorders"/
3	combat disorders/
4	psychological trauma/
5	stress disorders, post-traumatic/
6	stress disorders, traumatic, acute/
7	(PTSD or ((posttrauma* or post-trauma* or post trauma*) adj3 (stress* or disorder* or psych* or symptom?)) or acute stress disorder* or combat disorder* or war neuros*).ti,ab,kw.
8	(((acute or traumatic) adj stress*) and (expos* or psyc*)).ti,ab,kw.
9	(traumati#ed adj (victim? or survivor?)).ti,ab,kw.
10	(trauma* adj2 (event? or memor* or flashback* or nightmare?)).ti,ab,kw.
11	(EMDR or (eye movement desensiti#ation and reprocessing)).ti,kw.
12	((trauma* or posttrauma* or post-trauma* or victim* or survivor?) and (exposure adj3 (therap* or psychotherap* or training or counsel*))).ti,ab,kw.
13	(critical incident adj (stress or debrief* or de-brief*)).ti,ab,kw.
14	(debriefing or de-briefing).ti,ab,kw.
15	(crisis intervention? or CISD).ti,ab,kw.
16	((stress or group? or psychological or crisis) adj3 (debrief* or de-brief*)).ti,ab,kw.
17	(trauma* adj2 (event? or memor* or flashback* or nightmare?)).ti,ab,kw.
18	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

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(Continued)

19	crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/ or (random* or factorial* or crossover* or cross over* or placebo* or (doubl* adj blind*) or (singl* adj blind*) or assign* or allocat* or volunteer*).tw.
20	18 and 19

4. PsycINFO

Host: OVID
Date last searched: 13 November 2020
Search strategy:

#	Searches
1	posttraumatic stress disorder/ or complex ptsd/ or desnos/ or acute stress disorder/ or combat experience/ or "debriefing (psychological)"/ or emotional trauma/ or post-traumatic stress/ or exp stress reactions/ or traumatic neurosis/
2	exp disasters/
3	(PTSD or ((posttrauma* or post-trauma* or post trauma*) adj3 (stress* or disorder* or psych* or symptom?)) or acute stress disorder* or combat disorder* or war neuros*).ti,ab.
4	(((acute or traumatic) adj stress*) and (expos* or psyc*)).ti,ab.
5	(traumati#ed adj (victim? or survivor?)).ti,ab.
6	(trauma* adj2 (event? or memor* or flashback* or nightmare?)).ti,ab.
7	(EMDR or (eye movement desensiti#ation and reprocessing)).ti,ab.
8	((trauma* or posttrauma* or post-trauma* or victim* or survivor?) and (exposure adj3 (therap* or psychotherap* or training or counsel*))).ti,ab.
9	crisis intervention/
10	(critical incident adj (stress or debrief* or de-brief*)).ti,ab.
11	(debriefing or de-briefing).ti,ab.
12	(crisis intervention? or CISD).ti,ab.
13	((stress or group? or psychological or crisis) adj3 (debrief* or de-brief*)).ti,ab.
14	(trauma* adj2 (event? or memor* or flashback* or nightmare?)).ti,ab.
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16	clinical trials.sh.
17	(randomi#ed or randomi#ation or randomi#ing).ti,ab,id.

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(Continued)

18	(RCT or at random or (random* adj3 (assign* or allocat* or control* or crossover or cross-over or design* or divide* or division or number))).ti,ab,id.
19	(control* and (trial or study or group) and (placebo or waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,id,hw.
20	((single or double or triple or treble) adj2 (blind* or mask* or dummy)).ti,ab,id.
21	trial.ti.
22	placebo.ti,ab,id,hw.
23	treatment outcome.md.
24	treatment effectiveness evaluation.sh.
25	mental health program evaluation.sh.
26	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27	15 and 26

5. PILOTS: Published International Literature On Traumatic Stress

Host: Pro Quest
Data parameters: 1871 to Current (date limits applied, 2014 onwards)
Date searched: Monday 3 March 2018
Searched by: Chris Cooper
Hits: 879
Search strategy

Set#: S1 Searched for: ti((posttrauma* near/4 (stress* or disorder* or psych* or symptom*))) OR ab((posttrauma* near/4 (stress* or disorder* or psych* or symptom*))) Results: 16999*
Set#: S2 Searched for: ti((post-trauma* near/4 (stress* or disorder* or psych* or symptom*))) OR ab((post-trauma* near/4 (stress* or disorder* or psych* or symptom*))) Results: 6647°
Set#: S3 Searched for: ti((post trauma* near/4 (stress* or disorder* or psych* or symptom*))) OR ab((post trauma* near/4 (stress* or disorder* or psych* or symptom*))) Results: 7214°
Set#: S4 Searched for: ti((PTSD or acute stress disorder* or combat disorder* or war neuros*)) OR ab((PTSD or acute stress disorder* or combat disorder* or war neuros*)) Results: 30435*
Set#: S5 Searched for: ti((((acute or traumatic) near/2 stress*) and (expos* or psyc*))) OR ab((((acute or traumatic) near/2 stress*) and (expos* or psyc*))) Results: 2341°
Set#: S6 Searched for: ti((traumatised near/2 (victim* or survivor*))) OR ab((traumatised near/2 (victim* or survivor*))) Results: 84°
Set#: S7 Searched for: ti((trauma* near/3 (event* or memor* or flashback* or nightmare*))) OR ab((trauma* near/3 (event* or memor* or flashback* or nightmare*))) Results: 6974°
Set#: S8 Searched for: ti(((trauma* or posttrauma* or post-trauma* or victim* or survivor*) and (exposure near/4 (therap* or psychotherap* or training or counsel*)))) OR ab(((trauma* or posttrauma* or post-trauma* or victim* or survivor*) and (exposure near/4 (therap* or psychotherap* or training or counsel*)))) Results: 787°
Set#: S9 Searched for: ti((critical incident near/2 (stress or debrief* or de-brief*))) OR ab((critical incident near/2 (stress or debrief* or de-brief*))) Results: 385°
Set#: S10 Searched for: ti((debriefing or de-briefing)) OR ab((debriefing or de-briefing)) Results: 685°
Set#: S11 Searched for: ti((crisis intervention* or CISD)) OR ab((crisis intervention* or CISD)) Results: 784°
Set#: S12 Searched for: ti(((stress or group* or psychological or crisis) near/4 (debrief* or de-brief*))) OR ab(((stress or group* or psychological or crisis) near/4 (debrief* or de-brief*))) Results: 464°
Set#: S13 Searched for: ti((trauma* near/3 (event* or memor* or flashback* or nightmare*))) OR ab((trauma* near/3 (event* or memor* or flashback* or nightmare*))) Results: 6974°
Set#: S14 Searched for: ti((EMDR or (eye movement desensitisation and reprocessing))) OR ab((EMDR or (eye movement desensitisation and reprocessing))) Results: 888°

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Set#: S15 Searched for: ti((EMDR or (eye movement desensitiZation and reprocessing))) OR ab((EMDR or (eye movement desensitiZation and reprocessing))) Results: 888°
Set#: S16 Searched for: (s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14 or s15) Results: 36840*
Set#: S17 Searched for: MAINSUBJECT.EXACT("Randomized Clinical Trial") Results: 1210°
Set#: S18 Searched for: ab((randomized or randomised or placebo or randomly)) Results: 2931°
Set#: S19 Searched for: ti(trial) Results: 784°
Set#: S20 Searched for: (S17 or S18 or S19) Results: 3226°
Set#: S21 Searched for: S16 and s20 Results: 2654°

Appendix 3. Search update strategy 23 January 2023

On 23 January 2023, update searches were run by an Information Specialist (HF), using all the databases from the original searches. The update searches used near identical search strategies: some minor changes were made to the strategy for CENTRAL to accommodate for how the database reads terms separated with a hyphen or space, which is why double quotation marks have been used to search for some terms as exact phrases, or NEXT has been input between certain terms. The contents of the database Published International Literature On Traumatic Stress (PILOTS), which was utilised in the original searches, was searched via PTSDPubs, which is why it has been documented this way in these update searches. The search strategy for PTSDPubs uses the same search terms but was entered as a single search block. For all the update search strategies, date limits of 2020 – current were applied. The results of the databases were deduplicated against each other in EndNote 20.

Date: 23 January 2023

Searcher: Helen Fulbright

Platform	Database	Date searched	Hits	Results after de-duplication
Ovid	MEDLINE	23 January 2023	1862	1829
Ovid	Embase	23 January 2023	3586	2091
Ovid	PsycINFO	23 January 2023	1418	576
Wiley	Cochrane CENTRAL	23 January 2023	2751	1054
ProQuest	PTSDPubs	23 January 2023	555	15
Total			10,172	**5565**

Amended search strategy for CENTRAL

#1 [mh ^"Stress Disorders, Post-Traumatic"]

#2 (PTSD or ((posttrauma* or post NEXT trauma*) near/3 (stress* or disorder* or psych* or symptom*)) or "acute stress disorder*" or combat NEXT disorder* or war NEXT neuros*)

#3 (((acute or traumatic) near/1 stress*) and (expos* or psyc*))

#4 (traumatised near/1 (victim* or survivor*))

#5 (traumatized near/1 (victim* or survivor*))

#6 (trauma* near/2 (event* or memor* or flashback* or nightmare*))

#7 ((trauma* or posttrauma* or post-trauma* or victim* or survivor*) and (exposure near/3 (therap* or psychotherap* or training or counsel*)))

#8 [mh ^"Crisis Intervention"]

#9 ("critical incident" near/1 (stress or debrief* or de NEXT brief*))

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#10 (debriefing)

#11 ("crisis intervention*" or CISD)

#12 ((stress or group* or psychological or crisis) near/3 debrief*)

#13 (trauma* near/2 (event* or memor* or flashback* or nightmare*))

#14 (EMDR or ("eye movement desensitization and reprocessing"))

#15 (EMDR or ("eye movement desensitisation and reprocessing"))

#16 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 with Publication Year from 2020 to 2023, in Trials

Ovid Embase search re-run

As Wolters Kluwer later disclosed a processing issue affecting the Ovid database, on 23 February the Ovid Embase search was re-run using the fix provided by Ovid. There were 192 papers available with the limit for restored records. These have been de-duplicated against the existing 5565 records library, leaving one record.

Date: 23 February 2023

Searcher: Helen Fulbright

Database: Embase <1974 to 2023 February 22>
Search strategy:
---
1 posttraumatic stress disorder/ (77644)
2 "trauma and stressor related disorders"/ (66686)
3 combat disorders/ (171)
4 psychological trauma/ (8956)
5 stress disorders, post-traumatic/ (42494)
6 stress disorders, traumatic, acute/ (1367)
7 (PTSD or ((posttrauma* or post-trauma* or post trauma*) adj3 (stress* or disorder* or psych* or symptom?)) or acute stress disorder* or combat disorder* or war neuros*).ti,ab,kw. (64702)
8 (((acute or traumatic) adj stress*) and (expos* or psyc*)).ti,ab,kw. (24376)
9 (traumati#ed adj (victim? or survivor?)).ti,ab,kw. (62)
10 (trauma* adj2 (event? or memor* or flashback* or nightmare?)).ti,ab,kw. (16858)
11 (EMDR or (eye movement desensiti#ation and reprocessing)).ti,kw. (777)
12 ((trauma* or posttrauma* or post-trauma* or victim* or survivor?) and (exposure adj3 (therap* or psychotherap* or training or counsel*))).ti,ab,kw. (1758)
13 (critical incident adj (stress or debrief* or de-brief*)).ti,ab,kw. (308)
14 (debriefing or de-briefing).ti,ab,kw. (7534)
15 (crisis intervention? or CISD).ti,ab,kw. (2779)
16 ((stress or group? or psychological or crisis) adj3 (debrief* or de-brief*)).ti,ab,kw. (914)
17 (trauma* adj2 (event? or memor* or flashback* or nightmare?)).ti,ab,kw. (16858)
18 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (118361)
19 crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/ or (random* or factorial* or crossover* or cross over* or placebo* or (doubl* adj blind*) or (singl* adj blind*) or assign* or allocat* or volunteer*).tw. (2861598)
20 18 and 19 (13291)
21 limit 20 to yr="2020 -Current" (3885)
22 remove duplicates from 21 (3661)
23 limit 22 to restoredrecords (192)

HISTORY

Protocol first published: Issue 5, 2020

CONTRIBUTIONS OF AUTHORS

All authors, other than DS and TW, contributed to the protocol. DS and TW joined the author team at the review stage.

FB: writing of protocol and review, development of the selection criteria and methodology, screening search results, data extraction, risk of bias and certainty of evidence (GRADE) assessment, interpretation of results (clinical perspective).

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LR: screening search results, data extraction, risk of bias assessment, interpretation of results (methodological perspective).

JIB: development of the selection criteria, interpretation of results (clinical perspective).

RC: interpretation of results (clinical perspective).

NM: assisted in writing the protocol. Development of the methodology, assisted with risk of bias ratings and GRADE assessment, contributed to the writing of the results. Interpretation of results (methodological perspective).

GO: writing of the review, screening search results, data extraction, risk of bias and certainty of evidence (GRADE) assessment, interpretation of results (clinical perspective).

DS: interpretation of results (clinical perspective).

TW: interpretation of results (clinical perspective).

CB: contributed to the write-up of the review, interpretation of results (clinical perspective).

DECLARATIONS OF INTEREST

FB: no conflicts of interest

LR: no conflicts of interest

JIB: has been involved in the development of a guided self-help programme for post-traumatic stress disorder (PTSD), which has been tested in a Phase II randomised controlled trial (RCT) in partnership with the Healthcare Learning Company. JIB is leading an application for grant funding for a Phase III RCT of the programme. Cardiff University and JIB stand to benefit from royalties if the product is commercialised.

RC: leads and has responsibility for Cochrane Common Mental Disorders, which has supported parts of the review process and is largely funded by a grant from the National Institute for Health Research (NIHR) in the UK.

NM: no conflicts of interest

GO: no conflicts of interest

DS: has received research grants and/or consultancy honoraria from AMBRF, Biocodex, Cipla, Lundbeck, National Responsible Gambling Foundation, Novartis, Servier and Sun.

TA: no conflicts of interest

CB: no conflicts of interest

LR, NM, CB are Cochrane editors. None of them were involved in the editorial process for this review.

SOURCES OF SUPPORT

Internal sources

- University of Verona, Italy

  Salary for FB, GO, CB
- University of York, UK

  Hosted FB as a Visiting Fellow

External sources

- National Institute for Health Research (NIHR), UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Dealing with missing dichotomous data

At the protocol stage, for the outcome PTSD rate, we planned to consider missing participants as participants who had the negative event (PTSD). In consideration of the high attrition rate, we felt that this approach made an unrealistically strong assumption, particularly in the context of a preventive intervention. Therefore, our main analyses used observed case data (i.e. the number of participants with the event divided by those who completed). However, we performed sensitivity analyses where the number of randomised participants was used as the denominator.

Methods or analyses that could not be implemented

The following methods or analyses could not be implemented due to an insufficient number of studies:

- Assessment of reporting biases: visual inspection of funnel plots, test for asymmetry and investigation of possible reasons for funnel plot asymmetry; Egger's regression test.
- Subgroup analysis and investigation of heterogeneity: for primary outcomes only, we planned to assess the impact on effectiveness by subgrouping according to the recruitment setting and by considering patients fulfilling and not fulfilling ASD criteria.
- Sensitivity analyses: for all outcomes, we planned to investigate the impact of using ITT data versus completer outcomes and the impact of excluding cluster-RCTs.

Methods for network meta-analysis

As we were expecting a multitude of interventions, we made plans for a network meta-analysis. The lack of direct comparisons between interventions prevented its execution. In addition to what was planned for the pair-wise meta-analysis, we planned the following methods:

Multiple treatment group studies

We would have adjusted for correlations inherent in multiple-arm trials using standard methods (e.g. Dias 2013).

Assessment of heterogeneity

We would have assumed a common between-study heterogeneity standard deviation and use uniform non-informative priors (0,5). We would have assessed the transitivity assumption in several steps. First, by assessing the distribution of potential effect modifiers across treatment comparisons for the following study characteristics: year of publication, study setting, type of trauma, criteria for enrolling, age, gender, history of previous trauma of participants, time from traumatic event to treatment, period over which the treatment has been administered. Second, we would have used standard methods to conduct a global assessment of inconsistency using WinBUGS/OpenBUGS (Dias 2013a; WinBUGS 2000). We would have compared the goodness of fit of an inconsistency model with the network meta-analysis model used in the main analyses, which assumes consistency between direct and indirect evidence. We would have assessed the impact on between-study SD (i.e. heterogeneity) and goodness of fit statistics (residual deviance and deviance information criterion (DIC)). Third, in case of sufficient evidence of potential inconsistency (e.g. improved fit of the inconsistency model of 5 or more on the DIC, substantial reduction in between-study deviation), then we would have fitted node-splitting models (van Valkenhoef 2016), using the Graphical Mixed Treatments Comparisons (GeMTC) package in R (R 2017).

Data synthesis

We would have performed a network meta-analysis using Markov Chain Monte Carlo methods. We would have fit random-effects models in a Bayesian framework using WinBUGS/OpenBUGS (WinBUGS 2000), with standard code (Dias 2013). The binomial likelihood would have been used for dichotomous data and the normal likelihood for continuous data. Normal non-informative priors (0,100) would have been used for trial baselines and treatment effects. We would have assessed convergence of three chains (using different initial values) based on visual inspection of history, Brooks-Gelman Rubin and autocorrelation plots. In the case of chains judged to have converged, the preceding iterations will have been discarded, and a further 50,000 iterations will have been run. Estimates would have been based on the latter iterations. We planned to report posterior medians with 95% credible intervals for all treatment effects, between-study standard deviations (to assess heterogeneity) and total residual deviance (to assess goodness of fit). We planned to calculate the mean rank and probability of being most effective for each treatment (both with 95% credible intervals). We planned to perform the network meta-analysis at individual medicine level, but should this not have been feasible, we would also have considered fitting models at drug class level using the WHO's ATC/DDD Index 2019 as reference (WHO 2018), or including both individual medicine and drug class levels.

Sensitivity analysis

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

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Summary of findings

We would have used the five GRADE domains (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of the evidence from the network meta-analysis, using the standard methods (Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)), but with modifications to reflect specific issues in network meta-analysis. As proposed by Salanti 2014, we would have: evaluated each piece of direct evidence in the network and classified it as either at low, moderate or high risk of bias, according to the usual GRADE guidelines; for each pair-wise network estimate, considering the contribution of all direct estimates feeding into it, using the contributions matrix; illustrated the risk of bias assessments according to the contributions of each source of direct evidence to each network meta-analysis effect estimate. We would have displayed this in a bar chart using green, yellow and red to represent low, moderate and high risk of bias, respectively; for each pair-wise comparison, we would have integrated the risk of bias judgements and the respective contributions into a single judgement about study limitations and considered whether to downgrade the certainty of the evidence. We would have assigned numerical scores to each risk of bias judgement (e.g. 0 for low, -1 for moderate and -2 for high risk of bias), and taken a weighted average of these using the contribution of each direct estimate to the network estimates from the contributions matrix.
We planned to use GRADEpro GDT and CINeMA software (CINeMA 2007; GRADEpro GDT 2015) to generate data for the summary of findings tables, which we would have presented according to Yepes-Nunez 2019, using placebo as comparator. We would have justified all decisions to downgrade or upgrade the quality of the evidence using footnotes and made comments to aid the reader's understanding of the review, where necessary (Salanti 2014).

Title change

The title of the protocol for this review was 'Early pharmacological interventions for acute traumatic stress symptoms: a network meta-analysis'. We have changed the title of the full review to 'Early pharmacological interventions for prevention of post-traumatic stress disorder (PTSD) in individuals experiencing acute traumatic stress symptoms' in consideration of the unfeasibility of the network meta-analysis, and to better reflect the scope of the review.

World Health Organization trials portal and the National Institute of Health trials website

At the protocol stage, we stated that we would search the World Health Organization's trials portal (ICTRP), and the National Institute of Health's trials website (ClinicalTrials.gov). This has not been done as these resources are already covered by the CENTRAL database.

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