Pharmacological therapy for post-traumatic stress disorder: a systematic review and meta-analysis of monotherapy, augmentation and head-to-head approaches

Mathew D. Hoskins, Jack Bridges, Robert Sinnerton, Anna Nakamura, Jack F. G. Underwood, Alan Slater, Matthew R. D. Lee, Liam Clarke, Catrin Lewis, Neil P. Roberts & Jonathan I. Bisson

To cite this article: Mathew D. Hoskins, Jack Bridges, Robert Sinnerton, Anna Nakamura, Jack F. G. Underwood, Alan Slater, Matthew R. D. Lee, Liam Clarke, Catrin Lewis, Neil P. Roberts & Jonathan I. Bisson (2021) Pharmacological therapy for post-traumatic stress disorder: a systematic review and meta-analysis of monotherapy, augmentation and head-to-head approaches, European Journal of Psychotraumatology, 12:1, 1802920, DOI: 10.1080/20008198.2020.1802920

To link to this article: https://doi.org/10.1080/20008198.2020.1802920

© 2021 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.

Published online: 26 Jan 2021.

Submit your article to this journal

Article views: 293

View related articles

View Crossmark data

Citing articles: 1 View citing articles
Pharmacological therapy for post-traumatic stress disorder: a systematic review and meta-analysis of monotherapy, augmentation and head-to-head approaches

Mathew D. Hoskins, Jack Bridges, Robert Sinnerton, Anna Nakamura, Jack F. G. Underwood, Alan Slater, Matthew R. D. Lee, Liam Clarke, Catrin Lewis, Neil P. Roberts and Jonathan I. Bisson

Division of Psychological Medicine and Clinical Neuroscience, Cardiff University, Cardiff, UK

ABSTRACT

Background: Pharmacological approaches are widely used for post-traumatic stress disorder (PTSD) despite uncertainty over efficacy.

Objectives: To determine the efficacy of all pharmacological approaches, including mono-therapy, augmentation and head-to-head approaches (drug versus drug, drug versus psychotherapy), in reducing PTSD symptom severity.

Method: A systematic review and meta-analysis of randomised controlled trials were undertaken; 115 studies were included.

Results: Selective serotonin reuptake inhibitors (SSRIs) were found to be statistically superior to placebo in reduction of PTSD symptoms but the effect size was small (standardised mean difference –0.28, 95% CI –0.39 to –0.17). For individual monotherapy agents compared to placebo in two or more studies, we found small statistically significant evidence for the antidepressants fluoxetine, paroxetine, sertraline, venlafaxine and the antipsychotic quetiapine. For pharmacological augmentation, we found small statistically significant evidence for prazosin and risperidone.

Conclusions: Some medications have a small positive effect on reducing PTSD symptom severity and can be considered as potential monotherapy treatments; these include fluoxetine, paroxetine, sertraline, venlafaxine and quetiapine. Two medications, prazosin and risperidone, also have a small positive effect when used to augment pharmacological monotherapy. There was no evidence of superiority for one intervention over another in the small number of head-to-head comparison studies.

Tratamiento farmacológico para el trastorno de estrés postraumático: una revisión sistemática y metanálisis de monoterapia, potenciación y abordajes comparativos

Antecedentes: Los abordajes farmacológicos se usan ampliamente para el trastorno de estrés postraumático (TEPT) a pesar de su eficacia incierta.

Objetivos: Determinar la eficacia de todos los abordajes farmacológicos, incluyendo monoterapia, potenciación y abordajes comparativos (droga versus droga, droga versus psicoterapia), en la reducción de la severidad de los síntomas de TEPT.

Método: Se llevó a cabo una revisión sistemática y metanálisis de estudios controlados aleatorizados; se incluyeron 115 estudios.

Resultados: Se encontró que los inhibidores selectivos de la recaptación de serotonina (ISRSs) fueron estadísticamente superiores a placebo en la reducción de los síntomas de TEPT, pero el tamaño de efecto fue pequeño (diferencia media estandarizada –0.28, IC 95% –0.39 a –0.17). Para agentes en monoterapia individuales comparados con placebo en dos o más estudios, encontramos para los antidepresivos fluoxetina, paroxetina, sertralina, venlafaxina y el antipsicótico quetiapina una evidencia estadísticamente significativa pequeña. Para la potenciación farmacológica, encontramos para prazosina y risperidona, evidencia estadísticamente significativa pequeña.

Conclusiones: Algunos medicamentos tienen un efecto positivo pequeño en la reducción de la severidad de los síntomas de TEPT y pueden ser considerados como potenciales tratamientos en monoterapia; estos incluyen fluoxetina, paroxetina, sertralina, venlafaxina y quetiapina. Dos medicamentos, prazosina y risperidona, también tienen un efecto positivo pequeño cuando se usan para potenciar la monoterapia farmacológica. En el pequeño número de estudios comparativos, no hubo evidencia de superioridad para una intervención sobre otra.

CONTACT Mathew D. Hoskins, hoskinsmd1@cardiff.ac.uk Division of Psychological Medicine and Clinical Neuroscience, Cardiff University, Cardiff, UK

© 2021 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.
1. Background

Post traumatic stress disorder (PTSD) is a common, severe and debilitating mental illness that may occur in people who have been exposed to one or more exceptionally threatening or horrifying events, such as car accidents, physical assault, sexual assault or combat trauma (American Psychiatric Association, 2013). Since the emergence of PTSD requires an environmental exposure (trauma), the prevalence of PTSD varies across time and geography. Across the world, there is an estimated 12-month prevalence of 3–4% (Karam et al., 2009). In conflict-affected areas, the prevalence is much higher, between 13% and 25% (Steel et al., 2009), and reaches more than 50% in survivors of sexual assault (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1996).

PTSD is characterised by re-experiencing the trauma, avoidance of reminders, negative affect, distorted cognitions and altered arousal and reactivity (American Psychiatric Association, 2013). It causes considerable distress and runs a chronic course in around a third of individuals (Kessler, Chiu, Demler, Merikangas, & Walters, 2005); keeping them off work, in receipt of long-term incapacity benefits and requiring support from medical services for many years (Ferry et al., 2008). PTSD is also associated with high rates of debilitating comorbidities, with up to 50% suffering from depression (Pietrzak, Goldstein, Southwick, & Grant, 2011) and drug and alcohol abuse (Roberts, Kitchiner, Kenardy, & Bisson, 2010), and 19% will attempt suicide (Kessler et al., 1996).

Medication is often used in people who seek out treatment for PTSD, either as monotherapy, augmentation or in combination with a psychological therapy. However, there have been inconsistent findings and recommendations from previous reviews of pharmacotherapy, which, when coupled with potential delays in dissemination and implementation, means that the full potential of evidence-based prescribing may not be fully realised for patients with PTSD. We completed a review of pharmacological monotherapy in 2015 which found that paroxetine, fluoxetine, sertraline and venlafaxine could be effective for PTSD, but the magnitude of the effect was small and the clinical relevance was unclear (Hoskins et al., 2015).

Trauma-focused psychological therapies (TFPT) are the best evidenced and recommended first line of treatment for PTSD (Bisson, Roberts, Andrew, Cooper, & Lewis, 2013; Forbes et al., 2010). Unfortunately, despite this, clinical trials of TFPT are associated with high dropout rates (up to 54%) (Schottenbauer, Glass, Arnkoff, Tendick, & Gray, 2008), and TFPT is ineffective in nearly half of patients who are able to tolerate it (Schottenbauer et al., 2008); with higher PTSD severity predicting a poor response (Blanchard et al., 2003).

In addition to concerns about the tolerability and efficacy of TFPT, people with PTSD may live in areas of the world without access to it or, where they can access it, face long waiting lists for therapy, keeping them off work, in receipt of long-term incapacity benefits and requiring medical support (Wang et al., 2007). It is unlikely to be helpful for people with PTSD who are living in the presence of an ongoing trauma or have very insecure social circumstances, and some people prefer not to engage with psychological therapies (McHugh, Whitton, Peckham, Welge, & Otto, 2013).

Pharmacological augmentation, the practice of first treating with one medication, and then adding in a second medication to hopefully improve the clinical outcome, is a common strategy in other serious mental health conditions (Strawbridge, Carter, Marwood, & Bandelow, 2019) and a logical next step for people with PTSD who have not responded to monotherapy alone. We are not aware of any reviews that have explored the evidence-base for strict augmentation strategies in PTSD, favouring instead to combine monotherapy and augmentation randomised controlled trials for the same medication (Forman-Hoffman et al., 2018a).

Furthermore, some people with PTSD may want to choose between a trauma-focused therapy and a medication for a number of reasons, and it would be useful for clinicians to compare the effectiveness of each intervention in clinical trials of psychotherapy versus medication. Additionally, when deciding which pharmacological agent to use, clinicians and patients would benefit from knowing which is the most efficacious and tolerable, and this information may be gleaned from
clinical trials of direct head-to-head comparisons of medications.

This review was commissioned by the International Society for Traumatic Stress Studies (ISTSS), to investigate the evidence base for pharmacological approaches when treating PTSD, and to inform their treatment guidelines. The original scoping question from the ISTSS covered monotherapy and drug-assisted therapy approaches, and the latter review will be published separately. This review will focus on pharmacological monotherapy approaches, as well as pharmacological augmentation and head-to-head approaches (pharmacotherapy versus pharmacotherapy, and pharmacotherapy versus psychotherapy).

2. Method

This was a systematic review and meta-analysis adhering to the Cochrane Collaboration’s standard methodology.

2.1. Participants

All studies where at least 70% of participants diagnosed with PTSD according to ICD or DSM criteria by means of a structured interview or diagnosis by a clinician were eligible. The lower age limit was 18 years with no restriction on the upper age limit. There was no restriction on the basis of gender or of comorbidity but PTSD was required to be the primary diagnosis. The duration of PTSD symptoms was required to be at least 3 months. There was no restriction on the basis of the severity of PTSD symptoms or the type of traumatic event. There was no minimum sample size and unpublished studies were eligible. Only studies published in English were eligible.

2.2. Interventions

Any randomised controlled trial evaluating the efficacy of pharmacological interventions aimed at reducing the symptoms of PTSD in adults was eligible for inclusion; for monotherapy studies, the comparator of at least one arm was a placebo; for augmentation studies, the comparator arms included participants treated with a pharmacological agent plus augmentation versus a pharmacological agent plus placebo; for head-to-head studies, the comparator was another pharmacological or psychological intervention.

2.3. Outcome measures

The primary outcomes of interest were clinician-administered continuous measures of PTSD symptom severity such as the Clinician Administered PTSD Scale (CAPS). Self-rated PTSD symptom scales were also considered if the above was not reported.

2.4. Search strategy

This review used a common search strategy with the Cochrane review of early psychological interventions (Roberts et al., 2010). Following on from this previous search, we undertook a systematic computerized literature search of the Cochrane Common Mental Disorders Group clinical trials registers databases for studies published from January 2008 to May 2016 using the search terms PTSD or post-trauma* or post-trauma* or 'post trauma*' or 'combat disorder*' or 'stress disorder*'. These databases are collated and updated on a weekly basis from MEDLINE, EMBASE and PsycINFO. A further search was undertaken in May 2018. Studies were additionally sought from the inclusion/exclusion list from a previous systematic review of pharmacotherapy (Hoskins et al., 2015), which included studies until February 2013.

Searches were undertaken as part of a search process to support the development of new PTSD treatment guidelines for the International Society for Traumatic Stress Studies (ISTSS). We checked the reference lists of studies identified in the search, related review articles and management guidelines. We contacted authors of unpublished studies that had completed recruitment where there was a registered protocol on a trial register, such as Clinical Trials. We posted a list of identified studies on the website of the International Society for Traumatic Stress website and asked the membership to identify studies that we might have missed.

2.5. Study selection

The lead author received the Cochrane database pharmacological search hits in an EndNoteX4 file. Studies identified from our previous review were added and duplicates were removed. A small team of secondary reviewers (co-authors) were allocated segments of the search hits and alongside the lead author, independently screened the titles, and then abstracts. Studies that were clearly irrelevant were excluded and potentially relevant ones were assessed for inclusion as full texts. The full texts of included studies were read and then sorted into five categories; monotherapy; augmentation; pharmacological-assisted therapy; pharmacotherapy versus pharmacotherapy; pharmacotherapy versus psychotherapy. Any discrepancies between reviewers’ decisions were resolved by discussion with a third reviewer.

2.6. Data extraction and risk of bias assessment

All data from newly identified studies were double-extracted by the lead author and a second independent reviewer into a standard table and any
discrepancies were discussed with a third reviewer. Data for pre-post mean change and standard deviation (SD) was extracted where available. However, it was not possible to extract this data from all studies, so a decision was made to include data from studies that reported only endpoint mean and SD data. This would enable the maximum number of studies to be included in the meta-analysis for efficacy, although ideally one set of outcomes should be analysed and this should be taken into account when interpreting results. The directionality of effect is preserved when using both mean change and endpoint data, with a lower (or more negative) mean change number corresponding with a lower (or more effective) endpoint mean.

Continuous data were extracted for clinician-administered PTSD symptom severity using the Clinician Administered PTSD Scale as the gold standard; for self-rated PTSD, the Davidson Trauma Scale was used as the gold standard. If these scales were not used, data from alternative scales were extracted.

The lead author entered the outcome data in Review Manager 5 software (Review Manager (RevMan), 2014), which was then checked by an independent second reviewer. Data from studies included in our previous review were entered by the lead author and then independently checked for accuracy by a second reviewer and any discrepancies were discussed with a third reviewer.

2.7. Risk of bias

The lead author and a small team of independent second reviewers assessed the risk of bias for each study, using the domain-based evaluation method recommended by the Cochrane Collaboration (Higgins & Green, 2011). This method considers the following domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessors; incomplete outcome reporting; selective reporting; and any other sources of bias. Any discrepancies between the reviewers’ decisions were discussed with a third reviewer.

2.8. Statistical analysis

Review Manager 5 was used to synthesise data using meta-analysis and to provide forest plots for continuous data. Confidence intervals were set at 95% for all analyses and standard mean differences were used (SMD). The degree of heterogeneity was calculated using the $I^2$ statistic, and where this was less than 30%, a fixed effects model was used; otherwise, where $I^2$ was over 30% a random effects model was used. Data were analysed from the intention to treat (ITT) sample, where possible, to avoid the effects of bias from completers-only analyses. A significant proportion of studies used a modified intention to treat (mITT) method, where participants were analysed, provided they had been randomised and received at least one post-baseline assessment (sometimes before or after the first dose of a study medication or placebo). Whilst this does not adhere to the ITT principle of ‘once randomised, always analysed’, because of the number of studies that employed this method it was necessary to allow it in order to conduct a meaningful review.

3. Results

The initial search yielded 10,317 records, with an additional 51 identified from our previous review. A total of 19 duplicates were removed, leaving 10,349 titles that were screened. A total of 460 full abstracts were reviewed, with 306 excluded as irrelevant. This then left 154 full-text articles which were read and 39 were removed as not meeting the inclusion criteria. A total of 115 studies were included for our series of pharmacological reviews (Figure 1); with 49 studies (Baker et al., 1995; Brady et al., 2000, 2005; Braun, Greenberg, Dasberg, & Lerer, 1991; Butterfield et al., 2001; Carey, Suliman, Ganesan, Seedat, & Stein, 2012; Connor, Sutherland, Tupil, Malik, & Davidson, 1999; Davidson, 2004; Davidson et al., 2006; Davidson, Brady, Mellman, Stein, & Pollack, 2007; Davidson et al., 2005, 1990; Davidson, Rothenbaum, & Tucker, 2006; Davidson, Rothbaum, van der Kolk, Sikes, & Farfel, 2001; Davidson et al., 2003; Davis et al., 2008, 2004; Dunlop et al., 2017; Feder et al., 2014; Friedman, Marmar, Baker, Sikes, & Farfel, 2007; Hertzberg et al., 1999; Hertzberg, Feldman, Beckham, Kudler, & Davidson, 2000; Katz et al., 1994; Kosten, Frank, Dan, McDougle, & Giller, 1991; Kwako et al., 2015; Li et al., 2017; Marshall, Beebe, Oldham, & Zaninelli, 2001; Marshall et al., 2007; Martenyi, Brown, & Caldwell, 2007; Martenyi, Brown, Zhang, Prakash, & Koke, 2002; Matthew et al., 2011; Padala et al., 2006; Panahi et al., 2011; Pfizer588 – sertraline; Rasmussen et al., 2017; Reist et al., 1989; Shalev et al., 2011; Shestatzky, Greenberg, & Lerer, 1988; SKB627, Bryson, Lawrinson, GJ, & KM, unpublished; SKB650, Bryson, KE, & Jeffery, unpublished; Sonne et al., 2006; Tucker et al., 2003, 2007, 2001; van der Kolk et al., 1994, 2007; Villarreal et al., 2016; Yeh et al., 2010) included for our systematic review of monotherapy approaches; 34 studies (Ahmadpanah et al., 2014; Akuchekian & Amanat, 2004; Attari, Rajabi, & Maracy, 2014; Banihasadi, Hosseini, Fayyazi Bordbar, Rezaei Ardani, & Mostafavi Toroghi, 2014; Bartzokis, Lu, Turner, Mintz, & Saunders, 2005; Batki et al., 2014; Becker et al., 2007; Germain et al., 2012; Golier, Caramanica, Demaria, & Yehuda, 2012; Hamner et al., 2009, 2000; Heresco-Levy et al., 2002;
Jetly, Heber, Fraser, & Boisvert, 2015; Krystal et al., 2011; Lindley, Carlson, & Hill, 2007; Ludascher et al., 2015; Manteghi, Hebrani, Mortezania, Haghighi, & Javanbakht, 2014; Monnelly, Ciraulo, Knapp, & Keane, 2003; Naylor et al., 2015; Neylan et al., 2006; Petrakis et al., 2016; Pollack et al., 2011; Ramaswamy, Driscoll, Smith, Bhatia, & Petty, 2016; Raskind et al., 2013; Reich, Winternitz, Hennen, Watts, & Stanculescu, 2004; Rothbaum et al., 2008; Schneier et al., 2015; Simpson et al., 2015; Stein, Kline, & Matloff, 2002; Taylor et al., 2008; Zohar et al., 2002) included for our systematic review of augmentation approaches; seven studies (Davidson et al., 2006; Katz et al., 1994; McRae et al., 2004; Petrakis et al., 2012; Saygin, Sungur, Sabol, & Cetinkaya, 2002; Sonne et al., 2006; Van Liempt et al., 2012) included for our systematic review of pharmacotherapy versus pharmacotherapy approaches; and five studies (Buhmann, Nordentoft, Ekstroem, Carlsson, & Mortensen, 2016; Frommerber et al., 2004; Jerud, Pruitt, Zoellner, & Feeny, 2016; Spivak et al., 2006; van der Kolk et al., 1994) included for pharmacotherapy versus psychotherapy. Twenty-one studies were
included for our drug-assisted therapy review and will be published in a separate article. From here, we will discuss the results in three sections.

3.1. Monotherapy studies

3.1.1. Description of monotherapy studies

The characteristics of the included 49 monotherapy studies are detailed in Table 1. All studies employed at least two parallel comparator arms, where one was a pharmacological intervention and the other a placebo. Three studies employed an additional pharmacological comparator arm (Davidson et al., 2006; Katz et al., 1994; Sonne et al., 2006) and data from these arms will additionally be considered in part of our pharmacotherapy head-to-head meta-analysis.

There were 25 selective Serotonin Reuptake Inhibitor (SSRI) studies, of which seven assessed fluoxetine (Connor et al., 1999; Davidson et al., 2005; Hertzberg et al., 2000; Martenyt et al., 2007, 2002; van der Kolk et al., 1994, 2007), five assessed paroxetine (Marshall et al., 2001, 2007; SKB627 et al., unpublished; SKB650 et al., unpublished; Tucker et al., 2001), 11 assessed sertraline (Brady et al., 2000, 2005; Davidson, 2004; Davidson et al., 2006, 2001; Friedman et al., 2007; Li et al., 2017; Panahi et al., 2011; Pfizer588 – sertraline; Tucker et al., 2003; Zohar et al., 2002), and two assessed citalopram (Shalev et al., 2011; Tucker et al., 2003). Two studies assessed Serotonin Noradrenaline Reuptake Inhibitors (SNRIs) (Davidson et al., 2006, 2006) and two assessed Monoamine Oxidase Inhibitors (MAOIs) (Baker et al., 1995; Kosten et al., 1991; Shesatzytsky et al., 1988). Four studies assessed antipsychotic medications (Butterfield et al., 2001; Carey et al., 2012; Padala et al., 2006; Villarreal et al., 2016) and 16 studies assessed other agents (Braun et al., 1991; Davidson et al., 2007, 1990, 2003; Davis et al., 2008, 2004; Dunlop et al., 2017; Feder et al., 2014; Hertzberg et al., 1999; Katz et al., 1994; Kwako et al., 2015; Matthew et al., 2011; Rasmussen et al., 2017; Reist et al., 1989; Tucker et al., 2007; Yeh et al., 2010).

The average duration of the trials was 13.5 (±14.4) weeks, with an average age of 40.6 (±5.1) years and average sample size of 128 (±138.1) participants. Thirty-six of the studies took place in the USA, with four in Israel, one in Iran, one in Brazil and one in China. One study was international and five studies were of an unknown location.

Combat trauma was the predominant trauma type in 17 studies, with physical violence being the next most common in 10 studies, unknown trauma in eight studies, mixed physical/sexual assaults in six studies, sexual assault in six studies and road traffic accidents in one.

3.1.2. Risk of bias monotherapy assessments

Risk of bias assessments is included in Table 1. The vast majority of studies failed to adequately report their methodology and were deemed to have an unclear risk of bias across most domains. Where there was insufficient information, the authors were contacted via email and the vast majority did not respond with additional information. Every study described itself as randomised, but only 13 studies adequately described the method of random sequence generation and six adequately described the method of allocation concealment and were deemed to have a low risk of bias. Blinding of participants and personnel was adequately reported and deemed to have a low risk of bias in eight studies. Blinding of outcome assessors where a clinician-rated scale was used was deemed to have a low risk of bias in eight studies. Incomplete outcome data were addressed adequately in 11 studies. All prespecified outcome variables were adequately reported in three studies, where protocols were available.

3.1.3. Efficacy of pharmacological monotherapy

Data from 39 studies (n = 4,951) were available for inclusion in a meta-analysis of reduction in severity of PTSD symptoms for any agent versus placebo (Figure 2).

A funnel plot of all included monotherapy studies with usable data shows a degree of asymmetry, with an absence of expected studies of small size and low effect, suggesting possible publication bias (Figure 3). Data from 19 studies of SSRI medications were meta-analysed and a small positive effect for SSRIs as a class when compared against placebo was found (Figure 4) (Studies that investigated more than one SSRI in parallel arms appear twice in the forest plot).

The results of meta-analysis for individual agents when tested against placebo in at least two RCTs or where there are more than 20 participants in each arm are presented in Table 2.

Four medications were significantly superior to placebo on reducing either clinician- or self-rated PTSD symptom severity; paroxetine, venlafaxine, fluoxetine and sertraline. Additionally, there was a single RCT of quetiapine which had more than 20 participants per arm and demonstrated superiority over placebo. There was insufficient evidence for other agents.

3.2. Augmentation studies

3.2.1. Description of studies

The characteristics of the 34 included studies (Ahmadpanah et al., 2014; Akuchekian & Amanat, 2004; Attari et al., 2014; Baniasadi et al., 2014; Bartzokis et al., 2005; Batki et al., 2014; Becker et al., 2007; Germain et al., 2012; Golier et al., 2004; Reist et al., 2011; Rasmussen et al., 2017; Sonne et al., 2006) were of an unknown location.

The results of meta-analysis for individual agents when tested against placebo in at least two RCTs or where there are more than 20 participants in each arm are presented in Table 2.
| Study ID: Baker 1995a USA | Study type: Multicentre, randomised, double-blind, parallel, placebo controlled, flexible dose | Duration: 12 weeks | Participants: N = 118 | Mean age: 44 years | Sex: 19% female | Diagnosis: DSM-III-TR | Predominant trauma type: combat | Mean duration of Sx: 12.8 years | CAPS | IES | Group 1: Brofaromine up to 150 mg | n = 56 | Group 2: Placebo | n = 58 | Risk of bias: low/unclear/high | Low | High | High | High | Unclear |
|-------------------------|-----------------------------------------------------|-------------------|-----------------------|------------------|--------------|------------------|-----------------|-------------------|-------|-------|-------------------------------|-------|-----------------|-------|----------------------|-------|-------|-------|-------|---------|
| Study ID: Brady 2000 USA | Study type: Multicentre, randomised, double-blind, parallel, placebo controlled, flexible dose | Duration: 12 weeks | Participants: N = 187 | Mean age: 44 years | Sex: 72.2% female | Diagnosis: DSM-III-TR | Predominant trauma type: sexual assault | Mean duration of Sx: 12.8 years | CAPS | DTS | IES | CGI-S | CGI-I | HAM-D | Group 1: Sertraline 50–200 mg | (mean dose 133.3 mg) | n = 94 | Group 2: placebo | n = 93 | Risk of bias: low/unclear/high | Low | Unclear | Unclear | Unclear | Unclear | Industry support for author. |
| Study ID: Brady 2005 USA | Study type: Single centre, randomised, double-blind, parallel, placebo controlled, fixed dose | Duration: 12 weeks | Participants: N = 94 | Mean age: 36.7 years | Sex: 46% female | Diagnosis: DSM-IV | Predominant trauma type: physical assault | Mean duration of Sx: unknown | CAPS | HAM-D | ASI | OCDS | Alcohol Use Severity | Group 1: Sertraline 150 mg | n = 49 | Group 2: placebo | n = 45 | Risk of bias: low/unclear/high | Low | Unclear | Unclear | Unclear | High | Industry support |
| Study ID: Braun 1991 Israel | Study type: Single centre, randomised, double-blind, cross over, placebo controlled, 2 week titrated placebo washout flexible dose | Duration: 5 weeks | Participants: N = 16 | Mean age: 37.7 years | Sex: unclear | Diagnosis: DSM-III-TR | Predominant trauma type: combat | Mean duration of Sx: 4.3 years | DSM-based PTSD scale | IES | HAM-D | HAM-A | Group 1: Alprazolam 1.5–6 mg | (mean dose 4.65 mg) | n = 7 | Group 2: placebo | n = 9 | Risk of bias: low/unclear/high | Low | Unclear | Unclear | Unclear | High | Unclear | High |
| Study ID: Butterfield 2001 USA | Study type: Randomised, double-blind, parallel, placebo controlled, flexible dose | Duration: 10 weeks | Participants: N = 15 | Mean age: 43.2 years | Sex: 93% female | Diagnosis: DSM-IV | Predominant trauma type: rape | Mean duration of Sx: unknown | TOP-8 | SPRINT | DTS | SIP | IES | CGI-I | SDS | BAS | AIMS | Group 1: Olanzapine 5–20 mg | (mean dose 14.1 mg) | n = 10 | Group 2: placebo | n = 5 | Risk of bias: low/unclear/high | Unclear | Unclear | Unclear | Unclear | High | Industry funded. |

**Table 1. Characteristics of included monotherapy studies.**
| Study ID: Carey 2012 South Africa | Methods | Participants | Outcomes | Interventions | Notes | Risk of bias (low/unclear/high) |
| --- | --- | --- | --- | --- | --- | --- |
| Study type: Single centre, randomised, double-blind, parallel, placebo controlled, flexible dose | Duration: 8 weeks | N = 34 Mean age: 40.5 years Sex: 60% female | Diagnosis: DSM-IV Predominant trauma type: mixed domestic and criminal violence | Mean duration of Sx: unknown | Group 1: Olanzapine 5–15 mg (mean dose 9.2 mg) n = 14 | Industry funded Unclear Unclear Low Unclear High High |

| Study ID: Connor 1999 USA | Methods | Participants | Outcomes | Interventions | Notes | Risk of bias (low/unclear/high) |
| --- | --- | --- | --- | --- | --- | --- |
| Study type: Randomised, double-blind, parallel, placebo-controlled, flexible dose | Duration: 12 weeks | N = 54 Mean age: 32 years Sex: 91% female | Diagnosis: DSM-III-TR Predominant trauma type: rape Mean duration of Sx: 6 years | | Group 1: Fluoxetine 10–60 mg (mean dose 30 mg) n = 27 | Low Low Low Unclear Unclear Unclear Unclear |

| Study ID: Davidson 1990 USA | Methods | Participants | Outcomes | Interventions | Notes | Risk of bias (low/unclear/high) |
| --- | --- | --- | --- | --- | --- | --- |
| Study type: Randomised, double-blind, parallel, placebo-controlled, flexible dose | Duration: 8 weeks | N = 46 Mean age: unknown Sex: unknown | Diagnosis: DSM-III Predominant trauma type: combat Mean duration of Sx: unknown | | Group 1: Amitriptyline 50–300 mg (mean dose 169 mg) n = 25 | Author supported by industry Unclear Unclear Unclear Unclear High High High |

| Study ID: Davidson 2001a USA | Methods | Participants | Outcomes | Interventions | Notes | Risk of bias (low/unclear/high) |
| --- | --- | --- | --- | --- | --- | --- |
| Study type: Multicentre, randomised, double-blind, parallel, placebo-controlled, flexible dose | Duration: 12 weeks | N = 208 Mean age: 37.1 years Sex: 22% female | Diagnosis: DSM-III-R Predominant trauma type: physical/sexual assault Mean duration of Sx: 12.2 years | 1-week placebo run-in | Group 1: mirtazapine 15–45 mg (mean dose 38.8 mg) n = 17 Group 2: placebo n = 9 | Low Low Low Unclear Unclear Unclear Unclear High High |

| Study ID: Davidson 2004 USA | Methods | Participants | Outcomes | Interventions | Notes | Risk of bias (low/unclear/high) |
| --- | --- | --- | --- | --- | --- | --- |
| Study type: Multicentre, randomised, double-blind, parallel, placebo-controlled, flexible dose | Duration: 12 weeks | N = 384 Mean age: 38 years Sex: 75.5% female | Diagnosis: DSM-III-R Predominant trauma type: physical/sexual assault Mean duration of Sx: 12.1 years | | Group 1: sertraline n = 190 Group 2: fluoxetine n = 194 | Insufficient data reported Unclear Unclear Unclear Unclear Unclear Unclear Unclear |

(Continued)
| Study ID: Davidson 2005 USA | Study type: 6 months open label treatment followed by 6 months randomised, double-blind, placebo-controlled | Duration: 6 months discontinuation |
|---|---|---|
| Methods Participants | Outcomes | Interventions Notes |
| N = 62 Mean age: 34 years Sex: 50% female Diagnosis: MINI criteria Predominant trauma type: combat Mean duration of Sx: unknown | SPRINT CGI-S DTS | Group 1: Fluoxetine 10–60 mg (48.6 mg) Insufficient data reported |

| Study ID: Davidson 2006a USA | Study type: Multicentre, randomised, double blind, three parallel arms, placebo controlled, flexible dose | Duration: 12 weeks |
|---|---|---|
| Methods Participants | Outcomes | Interventions Notes |
| N = 538 Mean age: 32 years Sex: 65.4% female Diagnosis: DSM-IV Predominant trauma type: non-sexual abuse Mean duration of Sx: unknown | CAPS CGI-S DTS | Group 1: Sertraline 25–200 mg (mean dose: 110.2 mg) n = 173 Group 2: Venlafaxine 37.5–300 mg (164.4 mg) n = 179 Group 3: placebo n = 179 |

| Study ID: Davidson 2006 USA | Study type: Multicentre, randomised, double blind, parallel, placebo controlled, flexible dose | Duration: 24 weeks |
|---|---|---|
| Methods Participants | Outcomes | Interventions Notes |
| N = 392 Mean age: 41.35 years Sex: 54.1% female Diagnosis: DSM-IV Predominant trauma type: assault Mean duration of Sx: unknown | CAPS-SX17 CGI-S GAF HAM-D17 CD-RISC Q-LES-Q-SF SDS | Group 1: Venlafaxine 37.5–300 mg (181.7 mg) n = 161 Group 2: placebo n = 168 |

| Study ID: Davidson 2007 USA | Study type: Multicentre, randomised, double blind, parallel, placebo controlled, flexible dose | Duration: 12 |
|---|---|---|
| Methods Participants | Outcomes | Interventions Notes |
| N = 232 Mean age: 42.6 years Sex: 56% female Diagnosis: DSM-IV Predominant trauma type: physical/sexual assault Mean duration of Sx: 13.1 | CAPS DTS TOP-8 CGI-C CDR-S SDS | Group 1: Tiagabine 4–16 mg (11.2 mg) n = 116 Group 2: placebo n = 116 |

| Study ID: Davis 2004 USA | Study type: Randomised, double-blind, parallel, placebo-controlled, flexible dose | Duration: 12 |
|---|---|---|
| Methods Participants | Outcomes | Interventions Notes |
| N = 42 Mean age: 53.8 years Sex: 2% female Diagnosis: DSM-IV Predominant trauma type: combat Mean duration of Sx: 29.9 | CAPS HAM-A HAM-D PTSD checklist GAFS CGI | Group 1: Nefazodone 200–600 mg (435 mg) n = 26 Group 2: placebo n = 15 |

| Study ID: Davis 2008 USA | Study type: Randomised, double-blind, parallel, placebo-controlled, flexible dose | Duration: 8 |
|---|---|---|
| Methods Participants | Outcomes | Interventions Notes |
| N = 85 Mean age: 55.2 years Sex: 2% female Diagnosis: DSM-IV Predominant trauma type: combat Mean duration of Sx: 24.4 years | CAPS TOP-8 MADRS CGI-S CGI-I | Group 1: Divalproex 500–3000 mg (mean dose: 2309 mg) n = 44 Group 2: placebo n = 41 |

(Continued)
| Study ID: Dunlop 2017 USA |
|--------------------------|
| **Study type:** Multicentre, randomised, double-blind, placebo controlled, parallel arm, fixed dose |
| **Duration:** 6 weeks |
| **N = 128** |
| **Mean age:** 40.5 years |
| **Sex:** 100% female |
| **Diagnosis:** DSM-IV-TR |
| **Predominant trauma type:** unknown |
| **Mean duration of Sx:** unknown |
| **Methods** |
| **Participants** |
| **Outcomes** |
| **Interventions** |
| **Notes** |
| **Sequence generation** |
| **Allocation concealment** |
| **Blinding participants/personnel** |
| **Blinding outcome assessors** |
| **Incomplete outcome data** |
| **Free of selective reporting** |
| **Any other bias** |
| Insufficient data reported |

| Study ID: Feder 2014 USA |
|--------------------------|
| **Study type:** Single centre, randomised, double-blind, placebo controlled, fixed dose, crossover single ketamine infusion versus active placebo midazolam |
| **Duration:** 3 weeks |
| **N = 41** |
| **Mean age:** 36 years |
| **Sex:** 46% female |
| **Diagnosis:** DSM-IV-TR |
| **Predominant trauma type:** sexual assault |
| **Mean duration of Sx:** 13 years |
| **Methods** |
| **Participants** |
| **Outcomes** |
| **Interventions** |
| **Notes** |
| **Sequence generation** |
| **Allocation concealment** |
| **Blinding participants/personnel** |
| **Blinding outcome assessors** |
| **Incomplete outcome data** |
| **Free of selective reporting** |
| **Any other bias** |
| Proof of concept, rapid reduction in PTSD Sx severity for ket and midaz |
| Baseline characteristics were not homogenous, far more women and sexual assault in Ket group |
| Second infusion wasn't given if CAPS dropped below 50 two weeks after first infusion |
| Authors named on patent for ketamine use in depression |
| Considerable variation in duration of effect seen in depression studies (3–30 days), so a crossover washout period of 7 days likely to be too short here. We have analysed Ketamine first infusion group vs midazolam first infusion group and discarded crossover group data. |

| Study ID: Friedman 2007 USA |
|--------------------------|
| **Study type:** Multicentre, randomised, double-blind, placebo controlled, flexible dose |
| **Duration:** 12 |
| **N = 169** |
| **Mean age:** 45.5 years |
| **Sex:** 21.3% female |
| **Diagnosis:** DSM-III-R |
| **Predominant trauma type:** combat |
| **Mean duration of Sx:** 18 years |
| **Methods** |
| **Participants** |
| **Outcomes** |
| **Interventions** |
| **Notes** |
| **Sequence generation** |
| **Allocation concealment** |
| **Blinding participants/personnel** |
| **Blinding outcome assessors** |
| **Incomplete outcome data** |
| **Free of selective reporting** |
| **Any other bias** |
| Editorial assistant has received consulting income from drug company |

| Study ID: Hertzberg 1999 USA |
|--------------------------|
| **Study type:** Randomised, double-blind, parallel, placebo-controlled, flexible dose |
| **Duration:** 12 weeks |
| **N = 15** |
| **Mean age:** 43.4 years |
| **Sex:** 36% female |
| **Diagnosis:** DSM-IV |
| **Predominant trauma type:** combat |
| **Mean duration of Sx:** unknown |
| **Methods** |
| **Participants** |
| **Outcomes** |
| **Interventions** |
| **Notes** |
| **Sequence generation** |
| **Allocation concealment** |
| **Blinding participants/personnel** |
| **Blinding outcome assessors** |
| **Incomplete outcome data** |
| **Free of selective reporting** |
| **Any other bias** |
| Industry funded |

(Continued)
| Methods | Participants | Outcomes | Interventions | Notes | Sequence generation | Allocation concealment | Blinding participants/personnel | Blinding outcome assessors | Incomplete outcome data | Free of selective reporting | Any other bias |
|---------|--------------|----------|---------------|-------|---------------------|------------------------|---------------------------|-------------------------------|---------------------|-------------------------|-------------------------|
| Study ID: Hertzberg 2000 USA | N = 12 | Mean age: 46 years | Sex: 100% male | Diagnosis: DSM-III-R | Predominant trauma type: combat | Mean duration of Sx: unknown | DGRP | DTB | Group 1: Fluoxetine 10–60 mg (48 mg) | n = 6 | Unclear | Unclear | Unclear | Unclear | Unclear | High |
| Study type: Randomised, double-blind, parallel, placebo-controlled, flexible dose | Duration: 12 weeks |
| Study ID: Katz 1994 USA | N = 68 | Mean age: 39 years | Sex: 24% female | Diagnosis: DSM-III-R | Predominant trauma type: physical assault | Mean duration of Sx: 2.8 years | CAPS | CGI | Group 1: Bupropion 50–150 mg | n = 33 | Industry funded | Unclear | Unclear | Unclear | Unclear | Low | Unclear | High |
| Study type: Multicentre, randomised, double-blind, parallel, placebo-controlled, flexible dose | Duration: 14 weeks |
| Study ID: Kosten 1991 USA | N = 60 | Mean age: 39 years | Sex: 100% male | Diagnosis: DSM-III | Predominant trauma type: combat | Mean duration of Sx: unknown | IES | HAM-A | HAM-D | Group 1: Mirtazapine 15–45 mg | n = 19 | Unclear | Unclear | Unclear | High | Unclear | High |
| Study type: Multicentre, randomised, double-blind, three parallel arms, placebo-controlled, flexible dose | Duration: 8 weeks |
| Study ID: Kwako 2015 USA | N = 53 | Mean age: 40.8 years | Sex: 45.3% female | Diagnosis: DSM-IV | Predominant trauma type: unknown | Mean duration of Sx: unknown | IES-R | CGI-S | Group 1: Aprepitant 125 mg | n = 26 | Co-morbid alcohol | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear |
| Study type: Single centre, randomised, double blind, placebo controlled, parallel arm, fixed dose | Duration: 4 weeks |
| Study ID: Li 2017 China | N = 72 | Mean age: 46 years | Sex: 12.5% female | Diagnosis: DSM-IV | Predominant trauma type: combat | Mean duration of Sx: unknown | IES-R | CGI-S | Group 1: Sertraline 135 mg | n = 36 | Low | Low | Low | Low | Low | Unclear | Low |
| Study type: Multicentre, randomised, double blind, placebo controlled, parallel arm, fixed dose | Duration: 12 weeks |
| Study ID: Marshall 2001 USA | N = 563 | Mean age: 41.8 years | Sex: 57% female | Diagnosis: DSM-IV | Predominant trauma type: physical/sexual assault | Mean duration of Sx: 15.7 years | CAPS-2 | CGI-H | DTS | TOP-8 | SDS | MADRS | Group 1: Paroxetine 20 mg | n = 188 | Industry funded | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | High |
| Study type: Multicentre, randomised, double-blind, three parallel arms, placebo-controlled, fixed dose | Duration: 12 weeks |
| Study ID: Marshall 2007 USA | Study type: Single centre, randomised, double-blind, parallel, placebo-controlled, flexible dose | Duration: 10 weeks |
|---------------------------|-------------------------------------------------|------------------|
| Study ID: Martenyi 2002a International | Study type: Multicentre, randomised, double-blind, parallel, placebo-controlled, flexible dose | Duration: 12 weeks |
| Study ID: Martenyi 2007 USA | Study type: Multicenter, randomised, double-blind, parallel, placebo-controlled, fixed dose | Duration: 12 weeks |
| Study ID: Matthew 2011 USA | Study type: Multicenter, randomised, double-blind, parallel, placebo-controlled, fixed dose | Duration: 8 weeks |
| Study ID: Padala 2006 USA | Study type: Single centre, randomised, double-blind, parallel, placebo-controlled, flexible dose | Duration: 12 weeks |
| Study ID: Panahi 2011 Iran | Study type: Single centre, randomised, double-blind, parallel, placebo-controlled, flexible dose | Duration: 10 weeks |

**Table 1. (Continued).**

| Study ID | USA | Study type | Duration | N | Mean age | Sex % | Diagnosis | Predominant trauma type | Mean duration of Sx | Interventions | Notes |
|----------|-----|------------|----------|---|----------|-------|-----------|------------------------|-------------------|-------------|-------|
| Marshall 2007 | Single centre, randomised, double-blind, parallel, placebo-controlled, flexible dose | 10 weeks | 63 | 39.8 years | 100% male | DSM-IV | Physical assault or abuse | unknown | Paroxetine 10–60 mg | Group 1: Paroxetine 10–60 mg | 1-week placebo run-in | Unclear | Unclear | Unclear | Unclear | Unclear | High |
| Martenyi 2002a International | Multicentre, randomised, double-blind, parallel, placebo-controlled, flexible dose | 12 weeks | 301 | 37.9 years | 19% female | DSM-IV | Combat | unknown | Placebo | Group 1: Fluoxetine 20–80 mg (57.8 mg) | Industry funded | Unclear | Unclear | Unclear | Unclear | High | Unclear | Unclear | Unclear | High |
| Martenyi 2007 USA | Multicenter, randomised, double-blind, parallel, placebo-controlled, fixed dose | 12 weeks | 411 | 40.7 years | 71.5% female | DSM-IV | Sexual assault | unknown | Fluoxetine 20 mg | Group 1: Fluoxetine 20 mg | Industry funded | Unclear | Unclear | Unclear | Unclear | Low | Unclear | High |
| Matthew 2011 USA | Multicenter, randomised, double-blind, parallel, placebo-controlled, fixed dose | 8 weeks | 47 | 41 years | 59% female | DSM-IV | Physical/sexual assault | unknown | Group 1: GR205171 5 mg | Industry funded | 2-week placebo lead-in | Unclear | Unclear | Unclear | Low | High | Unclear | High |
| Padala 2006 USA | Single centre, randomised, double-blind, parallel, placebo-controlled, flexible dose | 12 weeks | 70 | 46.6 years | 100% male | DSM-IV-TR | Unknown | unknown | Sertraline 50–200 mg (140 mg) | Insufficient data reported | Unclear | Unclear | Unclear | Unclear | Unclear | High |
| Panahi 2011 Iran | Single centre, randomised, double-blind, parallel, placebo-controlled, flexible dose | 10 weeks | 70 | 45.6 years | 100% male | DSM-IV-TR | Combat | 24.1 years | Group 1: Sertraline | Group 1: Sertraline | Low | Unclear | Unclear | Low | Low | Unclear | High |
| Study ID | Location | Type | Duration | N | Mean age | Gender | Diagnosis | Trauma type | Mean duration of Sx | Interventions | Notes | Risk of bias |
|----------|----------|------|----------|---|----------|--------|-----------|-------------|----------------|---------------|-------|--------------|
| Pfizer 588 | Unknown | Multicentre, randomised placebo-controlled, double-blind, parallel, flexible dose | 74 days | 193 | Mean age: 37 years | 74.65% female | DSM-IV | Predominant trauma type: physical/sexual assault | Mean duration of Sx: 10.5 years | CAPS-2 | Group 1: Sertraline (156 mg) | Industry funded, unpublished | Unclear | Unclear | Unclear | Unclear | Unclear | High | High |
| Rasmusson 2017 | USA | Multicentre, randomised, double blind, placebo controlled, parallel arm, flexible dose | 6 weeks | 112 | Mean age: 38.3 years | 21% female | DSM-IV | Predominant trauma type: combat | Mean duration of Sx: unknown | CAPS | Group 1: Galanoxone 200–600 mg (unknown mean dose) | Several authors have industry ties | Low | Low | Low | Unclear | Unclear | Low | High |
| Reist 1989 | USA | Multicentre, randomised, double blind, crossover, placebo controlled, flexible dose | 8 weeks | 27 | Mean age: 38 years | 100% male | DSM-III-R | Predominant trauma type: combat | Mean duration of Sx: unknown | IES | Group 1: Desipramine 50–200 mg (165 mg) | Insufficient data reported | Unclear | Unclear | Unclear | Unclear | High | Low | Unclear |
| Shalev 2011 | Israel | Single centre, randomised, double blind, parallel, placebo controlled, fixed dose | 20 weeks | 46 | Mean age: 38.6 years | 44.2% female | DSM-IV | Predominant trauma type: road traffic accident | Mean duration of Sx: 144 days | PSS-SR | Group 1: Escitalopram 10–20 mg | Industry funded | Low | Unclear | Low | Low | High | Unclear | High |
| Shestatky 1986 | Israel | Single centre, randomised, double blind, parallel arm, 5 week crossover | 12 weeks | 13 | Mean age: unknown | 44% female | DSM-III | Predominant trauma type: combat | Mean duration of Sx: 5.6 years | | Group 1: Phlezeine 45–75 mg (mean dose) | Insufficient data reported | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear |
| SKB627 | Unknown | Randomised, double-blind, parallel, placebo-controlled, flexible dose | 84 days | 322 | Mean age: unknown | 53.7% female | DSM-IV | Predominant trauma type: unknown | Mean duration of Sx: unknown | CAPS-2 | Group 1: Paroxetine 20–50 mg | Industry funded, unpublished | Unclear | Unclear | Unclear | Unclear | Unclear | High | High |

(Continued)
| Study ID: SKB650 | Unknown location | Study type: Randomised, double-blind, placebo-controlled, flexible dose | Duration: 252 days |
|----------------|-----------------|-------------------------------------------------|-----------------|
| Study ID: Sonne 2006 | Unknown location | Study type: Randomised, double-blind, parallel, placebo controlled, flexible dose | Duration: 12 weeks |
| Study ID: Tucker 2001 USA and Canada | Study type: Multicentre, randomised, double blind, parallel arm, placebo controlled, flexible dose | Duration: 12 weeks |
| Study ID: Tucker 2003 USA | Study type: Multicentre, randomised, double blind, parallel arm, placebo controlled, flexible dose | Duration: 10 weeks |
| Study ID: Tucker 2007 USA | Study type: Single centre, double blind, randomised, parallel arm, placebo controlled | Duration: 12 weeks |
| Study ID: van der Kolk 1994 USA | Study type: Multicentre, randomised, double-blind, parallel arm, placebo-controlled, flexible dose | Duration: 5 weeks |

| Methods | Participants | Outcomes | Interventions | Notes | Risk of bias (low/unclear/high) |
|---------|--------------|----------|---------------|-------|--------------------------------|
| N = 176 | CAPS-2 | Group 1: Paroxetine up to 50 mg (mean dose unknown) | Relapse prevention | Unclear |
| Mean age: unknown | DTS | Group 2: placebo | Insufficient data reported | Unclear |
| Sex: 66% female | MDRS | n = unknown | | Unclear |
| Diagnosis: DSM-IV | SDS | Group 2: placebo | | High |
| Predominant trauma type: unknown | | n = unknown | | High |
| Mean duration of Sx: unknown | | | | High |
| N = 25 | CAPS-2 | Group 1: paroxetine (mean dose 42.3 mg) | Insufficient data reported | Unclear |
| Mean age: 35.5 years | DTS | Group 2: | Full report unpublished | Unclear |
| Sex: unknown | | n = 13 | | Unclear |
| Diagnosis: DSM-IV | | Group 2: | | Unclear |
| Predominant trauma type: unknown | | n = 12 | | Unclear |
| Mean duration of Sx: unknown | | | | Unclear |
| N = 323 | CAPS-2 | Group 1: | Industry funded | Unclear |
| Mean age: 40.8 years | CG1 | n = | | Unclear |
| Sex: 66% female | DTS | Group 2: | | Unclear |
| Diagnosis: DSM-IV | Top-8 | n = | | Unclear |
| Predominant trauma type: unknown | SDS | | | High |
| Mean duration of Sx: 14.9 years | MADRS | | | High |
| N = 59 | CAPS | Group 1: Citalopram 20–50 mg (36.2 mg) | Industry funded | Unclear |
| Mean age: 38.5 years | IES | n = 25 | | Unclear |
| Sex: 72% female | BDI | Group 2: Sertraline 50–200 mg (134.1 mg) | | Unclear |
| Diagnosis: DSM-IV | | n = 23 | | Unclear |
| Predominant trauma type: physical abuse/assault | | Group 3: placebo | | Unclear |
| Mean duration of Sx: unknown | | n = 10 | | High |
| N = 40 | CAPS | Group 1: Topiramate (25–400 mg, mean dose 150 mg) | Authors affiliated with the industry | Low |
| Mean age: 41.5 years | HAM-A | n = 19 | | Unclear |
| Sex: 79% female | HAM-D | Group 2: placebo | | Unclear |
| Diagnosis: DSM-IV | CGI-5 | n = 19 | | Unclear |
| Predominant trauma type: childhood sexual abuse | CGI-1 | | | Unclear |
| Mean duration of Sx: unknown | DTS | | | High |
| N = 64 | CAPS | Group 1: Fluoxetine 20–60 mg (mean dose 40 mg) | Insufficient data reported | Unclear |
| Mean age: unknown | HAM-D | n = | | Unclear |
| Sex: 34.3% female | DES | Group 2: | | Unclear |
| Diagnosis: DSM-IV | DES | n = | | Unclear |
| Predominant trauma type: combat | | | | Unclear |
| Mean duration of Sx: unknown | | | | Unclear |

(Continued)
| Methods | Participations | Outcomes | Interventions | Notes | Risk of bias (low/unclear/high) |
|---------|----------------|----------|---------------|-------|--------------------------------|
| Study ID: van der Kolk 2007 USA | N = 59 | CAPS BDI | Group 1: Fluoxetine 20–60 mg (mean dose 40 mg) n = 30 | Authors affiliated with one of the interventions being tested | Unclear Unclear Unclear Unclear Low Unclear High |
| Study type: Multicentre, randomised, double-blind, three parallel arms, placebo-controlled, flexible dose | Mean age: 34.9 years Sex: 86.4% female Diagnosis: DSM-IV Predominant trauma type: interpersonal victimisation Mean duration of Sx: 13.1 years | Group 2: EMDR n = 29 Group 3: placebo n = 29 | | |
| Duration: 5 weeks | | | | |
| Study ID: Villarreal 2016 USA | N = 80 | CAPS BDI IOTS PANSS CGI HAMID HAMA | Group 1: Quetiapine (25–800 mg, mean dose 258 mg) n = 42 | 1-week placebo run-in Industry funded | Low Unclear Unclear Unclear High Unclear High |
| Study type: Multicentre, randomised, double-blind, placebo controlled, parallel arm, flexible dose | Mean age: 53 years Sex: 6% female Diagnosis: DSM-IV Predominant trauma type: combat Mean duration of Sx: unknown | Group 2: placebo n = 38 | | |
| Duration: 12 weeks | | | | |
| Study ID: Yeh 2010 Brazil | N = 35 | CAPS BDI CGI | Group 1: Topiramate 50–200 mg (102.9 mg) n = 17 | | Low Unclear Unclear Low Unclear Unclear High |
| Study type: Single centre, randomised, double-blind, parallel, placebo controlled | Mean age: 40.1 years Sex: 67% female Diagnosis: DSM-IV Predominant trauma type: violent trauma Mean duration of Sx: unknown | Group 2: placebo n = 18 | | |
| Duration: 12 weeks | | | | |
| Study ID: Zohar 2002 Israel | N = 51 | CAPS-2 CGI-1 CGI-S MADRS | Group 1: Sertraline 50–200 mg (120 mg) n = 23 | Baseline characteristics of sample not described well enough to identify whether samples are matched. Industry funded. | Unclear Unclear Unclear Unclear Low Unclear Unclear |
| Study type: Multicenter, randomised, double-blind, parallel arm, placebo-controlled, flexible dose | Mean age: known Sex: 37% female Diagnosis: DSM-III-R Predominant trauma type: unknown Mean duration of Sx: unknown | Group 2: placebo n = 19 | | |
| Duration: 10 weeks | | | | |


Table 3

| Study or Subgroup | Experimental | Control | Std. Mean Difference | Risk of Bias |
|-------------------|--------------|---------|----------------------|-------------|
|                   | Mean (SD)    | Mean (SD) | IV, Random, 95% CI   |             |
| Baker 1999 (ibuprofen) | 54.0 (33.9) | 54.0 (34.2) | 0.3 (0.0) |                         |
| Brady 2000 (peroxides) | -33.7 (27.022) | -23.1 (27.518) | -0.3 (0.05) |                         |
| Brady 2005 (peroxides) | 32.5 (15.68) | 49 (32.7) | 5.7 (0.01) |                         |
| Bray 1991 (percuprine) | 26.4 (7.3) | 26.8 (8.1) | 0.4 (0.04) |                         |
| Butterfield 2001 (cianooxime) | 19.2 (6.7) | 10 (17.5) | 0.6 (0.0) |                         |
| Carey 2012 (aminoglycosides) | 33.6 (28.2) | 14.3 (31.9) | 0.1 (0.03) |                         |
| Connor 1999 (flussulone) | 24.8 (25.8) | 26 (52.1) | 0.8 (0.01) |                         |
| Davidson 1990 (amphiptin) | 29 (11.6) | 17 (33.7) | 0.1 (0.01) |                         |
| Davidson 2005 (acetamid) | -33 (27.6) | -28 (28.2) | 0.4 (0.01) |                         |
| Davidson 2007 (acetamid) | 12.4 (8.6) | 17 (19.4) | 0.9 (0.01) |                         |
| Davidson 2006c (acetamid) | 30.4 (28.1) | 17.3 (31.7) | 0.7 (0.01) |                         |
| Davidson 2006e (acetamid) | 41.5 (21.361) | 17 (28.239) | 0.6 (0.01) |                         |
| Davidson 2005e (acetamid) | 29.2 (25.9) | 161 (38.1) | 20.4 (0.01) |                         |
| Davidson 2007 (acetamid) | -30.7 (25.1) | 116 (30.2) | 0.4 (0.0) |                         |
| Davis 2008 (neutrophores) | -16.6 (24) | 26 (13.0) | 5 (0.03) |                         |
| Davis 2008 (chelaporoxy) | 60.1 (24.4) | 41 (65.9) | 41 (0.03) |                         |
| Fedor 2014 (acetamid) | 54 (23.2) | 19 (65.9) | 16 (0.03) |                         |
| Fridman 2007 (acetamid) | 1.3 (27.1) | 12 (34.2) | 1 (0.03) |                         |
| Herberg 1999 (amnioglycoside) | 34.3 (12.2) | 10 (34.25) | 0.5 (0.06) |                         |
| Herberg 2005 (acetamid) | 47 (6) | 6 (42) | 0.5 (0.06) |                         |
| Katz 1994 (peroxides) | 43.6 (29.7) | 35 (57.1) | 3 (0.03) |                         |
| Kosten 1991 (amnioglycoside) | 27.4 (63) | 23 (31.3) | 1 (0.03) |                         |
| Kosten 1991 (amnioglycoside) | 17 (11.3) | 19 (31.3) | 1 (0.03) |                         |
| Li 2017 (acetamid) | 24.3 (7.8) | 16 (18.1) | 1 (0.03) |                         |
| Marshall 2007 (acetamid) | -33.8 (13.3) | 365 (25.9) | 0.5 (0.03) |                         |
| Marshall 2007 (acetamid) | 53.8 (3.3) | 25 (62.8) | 17 (0.0) |                         |
| Marren 2002a (acetamid v placebo) | 34.8 (28.1) | 226 (28.6) | 0.2 (0.01) |                         |
| Mattwell 2007 (acetamid) | -42.9 (20.5) | 323 (36.9) | 0.3 (0.01) |                         |
| Mather 2011 (neurotoxin-1-thio) | -31.7 (5.1) | 20 (29.2) | 1 (0.02) |                         |
| Paneth 2011 (acetamid) | -22.7 (7.3) | 26 (7.5) | 1 (0.02) |                         |
| Pflotzer 2001 (acetamid) | -27.4 (21.7) | 94 (27.9) | 0.2 (0.05) |                         |
| Ramsay 2017 (acetamid) | -17.4 (10.4) | 20 (16.1) | 0.2 (0.05) |                         |
| Shalev 2017 (acetamid) | 46.7 (23.65) | 18 (47.1) | 1 (0.02) |                         |
| Skjelvik 2002 (acetamid) | -36.9 (26.1) | 109 (90.8) | 0.2 (0.02) |                         |
| Tucker 2003 (acetamid v placebo) | 0.36 (21.5) | 25 (55.6) | 0.1 (0.02) |                         |
| Tucker 2003 (acetamid v placebo) | 42.3 (55.4) | 23 (55.5) | 0.1 (0.02) |                         |
| Tucker 2003 (acetamid v placebo) | -50.5 (39.1) | 19 (45.5) | 0.1 (0.02) |                         |
| van der Kogel 2007 (acetamid v placebo) | -42.7 (21.2) | 23 (45.5) | 0.1 (0.02) |                         |
| Van der Kogel 2007 (acetamid v placebo) | 53.9 (24.9) | 42 (65.8) | 0.1 (0.02) |                         |
| Yah 2010 (acetamid) | 30.4 (30.1) | 17 (35.8) | 0.6 (0.03) |                         |
| Zorn 2002 (acetamid) | 18.7 (6.7) | 23 (13.9) | 0.6 (0.03) |                         |

Figure 2. Any agent versus placebo.

Figure 3. Funnel plot of all monotherapy studies.

2012; Hamner et al., 2009, 2000; Heresco-Levy et al., 2002; Jetly et al., 2015; Krystal et al., 2011; Lindley et al., 2007; Ludascher et al., 2015; Manteghi et al., 2014; Monnelly et al., 2003; Naylor et al., 2015; Neylan et al., 2006; Petrakis et al., 2016; Pollack et al., 2011; Ramaswamy et al., 2016; Raskind et al., 2018, 2007, 2003, 2013; Reich et al., 2004; Rothbaum et al., 2008; Schneier et al., 2015; Simpson et al., 2015; Stein et al., 2002; Taylor et al., 2008; Zohar et al., 2002) are detailed in Table 3. All studies employed at least two parallel arms where concomitant pharmacological
treatment was augmented with a drug versus placebo. There were 10 studies that examined the use of prazosin (Ahmadpanah et al., 2014; Germain et al., 2012; Petrakis et al., 2016; Raskind et al., 2018, 2007, 2003, 2013; Simpson et al., 2015; Taylor et al., 2008; Van Liempt et al., 2012), an alpha-1 adrenoceptor antagonist. Six studies assessed risperidone (Bartzokis et al., 2005; Hamner et al., 2009; Krystal et al., 2011; Monnelly et al., 2003; Reich et al., 2004; Rothbaum et al., 2008), three assessed topiramate (Akuchekian & Amanat, 2004; Batki et al., 2014; Lindley et al., 2007), and two assessed d-cycloserine (Attari et al., 2014; Heresco-Levy et al., 2002). There were single studies assessing aripiprazole (Naylor et al., 2015), baclofen (Manteghi et al., 2014), bupropion (Becker et al., 2007), eszopiclone (Pollack et al., 2011), guanfacine (Neylan et al., 2006), hydrocortisone (Ludascher et al., 2015), mirtazapine (Schneier et al., 2015), nabilone (Jetly et al., 2015), olanzapine (Stein et al., 2002), pregabalin (Baniasadi et al., 2014), sodium valproate (Hamner et al., 2009) and ziprasidone (Ramaswamy et al., 2016).

The average duration of studies was 10.5 (±5.6) weeks, with an average age of 44.6 (±7.7) years and a mean sample size of 52.2 (±66.1) participants. Twenty-four studies took place in the USA, with the remaining five in Iran, and single studies in Canada, Germany, Israel and the Netherlands. Combat trauma was the predominant trauma type in 24 studies, with three being childhood sexual abuse, two physical abuse, one mixed and two unknown trauma types.

### 3.2.2. Risk of bias assessments

Risk of bias assessments is included in Table 3. The vast majority of studies failed to adequately report their methodology and were deemed to have an unclear risk of bias across most domains. Where there was insufficient information, the authors were contacted via email and the vast majority did not respond with additional information. Every study described itself as randomised, but only nine studies adequately described the method of random sequence generation and seven adequately described the method of allocation concealment and were deemed

### Table 2. Individual agents versus placebo.

| Active drug | PTSD symptoms |
|-------------|--------------|
| SSRIs        | Four studies (Marshall et al., 2001; Marshall et al., 2007; SR8267 et al., unpublished; Tucker et al., 2004), n = 1,122, SMD = −0.41 (95% CI −0.53 to −0.29) I² = 16% |
| Fluoxetine   | Five studies (Connor et al., 1999; Hertzberg et al., 2000; Martenyi et al., 2007; van der Kolk et al., 2007), n = 815, SMD = −0.29 (95% CI −0.55 to −0.03) I² = 46% |
| Sertraline   | Ten studies (Brady et al., 2000; Brady et al., 2005; Davidson et al., 2006; Davidson et al., 2001; Friedman et al., 2007; Li et al., 2017; Panahi et al., 2011; Pfizer 588 – sertraline; Tucker et al., 2003; Zohar et al., 2002), n = 1,901, SMD = −0.28 (95% CI −0.45 to −0.10) I² = 57% |
| SNRIs        | Two studies (Davidson et al., 2006; Davidson et al., 2001; Venlafaxine), n = 687, SMD = −0.29 (95% CI −0.44 to −0.14) I² = 0% |
| MAOIs        | Two studies (Baker et al., 1995; Katz et al., 1994), n = 159, SMD = −0.24 (95% CI −0.81 to 0.33) I² = 63% |
| Antipsychotics| Two studies (Butterfield et al., 2001; Carey et al., 2012), n = 43, SMD = −0.44 (95% CI −1.51 to 0.63) I² = 62% |
| Other drugs  | Two studies (Tucker et al., 2007; Yeh et al., 2010), n = 69, SMD = −0.29 (95% CI −0.76 to 0.19) I² = 0% |

### 3.2.2. Risk of bias assessments

Risk of bias assessments is included in Table 3. The vast majority of studies failed to adequately report their methodology and were deemed to have an unclear risk of bias across most domains. Where there was insufficient information, the authors were contacted via email and the vast majority did not respond with additional information. Every study described itself as randomised, but only nine studies adequately described the method of random sequence generation and seven adequately described the method of allocation concealment and were deemed
| Study ID: Ahmadpana 2014 | Methods | Participants | Interventions | Notes |
|-------------------------|---------|--------------|---------------|-------|
| N = 100 | Mean age: 35.1 years | Sex: 28% female | Diagnosis: DSM-IV-TR and severe sleep disorder | Predominant trauma type: combat | Mean duration of Sx: 7.8 years |
| Group 1: Prazosin 1–15 mg ON (all participants remained on 15 mg after 10 days) | n = 35 | Other medications included lorazepam, clonazepam or combinations including lorazepam with clonazepam, lorazepam with sertraline, lorazepam with alprazolam, and clonazepam with sertraline. Total dose of prazosin given at night, rather than divided. |
| Group 2: Hydantoin 10–100 mg ON (all participants remained on 100 mg after 10 days) | N = 35 | |
| Group 3: Placebo | n = 35 | |

| Study ID: Akuchekian 2004 | Methods | Participants | Interventions | Notes |
|-------------------------|---------|--------------|---------------|-------|
| N = 67 | Mean age: 39.8 years | Sex: 100% male | Diagnosis: DSM-IV | Predominant trauma type: combat | Mean duration of Sx: 17.9 years |
| CAPS | Group 1: Topiramate 50–500 mg | n = 34 | Topiramate was added to existing pharmacotherapy (such as: Neuroleptic, TCA, BZ, SSRI, Na – valporate, and Carbamazepine with no significant difference between two groups: P > 0.05). Mean topiramate dose was not reported. No declaration of conflicts of interest. |
| Group 2: Placebo | n = 33 | |

| Study ID: Attar 2014 | Methods | Participants | Interventions | Notes |
|---------------------|---------|--------------|---------------|-------|
| N = 67 | Mean age: 50 years | Sex: 100% male | Diagnosis: DSM-IV-TR | Predominant trauma type: combat | Mean duration of Sx: 28 years |
| CAPS | Group 1: DCS 25 mg | n = 31 | CAPS was performed at baseline and treatment endpoints but only a subscale was reported. No study protocol. Very short intervention period (4 weeks) with carryover effect reported in Second Period. Data from First Period total avoidance/numbing Sx intensity and functional impairment included in meta-analysis |
| Group 2: Placebo | n = 32 | |
| First period – 4 weeks | Crossover washout – 2 weeks | Second period – 4 weeks | |
| Group 1: Pregabalin 300 mg | n = 18 | Poorly reported study, with no descriptions that can aid ROB assessment. |
| Group 2: Placebo | n = 19 | |

| Study ID: Baniasadi 2014 | Methods | Participants | Interventions | Notes |
|-------------------------|---------|--------------|---------------|-------|
| N = 37 | Mean age: 48 years | Sex: 100% male | Diagnosis: DSM-IV-TR | Predominant trauma type: combat | Mean duration of Sx: 28.6 years |
| PCL-M | Group 1: Pregabalin 300 mg | n = 18 | Poorly reported study, with no descriptions that can aid ROB assessment. |
| HAM-D | Group 2: Placebo | n = 19 | |
| HAM-A | |
| SQLI | | | |

(Continued)
| Study ID: Bartzokis 2004 USA | Study type: Single centre, residential and outpatient, randomised, double blind, placebo controlled, parallel group, fixed dose | Duration: 16 weeks | N = 65 | Mean age: 51.6 years | Sex: 100% male | Diagnosis: DSM-IV | Predominant trauma type: combat | Mean duration of Sx: 28.6 years | CAPS | HAM-D | HAM-A | PANSS | Group 1: Risperidone 3 mg | Group 2: Placebo | n = 33 | n = 32 | Industry funded | 92% on stable meds | 8% were on risperidone/placebo monotherapy | Unclear | Unclear | Unclear | Unclear | High | Unclear | High |
| Study ID: Batki 2014 USA | Study type: Single centre, randomised, placebo controlled, parallel arm, flexible dose | Duration: 12 weeks | N = 30 | Mean age: 50 years | Sex: 6% female | Diagnosis: DSM-IV-TR and Alcohol Use Disorder | Predominant trauma type: combat | Mean duration of Sx: unknown | CAPS | PCL | BDI | BAI | OCDS | HVLT-R | Group 1: Topiramate 25–300 mg (mean dose 286 mg) | n = 14 | n = 16 | 'Participants were free to access any other standard psychological or pharmacologic treatments for PTSD and any psychosocial treatments for AUD, but they could not receive other AUD pharmacotherapy.' | Low | Low | Low | Low | Low | Low | Unclear | Low |
| Study ID: Becker 2007 USA | Study type: Single centre, randomised, double blind, placebo controlled, parallel arm, flexible dose | Duration: 10 weeks | N = 30 | Mean age: 50 years | Sex: 21% female | Diagnosis: DSM-IV | Predominant trauma type: combat | Mean duration of Sx: unknown | CAPS | DTS | BDI | BAI | PSQI | CGI-I | Group 1: Bupropion SR 100–150 mg BD max 300 mg daily (mean dose 180 mg) | n = 18 | n = 10 | Industry funded | DTS was used in meta-analysis as it was on mITT sample rather than completers only | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | High |
| Study ID: Germain 2012 USA | Study type: Single centre, outpatient, randomised, double blind, placebo controlled, parallel group, flexible dose | Duration: 8 weeks | N = 50 | Mean age: 40.9 years | Sex: 10% female | Diagnosis: DSM-IV | Predominant trauma type: combat | Mean duration of Sx: unknown | CGI-I | ISI | PSQI | PCL | BDI | BAI | SDS | Group 1: Prazosin 2–15 mg ON (mean 8.9 mg) | n = 18 | n = 17 | Group 2: Behavioural Sleep Intervention | 13/18 in prazosin group and 9/16 in placebo had PTSD | Unclear | Unclear | Low | Unclear | High | Unclear | High |

(Continued)
| Methods | Participants | Outcomes | Interventions | Notes | Risk of bias (low/unclear/high) |
|---------|--------------|----------|---------------|-------|-------------------------------|
| Study ID: Golier 2012 USA | N = 9 | CAPS PCL BDI Neuroendocrine variable | Group 1: mifepristone 600 mg n = 4 | No description of primary pharmacotherapy | Sequence allocation concealment Blinding of participants/blinding of outcome assessors Incomplete outcome data Selective reporting of outcomes Any other bias |
| Study ID: Hamner 2003 USA | N = 40 | CAPS PANSS HAM-D | Group 1: Risperidone 1–6 mg (mean 2.5 ± 1.25 mg) n = 20 | 'Most patients were receiving antidepressants (primarily selective serotonin reuptake inhibitors or nefazodone). Four patients in the risperidone group and two in the placebo group also received benzodiazepines. One patient was allowed to continue on lithium and one on carbamazepine. Some other patients were allowed to continue intermittent use of other medications for sleep (choral hydrate, low-dose trazodone or nortriptyline).' | Unclear Unclear Low Unclear High |
| Study ID: Heresco-Levy Israel | N = 11 | CAPS Wisconsin Card Sorting Test | Group 1: d-cycloserine 25 mg BD n = | Insufficient data reported | Unclear Unclear Unclear Unclear Unclear High |
| Study ID: Hamner 2009 USA | N = 29 | CAPS CGI HAM-D IES LSAC PSQI | Group 1: Divalproex 500–1500 mg (mean dose 1196 mg) n = 16 | Industry support for lead author | Unclear Unclear Low Unclear High |
| Study type: Single centre, outpatient, randomised, double blind, placebo controlled, fixed dose, parallel arm Duration: 1 week | Mean age: 48.8 years Sex: 100% male Diagnosis: DSM-IV Predominant trauma type: combat Mean duration of Sx: 'chronic' | | | |
| Study type: Single centre, outpatient, randomised, placebo controlled, flexible dose, parallel arm Duration: 5 weeks | Mean age: 52 years Sex: 100% male Diagnosis: DSM-IV and current psychosis Predominant trauma type: combat Mean duration of Sx: 'chronic' | | |
| Study type: Single centre, randomised, double blind, placebo controlled, parallel arm, flexible dose Duration: 10 weeks | Mean age: 52.3 years Sex: 3% female Diagnosis: DSM-IV Predominant trauma type: combat Mean duration of Sx: unknown | | |
| Study type: Single centre, randomised, double blind, placebo controlled, crossover, fixed dose Duration: 12 weeks | Mean age: 38.5 years Sex: 18% female Diagnosis: DSM-IV Predominant trauma type: mixed Mean duration of Sx: 7.7 years | | |

(Continued)
| Methods | Participants | Outcomes | Interventions | Notes | Risk of bias (low/unclear/high) |
|---------|--------------|----------|---------------|-------|---------------------------------|
| Study ID: Jetly 2015 Canada | N = 10 | CAPS CGI-C GWBQ | Group 1: nabilone 0.5–3 mg (mean 1.95 mg) n = 10 | 'subjects were allowed to continue any other medications and psychotherapy present at time of study entry. If on an antidepressant, subjects were required to be on a stable dose for at least four weeks prior to study entry.' | Unclear Unclear Low Unclear Low Low Unclear |
| Study type: Single centre, outpatient, randomised, double blind, placebo controlled, crossover, flexible dose | Mean age: 43.6 years Sex: 100% male Diagnosis: DSM-IV Predominant trauma type: combat Mean duration of Sx: unknown | | | | |
| Duration: 16 weeks | | | | | |
| | Study ID: Krystal 2011 USA | N = 296 | CAPS BDI CGI-S | Group 1: Risperidone 1–4 mg (mean dose 2.74 mg) n = 147 | Low Low Low Low High Low High |
| Study type: Multicentre, outpatient, randomised, double blind, placebo controlled, parallel group, flexible dose | Mean age: 54.4 years Sex: 3.6% female Diagnosis: DSM-IV Predominant trauma type: combat Mean duration of Sx: unknown | | | | |
| Duration: 24 weeks | | | | | |
| | Study ID: Lindley 2007 USA | N = 40 | CAPS BDI CGI-S | Group 1: topiramate 50–200 mg n = 20 | Insufficient data reported Unclear Unclear Unclear Unclear High High High |
| Study type: Single centre, randomised, double blind, placebo controlled, parallel group, flexible dose | Mean age: 53.4 years Sex: 100% male Diagnosis: DSM-IV Predominant trauma type: combat Mean duration of Sx: unknown | | | | |
| Duration: 7 weeks | | | | | |
| | Study ID: Ludascher 2015 Germany | N = 30 | CAPS IES-R | Group 1: hydrocortisone (HC) 10–30 mg n = 15 | Insufficient data reported Unclear Unclear Unclear Unclear Low Low Unclear |
| Study type: Single centre, inpatient, randomised, double blind, placebo controlled, crossover, fixed dose | Mean age: 30.7 years Sex: 100% female Diagnosis: DSM-IV Predominant trauma type: childhood sexual abuse Mean duration of Sx: unknown | | | | |
| Duration: 4 weeks | | | | | |
| Study ID: Manteghi 2014 Iran Study type: Single centre, randomised, double blind, placebo controlled, parallel group, flexible dose Duration: 8 weeks | N = 40 | Mean age: 44.6 years Sex: 100% male Diagnosis: DSM-IV Predominant trauma type: combat Mean duration of Sx: unknown | CAPS GAF HAM-D HAM-A | Group 1: citalopram (20–60 mg) plus baclofen 10–40 mg (mean dose unknown) n = 20 Group 2: citalopram (20–60 mg) plus placebo n = 20 | Unclear Unclear Low Unclear High Unclear Low |
| Study ID: Monnelly 2003 USA Study type: Single centre, randomised, double blind, placebo controlled, parallel group, flexible dose Duration: 6 weeks | N = 15 | Mean age: 48.9 years Sex: unknown Diagnosis: DSM-IV Predominant trauma type: combat Mean duration of Sx: unknown | PCL-M OAS | Group 1: risperidone 0.5–2 mg (mean dose) n = 7 Group 2: Placebo n = 8 | Insufficient data reported Unclear Unclear Unclear Unclear Unclear Unclear High |
| Study ID: Naylor 2015 USA Study type: Single centre, randomised, double blind, parallel arm, placebo controlled, flexible dose Duration: 10 weeks | N = 16 | Mean age: 34 years Sex: 100% male Diagnosis: DSM-IV Predominant trauma type: combat Mean duration of Sx: unknown | CAPS PCL BDI PANSS | Group 1: aripiprazole 5–20 mg (mean dose 10 mg) n = Group 2: Placebo n = | Unclear Unclear Unclear Unclear High Unclear High |
| Study ID: Neylan 2006 USA Study type: Single centre, outpatient, randomised, double blind, placebo controlled, parallel arm, fixed dose Duration: 8 weeks | N = 65 | Mean age: unknown Sex: unknown % female Diagnosis: chronic PTSD Predominant trauma type: combat Mean duration of Sx: unknown | CAPS IES HAM-D SC90 SSQI QOLI | Group 1: Guanfacine 0.5–3 mg (mean 2.4 mg) n = 29 Group 2: Placebo n = 34 | Unclear Unclear Low Low Low Low High High |
| Study ID | Type | Country | Duration | Sample size | Mean age | Sex | Diagnosis | Predominant trauma type | Mean duration of Sx | Interventions | Notes | Sequence generation | Allocation concealment | Blinding of participants/personnel | Blinding of outcome assessors | Incomplete outcome data | Free of selective reporting | Risk of bias (low/unclear/high) |
|----------|------|---------|----------|-------------|---------|-----|-----------|---------------------|------------------|--------------|-------|--------------------|------------------------|--------------------------------|-------------------------------|---------------------|-------------------------|--------------------------------|------------------------|
| Petrakis 2016 USA | Multicentre, outpatient, randomised, double blind, placebo controlled, parallel arm, flexible dose | 13 weeks | 96 | 44.5 | 100% male | DSM-IV PTSD and Alcohol Dependence | combat | unknown | n = 50 | Group 1: Prazosin 2–16 mg BD (mean dose 14.5 mg) | Group 2: Placebo n = 46 | Lead author ties to industry | Unclear | Unclear | Low | Unclear | Low | Low | Low | Unclear |
| Pollack 2011 USA | Single centre, outpatient, randomised, double blind, placebo controlled, crossover, fixed dose | 7 | 27 | 42 | 70.8% female | DSM-IV PTSD and comorbid sleep disturbance | unknown | 19 years | n = 24 | Group 1: Eszopiclone 3 mg | Group 2: Placebo n = 24 | Lead author ties to industry | Unclear | Unclear | Unclear | Unclear | Low | Low | High |
| Ramaswamy 2015 USA | Single centre, outpatient, randomised, double blind, placebo controlled, parallel arm, flexible dose | 9 | 30 | 38.9 | 87% female | DSM-IV PTSD and comorbid depression | unknown | unknown | n = 15 | Group 1: Ziprasidone 20–80 mg BD (mean dose unknown) | Group 2: Placebo n = 15 | Industry funded. Published 10 years after completion. | Unclear | Unclear | Unclear | Unclear | Unclear | Low | High |
| Raskind 2003 USA | Single centre, outpatient, randomised, double blind, placebo controlled, crossover, flexible dose | 20 | 10 | 53 | 100% male | DSM-IV PTSD and severe trauma-related nightmares | combat | 25 years | n = 5 | Group 1: Prazosin 1–10 mg divided dose (mean dose 9.5 mg) | Group 2: Placebo n = 5 | Very small study. | Unclear | Unclear | Unclear | Low | Low | Unclear | High |

(Continued)
| Study ID: Raskind 2007 USA | Study type: Single centre, outpatient, randomised, double blind, placebo controlled, parallel arm, flexible dose | Duration: 8 weeks | N = 40 | Mean age: 56 years | Sex: 5% female | Diagnosis: DSM-IV PTSD and frequent and severe trauma-related nightmares | Predominant trauma type: combat | Mean duration of Sx: 'chronic' | CAPS | PSQI | CGI | NFQ | PDRS | HAM-D | Total dose given ON | Low | Low | Low | Low | Low | Low | Low |
|----------------------------|-------------------------------------------------|------------------|--------|------------------|--------------|-------------------------------------------------|-----------------|-----------------|------|------|-----|-----|------|------|---------------------|------|------|------|------|------|------|------|
| Study ID: Raskind 2013 USA | Study type: Multicentre, outpatient, randomised, double blind, placebo controlled, parallel arm, flexible dose | Duration: 15 weeks | N = 67 | Mean age: 30.4 years | Sex: 13% female | Diagnosis: DSM-IV PTSD and severe trauma-related nightmares | Predominant trauma type: combat | Mean duration of Sx: unknown | CAPS | PSQI | CGI | HAM-D | PHQ9 | QOLI | Group 1: Prazosin 2–25 mg divided dose (mean 7 mg Om, 15.6 mg ON for men, 4 mg OM, 7 mg ON for women) | n = 32 | Group 2: Placebo n = 35 | Divided dose BD | Higher mean dose than in previous studies | Low | Low | Low | Low | Low | Low | Low |
| Study ID: Raskind 2018 USA | Study type: Multicentre, outpatient, randomised, double blind, placebo controlled, parallel arm, flexible dose | Duration: 26 weeks | N = 304 | Mean age: 51.8 years | Sex: 2% female | Diagnosis: DSM-IV PTSD and severe trauma-related nightmares | Predominant trauma type: combat | Mean duration of Sx: unknown | CAPS | PSQI | CGI-C | PCL-M | PHQ-9 | QOLI | SF-12 | AUDIT-C | Group 1: Prazosin 1–20 mg for men, 1–12 mg for women | n = 152 | Group 2: Placebo n = 152 | Divided dose BD | Authors affiliated with the intervention. | Low | Unclear | Low | Unclear | Low | Unclear | High |
| Study ID: Reich 2004 USA | Study type: Single centre, outpatient, randomised, double blind, placebo controlled, parallel arm, flexible dose | Duration: 8 weeks | N = 21 | Mean age: 27.4 years | Sex: 100% female | Diagnosis: DSM-III-R PTSD and severe trauma-related nightmares | Predominant trauma type: childhood abuse | Mean duration of Sx: unknown | CAPS | HAM-D | DES | AIMS | BAS | | | Group 1: Risperidone 0.5–8 mg (mean dose 1.41 mg) | n = 12 | Group 2: Placebo n = 9 | Unclear | Unclear | Unclear | Unclear | Low | Low | Low | (Continued) |
| Methods | Participants | Outcomes | Interventions | Notes |
|---------|--------------|----------|---------------|-------|
| Study ID: Rothbaum 2008 USA Study type: Multicentre, randomised, double blind, parallel arm, placebo controlled, flexible dose Duration: 8 weeks | N = 20 Mean age: 33 years Sex: % female Diagnosis: DSM-IV Predominant trauma type: sexual violence Mean duration of Sx: unknown | CAPS DTS CGI | Group 1: Risperidone 0.5–3 mg (mean dose 2.1 mg) n = 11 Group 2: Placebo n = 14 | Open label sertraline 50–200 mg for 8 weeks, if 70% decrease in CAPS not seen, then they entered phase 2 of the study (randomisation) Completers only analysis Authors have extensive ties to industry |
| Study ID: Schneier 2015 USA Study type: Single centre, outpatient, randomised, double blind, placebo controlled, parallel arm, flexible dose Duration: 24 weeks | N = 38 Mean age: 40 years Sex: 66% female Diagnosis: DSM-IV chronic PTSD Predominant trauma type: physical assault Mean duration of Sx: years | CAPS Clinical Global Impression Scale PCL Hamilton Rating Scale for Depression QLES Q SF12 SF12 PSS PSS-I PACS PCL-C | Group 1: mirtazapine 15–45 mg (mean dose 32.5 mg) plus sertraline 50–200 mg n = 18 Group 2: Placebo plus sertraline 50–200 mg n = 18 | Insufficient data reported |
| Study ID: Simpson 2015 USA Study type: Single centre, outpatient, randomised, double blind, placebo controlled, parallel arm, flexible dose Duration: 6 weeks | N = 30 Mean age: 43.3 years Sex: 37% female Diagnosis: DSM-IV and alcohol dependence Predominant trauma type: physical assault Mean duration of Sx: unclear | CAPS PSQI CES-DS CGI-S | Group 1: Prazosin 4 mg OM, 4 mg midday, 8 mg ON (mean dose not reported) n = 15 Group 2: Placebo n = 15 | Unclear Unclear Low Low Low High Unclear Unclear High |
| Study ID: Stein 2002 USA Study type: Single centre, outpatient, randomised, double blind, placebo controlled, parallel arm, fixed dose Duration: 8 weeks | N = 19 Mean age: 52.6 years Sex: 100% male Diagnosis: DSM-IV Predominant trauma type: combat Mean duration of Sx: unknown | CAPS PSQI CES-DS CGI-S | Group 1: Olanzapine 10 mg plus SSRI n = 10 Group 2: Placebo plus SSRI n = 9 | Brief report |
| | | | | | (Continued) |
### Table 3. (Continued).

| Study ID: Taylor 2008 USA | Study type: Single centre, outpatient, randomised, double blind, placebo controlled, crossover, flexible dose | Duration: 7 weeks |
|---------------------------|-------------------------------------------------|-------------------|
| N = 13                    | Mean age: 49 years                              | Sex: 85% female   |
|                           | Diagnosis: DSM-IV PTSD                          |                     |
|                           | and minimum score 4 on CAPS item 'recurrent distressing dreams' and 'difficulty falling/staying asleep' |                     |
|                           | Predominant trauma type: childhood sexual abuse |                     |
|                           | Mean duration of Sx: unknown                    |                   |

| Participants | Outcomes | Interventions | Notes | Risk of bias (low/unclear/high) |
|--------------|----------|---------------|-------|-------------------------------|
|              | PDRS     | Group 1: Prazosin 2–5 mg (mean dose 3.2 mg) | All participants received ongoing psychotherapy, 8 were on sertraline, 2 on duloxetine, and 3 on alprazolam. | Sequence generation: Unclear  Allocation concealment: Unclear  Blinding participants/personnel: Low  Blinding outcome assessors: Unclear  Incomplete outcome data: Low  Free of selective reporting: Unclear  Any other bias: Unclear |
|              | PCL-C    | Group 2: Placebo | n = |                         |
|              | CGI-I    | n = | First period: 3 weeks  |                   |
|              |          | n = | Crossover washout: 1 week |                   |
|              |          | n = | Second period: 3 weeks  |                   |

| Study ID: van Liempt 2012 Netherlands | Study type: Single centre, outpatient, randomised, double blind, placebo controlled, parallel arm, flexible dose | Duration: 8 weeks |
|--------------------------------------|-------------------------------------------------|-------------------|
| N = 14                                | Mean age: 44.2 years                             | Sex: 100% male    |
|                                      | Diagnosis: DSM-IV                                |                     |
|                                      | Predominant trauma type: combat                   |                     |
|                                      | Mean duration of Sx: unknown                     |                   |

| Participants | Outcomes | Interventions | Notes | Risk of bias (low/unclear/high) |
|--------------|----------|---------------|-------|-------------------------------|
|              | CAPS     | Group 1: Prazosin 2–5 mg ON (mean dose 3.2 mg) | n = 13 | Sequence generation: Unclear  Allocation concealment: Unclear  Blinding participants/personnel: Low  Blinding outcome assessors: Unclear  Incomplete outcome data: Low  Free of selective reporting: Unclear  Any other bias: Unclear |
|              | PSQI     | Group 2: Placebo | n = 13 |                         |
to have a low risk of bias. Blinding of participants and personnel was adequately reported and deemed to have a low risk of bias in 19 studies. Blinding of outcome assessors where a clinician-rated scale was used was deemed to have a low risk of bias in nine studies. Incomplete outcome data were addressed adequately in 19 studies. All pre-specified outcome variables were adequately reported in 11 studies, where protocols were available.

3.2.3. Efficacy of pharmacological augmentation

Data from 30 studies (n = 1,566) were available for inclusion in a meta-analysis of reduction in severity of PTSD symptoms for pharmacological versus placebo augmentation (Figure 5).

A funnel plot of all included augmentation studies with usable data shows relative symmetry, with an absence of studies published with greater standard error overall (Figure 6).

Data from 10 studies of prazosin augmentation (n = 652) were meta-analysed and found a small positive effect when compared against placebo (Figure 7). Data from five studies of risperidone augmentation (n = 390) were meta-analysed and found a small positive effect when compared to placebo augmentation (Figure 8).

Data from two studies of topiramate augmentation (n = 97) were meta-analysed and did not find a statistically significant superiority to placebo augmentation (Figure 9).

Single small studies of hydroxyzine, d-cycloserine, nabilone and eszopiclone demonstrated superiority to placebo augmentation. There was no evidence of efficacy for aripiprazole, baclofen, bupropion, guanfacine, hydrocortisone, mirtazapine, olanzapine (Hertzberg et al., 2000), pregabalin, sodium valproate and ziprasidone.

The results of meta-analyses for individual augmentation agents when tested against placebo in at least two RCTs or where there were more than 20 participants in each arm are presented in Table 4.

3.3. Head-to-head studies

3.3.1. Description of studies

3.3.1.1. Pharmacotherapy versus pharmacotherapy

The characteristics of the included studies (Davidson et al., 2006; Kosten et al., 1991; McRae et al., 2004; Petrakis et al., 2012; Saygin et al., 2002; Spivak et al., 2006; Tucker et al., 2003) are detailed in Table 5. Three of the included studies (Davidson et al., 2006; Kosten et al., 1991; Tucker et al., 2003) also utilised a placebo comparator arm and were also included in our monotherapy review. Four studies assessed the SSRI sertraline (Davidson et al., 2006; McRae et al., 2004; Saygin et al., 2002; Tucker et al., 2003), one study assessed paroxetine versus desipramine\textsuperscript{105}, one study assessed venlafaxine...
(Davidson et al., 2006), and one study assessed citalopram (Tucker et al., 2003). One study compared imipramine to phenelzine (Kosten et al., 1991), and two studies assessed nefazodone (McRae et al., 2004; Saygin et al., 2002).

The average duration of trials was 14.3 weeks, with an average age of 39.8 years and an average sample size of 129 participants. Five of the studies took place in the USA, with two others taking place in Israel and Turkey. The predominant trauma type was combat

Figure 6. Funnel plot of augmentation studies.

Figure 7. Prazosin versus placebo augmentation.

Figure 8. Risperidone versus placebo.
and physical assault in two studies, respectively, with single studies of motor vehicle and natural disaster traumas. The predominant traumatic event was unclear in one study.

3.3.1.2. Pharmacotherapy versus psychotherapy.
The characteristics of the included studies (Buhmann et al., 2016; Frommberger et al., 2004; Jerud et al., 2016; van der Kolk et al., 2007) are detailed in Table 6. Two of the studies (Buhmann et al., 2016; Jerud et al., 2016) assessed sertraline versus a flexible therapeutic approach and prolonged exposure, respectively. Two studies (Frommberger et al., 2004; Popiel, Zawadzki, Pragłowska, & Teichman, 2015) assessed paroxetine versus CBT and PE, respectively. The final study (van der Kolk et al., 2007) assessed fluoxetine versus EMDR. The average duration of trials was 12.6 weeks, with an average age of 40.9 years and an average sample size of 158 participants. Three of the studies took place in the US, with one each in Denmark, Germany and Poland. Each study assessed various trauma types, including asylum seekers, serious accidents, sexual assault, interpersonal victimisation and motor vehicle accidents.

3.3.2. Risk of bias assessments
3.3.2.1. Pharmacotherapy versus pharmacotherapy. Risk of bias assessments is included in Table 5. The vast majority of studies failed to adequately report their methodology and were deemed to have an unclear risk of bias across most domains. Where there was insufficient information, the authors were contacted via email and the vast majority did not respond with additional information. There was insufficient evidence reported in every study to assess the risk of selection bias. Blinding of participants was deemed to be of a low risk of bias in only one study.

3.3.2.2. Pharmacotherapy versus psychotherapy. Risk of bias assessments is included in Table 6. Only one study was deemed to have a low risk of selection bias. Due to the head-to-head nature of comparing medication to psychotherapy, blinding of participants and personnel was not attempted in any included study. There was a low risk of detection bias in one study, achieved with the use of independent blinded outcome assessors.

3.3.2.3. Efficacy of pharmacotherapy versus pharmacotherapy. Data from seven studies (n = 594) were available for inclusion in a meta-analysis of drug versus drug (Figure 10). Three studies (Kosten et al., 1991; Saygin et al., 2002; Tucker et al., 2003) demonstrated statistical superiority of one agent over another; sertraline was superior to both citalopram and nefazodone, and phenelzine was superior to imipramine. Data from four studies (Davidson et al., 2006; McRae et al., 2004; Saygin et al., 2002; Tucker et al., 2003) were available for inclusion in a meta-analysis of any agent versus sertraline (Figure 11). No statistical difference was found, although the trend was towards sertraline.

3.3.2.4. Efficacy of pharmacotherapy versus psychotherapy. Data from two studies (Buhmann et al., 2016; van der Kolk et al., 1994) were available for inclusion in a meta-analysis of an SSRI versus...
Table 5. Characteristics of included drug versus drug studies.

| Methods | Participants | Outcomes | Interventions | Notes | Risk of bias (low/unclear/high) |
|---------|--------------|----------|---------------|-------|---------------------------------|
| Study ID: Davidson 2006a USA Study type: Multicentre, randomised, double blind, three parallel arms, placebo controlled, flexible dose Duration: 12 weeks | N = 538 Mean age: 32 years Sex: 65.4% female Diagnosis: DSM-IV Predominant trauma type: non-sexual abuse Mean duration of Sx: unknown | CAPS CGI-S DTS | Group 1: Sertraline 25–200 mg (mean dose 110.2 mg) n = 173 Group 2: Venlafaxine 37.5–300 mg (164.4 mg) n = 179 Group 3: placebo n = 179 | Author supported by industry. | Unclear Unclear Unclear Unclear Unclear Unclear High |
| Study ID: Kosten 1991 USA Study type: Multicentre, randomised, double-blind, three parallel arms, placebo-controlled, flexible dose Duration: 8 weeks | N = 60 Mean age: 39 years Sex: 1005 male Diagnosis: DSM-III Predominant trauma type: combat Mean duration of Sx: unknown | IES HAM-A HAM-D | Group 1: Imipramine 50 mg/d – 300 mg (avg max. dose: 225 mg) n = 23 Group 2: Phenelzine 15 – 75 mg (avg max. dose: 68 mg) n = 19 Group 3: placebo n = 18 | Author supported by industry. | Unclear Unclear Unclear Unclear High Unclear High |
| Study ID: McRae 2004 USA Study type: Randomized, double-blind, parallel arm, flexible dose Duration: 12 weeks | N = 37 Mean age: 40.3 years Sex: unknown Diagnosis: DSM-IV Predominant trauma type: unknown Mean duration of Sx: unknown | CAPS-S CGI-I DTS MADRS HAM-A TOP-8 PSQI SDS | Group 1: 50–200 mg (mean dose 153 mg) n = 19 Group 2: Nefazodone 100–600 mg (mean dose 463 mg) n = 18 | Brief report. Industry funded. | Unclear Unclear Low Unclear Unclear Unclear Unclear High |

(Continued)
| Methods | Participants | Outcomes | Interventions | Notes | Risk of bias (low/unclear/high) |
|---------|--------------|----------|---------------|-------|-------------------------------|
| Study ID: Petrakis 2012 USA  
Study type: Single centre, randomised, double blind, placebo and active comparator controlled, parallel arm  
Duration: 10 weeks  
N = 88  
Mean age: 47.1 years  
Sex: 9% female  
Diagnosis: DSM-IV PTSD and alcohol dependence  
Predominant trauma type: combat  
Mean duration of Sx: unknown  
Group 1: Paroxetine  
n = 20  
Group 2: Desipramine  
n = 24  
Two additional groups (paroxetine plus naltrexone and desipramine plus naltrexone, were not used in this meta-analysis). | CAPS-HAM-D | | | | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | High |
| Study ID: Saygin 2002 Turkey  
Study type: Randomised, double-blind, parallel arm, flexible dose  
Duration: 24 weeks  
N = 60  
Mean age: 41.5 years  
Sex: unknown  
Diagnosis: Predominant trauma type: earthquake survivors  
Mean duration of Sx: unknown  
Group 1: Sertraline  
50–100 mg (mean dose 68.3 mg)  
n = 30  
Group 2: Nefazodone  
200–400 mg (mean dose 332.4 mg)  
n = 30 | TOP-8  
CGI-I  
CGI-S  
CGI-SE | | | | Unclear | Unclear | Unclear | Unclear | High | Unclear | Unclear |
| Study ID: Spivak 2006 Israel  
Study type: Randomised, double-blind, parallel arm, fixed dose  
Duration: 24 weeks  
N = 40  
Mean age: 40 years  
Sex: 47.5% female  
Diagnosis: DSM-IV Predominant trauma type: road traffic accidents  
Mean duration of Sx: unknown  
Group 1: Sertraline  
50–100 mg (mean dose 68.3 mg)  
n = 30  
Group 2: Nefazodone  
200–400 mg (mean dose 332.4 mg)  
n = 30 | CAPS  
TOP-8  
HAM-D  
HAM-A | | | | Insufficient data reported. Industry funded | Unclear | Unclear | Unclear | Unclear | High | Unclear | Unclear |
psychological therapy (Figure 12). No statistical difference was found.

4. Discussion

4.1. Monotherapy studies

There was robust evidence of a reasonable quality to recommend the use of paroxetine, fluoxetine, sertraline and venlafaxine in the treatment of PTSD. These medications will likely result in small but clinically significant benefits for patients with PTSD who take them. Additionally, there is enough evidence to recommend the use of quetiapine as a monotherapy agent albeit with less confidence than the other recommended medications. Four drugs – amitriptyline, GR205171 (a neurokinin-1 antagonist), mirtazapine and phenelzine – demonstrated superiority over placebo in single RCTs where there were less than 20 participants per arm, and these medications would be good candidates for future research.

RCTs of citalopram, escitalopram, imipramine, brofaromine, nefazodone, olanzapine, tiagabine, topiramate, semisodium valproate, ketamine, and ganaxolone provided no evidence to recommend their use as monotherapy agents. Most of the RCTs included within this review were of general outpatient populations who suffered from a variety of traumatic events, and as such the results should be generalisable to various populations.

To summarise and expand upon some of the discussion points of our previous review, we found little evidence of efficacy for a medication class effect in treating PTSD; although SSRIs as a class showed superiority over placebo, there was a lack of evidence for specific agents such as citalopram and escitalopram, which both showed a trend towards inferiority to placebo. Likewise, a single small study of the MAOI phenelzine out performed brofaromine, and a single study of the tricyclic antidepressant amitriptyline demonstrated superiority to placebo where imipramine could not. For the antipsychotics, a single study of quetiapine outperformed two small studies of olanzapine. These findings are striking and could be due to the inherent pharmacological differences between agents within the same class.

A recent network meta-analysis (NMA) by Cipriani and colleagues (Cipriani et al., 2018), which collated monotherapy versus placebo, augmentation and drug-versus-drug studies, provided evidence of superiority over placebo for phenelzine, desipramine, paroxetine, venlafaxine, fluoxetine, risperidone and sertraline in descending order of magnitude of efficacy. Whilst the limited number of studies and participants for certain drugs makes it difficult to recommend this hierarchy of drug effectiveness in clinical practice (phenelzine was
Table 6. Characteristics of included drug versus therapy studies.

| Methods | Participants | Outcomes | Interventions | Notes |
|---------|--------------|----------|---------------|-------|
| Study ID: Buhman 2018 Denmark Study type: Multicentre, pragmatic, randomised controlled trial with $2 \times 2$ factorial design, flexible dose Duration: 6 months | $N = 280$ Mean age: 49 years Sex: 41% female Diagnosis: DSM-IV PTSD Predominant trauma type: Asylum experience Mean duration of Sx: 14.7 years | HTQ HSCL-25 HRSD HRS A SCL-90 VAS SDS WHO-S | Group 1: Sertraline (25–200 mg, mean dose 132.1 mg) ± minaserin (10–30 mg, mean dose 20 mg) $n = 71$ Group 2: Sertraline (25–200 mg, mean dose 132.1 mg) ± minaserin (10–30 mg, mean dose 20 mg) plus therapy $n = 71$ Group 3: Therapy (16 sessions CBT over 6 months) $n = 70$ Group 4: Waiting list $n = 68$ | Risk of bias (low/unclear/high) 54% of sessions were translated. 25% in therapy actually received exposure treatment. Additionally, 27% of the therapy group received another antidepressant. |
| Study ID: Frommberger Germany Study type: Single centre, randomised, parallel arm, flexible dose Duration: 12 weeks | $N = 21$ Mean age: 42.6 years Sex: % female Diagnosis: DSM-III-R Predominant trauma type: serious accidents Mean duration of Sx: 2.8 years | CAPS ADIS MADRS HAM-A PSS BDI | Group 1: Paroxetine 10–50 mg (mean dose 28 mg) $n = 10$ Group 2: CBT $n = 11$ | Completers only analysis. Insufficient data reported. Industry funded. |
| Study ID: Jerud 2016 USA Study type: Single centre, randomised, parallel arm, flexible dose Duration: 10 weeks | $N = 200$ Mean age: unknown Sex: 75.5% female Diagnosis: DSM-IV Predominant trauma type: sexual assault Mean duration of Sx: 11.97 | SCID PSS-I ERQ NMR | Group 1: Sertraline 25–200 mg (mean dose 115 mg) $n = unknown$ Group 2: PE $n = unknown$ | Insufficient data reported. |
| Study ID: Popiel 2015 Poland Study type: Single centre, randomised, three parallel arms, flexible dose Duration: 12 weeks | $N = 228$ Mean age: 36.9 years Sex: unclear Diagnosis: DSM-IV-TR PTSD Predominant trauma type: Motor Vehicle Accident (100%) Mean duration of Sx: 17.7 months | SCID-I PDS BDHI | Group 1: Prolonged exposure (PE) x 12 weekly sessions $n = 114$ Group 2: Paroxetine 20 mg x 12 weeks $n = 57$ Group 3: PE plus paroxetine 20 mg x 12 weeks $n = 57$ | Insufficient data reported for PE group. |

(Continued)
represented by 19 participants in one study), this NMA similarly found clinically important differences in efficacy between various antidepressants and antipsychotics which shared a common class, respectively.

There still exists confusion and inconsistencies across published guidelines for the pharmacological treatment of PTSD. For instance, the recent NICE UK draft guidelines (National Institute for Health and Care Excellence Guideline: Post-traumatic stress disorder, 2018) recommend the use of SSRIs or venlafaxine in the treatment of PTSD and recommend considering the use of antipsychotics such as risperidone, quetiapine and olanzapine in secondary care. Under these guidelines, a patient receiving any SSRI but paroxetine, fluoxetine or sertraline would not be benefiting from an evidence-based treatment.

The Agency for Healthcare Research and Quality (AHRQ) US update (Forman-Hoffman et al., 2018b) recommends paroxetine, fluoxetine and venlafaxine based on a moderate strength of evidence, and prazosin, topiramate, olanzapine, risperidone and sertraline owing to a lower strength of evidence. Our review finds stronger evidence for sertraline than the AHRQ (2018) guidelines. We suspect that this is because their meta-analysis was based on seven sertraline studies, with this review analysing 10. Additionally, the AHRQ review found evidence to recommend topiramate, but their meta-analysis found support for this by including both monotherapy and augmentation studies. There are obvious confounding factors from the use of other drugs with the approach, and we have chosen to separately investigate monotherapy and augmentation studies. With these studies delineated, we found a lack of evidence to support topiramate as a monotherapy.

In comparison to our previous review, three new studies are notable for their impact and innovation; Li et al. (2017), Villarreal et al. (2016) and Feder et al. (2014). Li et al. published a multicentre RCT from China investigating the use of sertraline in a predominantly male combat trauma population and is notable for being the most well-reported study we encountered and deemed of low risk of bias in all fields apart from reporting bias, as unfortunately a protocol could not be located to establish if all pre-specified outcome variables were reported. The findings of Li et al. were in favour of sertraline and had the effect of further bolstering the evidence for this agent, and we hope that future pharmacological studies adhere to the scientific rigour exemplified by this study.

Villarreal et al. published an RCT from the USA investigating the use of quetiapine in a similar population of 80 mostly male combat veterans and is notable for the effect size demonstrated in favour of quetiapine, suggesting that this antipsychotic is
superior both to placebo, and, as mentioned, in comparison to the meta-analysis of two small studies of olanzapine. However, there were several methodological concerns with Villarreal et al.; this study was lacking in methodological detail with regards to adequate allocation, concealment and blinding practices, there were more than 40% data missing from randomised participants (with over half of those in the placebo arm having dropped out). Additionally, the study was funded by a grant from a pharmaceutical company. Taken together, it would be useful to consider this an agent with emerging evidence, and more research is needed.

Feder et al. (2014) published a novel study of an intravenous infusion of the dissociative psychedelic drug ketamine, compared to midazolam and crossed over after 2 weeks. Over recent years there has been renewed interest in the potential for psychedelic drugs in the treatment of serious psychiatric conditions, most topically with MDMA-assisted psychotherapies for PTSD, which we will consider in our pharmacotherapy-assisted psychotherapy review within this series of meta-analyses (reference to be inserted by JOTS). There is growing evidence for the use of ketamine infusions in the treatment of refractory depression, but there is significant debate surrounding the optimal dose, route of administration and control of environmental and psychological factors (set and setting). This first study of ketamine in PTSD did not demonstrate superiority over placebo;
however, the trend was towards ketamine and future research in this field is clearly warranted to establish if this novel approach could have clinical benefit.

4.2. Augmentation studies

This review found evidence of efficacy for prazosin and risperidone as augmenting agents, and the evidence was strong enough to recommend their use in the pharmacological treatment of patients with PTSD. However, the majority of participants included in this review suffered from combat trauma, so it is unclear how these results would generalise to a civilian population.

Prazosin is an alpha-1 adrenoceptor antagonist that is primarily used in the management of cardiovascular disease, and the first RCT assessing it in patients with PTSD noted that it had particular efficacy in reducing the severity and frequency of trauma-related nightmares (Dunlop et al., 2017). There is additional evidence that it may also reduce day-time intrusive and hyperarousal symptoms, although to a lesser degree (Raskind et al., 2003). Prazosin has a short half-life in the body, and would probably benefit patients the most when given in divided doses. Of the ten studies included in this review, six gave prazosin as a single night-time dose, with the remaining four opting for a divided dose, with a larger dose in the evening. It is interesting to note that the two studies with the most favourable result for prazosin (Ahmadpana et al., 2014; Raskind et al., 2003) gave prazosin as a single night-time and divided dose, respectively.

There was a wide variety of mean doses delivered across prazosin studies (from 3.2 mg to 15.6 mg). The two studies with the highest mean night-time dose also happened to be the most effective, with Ahmadpana et al. (2014) giving a single 15 mg dose at night, and Raskind et al. (2003) giving a mean night-time dose of 15.6 mg in male participants (and a mean dose of 7 mg in female participants).

Prazosin is an unlicensed treatment for PTSD and as such there are currently no manufacturers prescribing guidelines for its use. This same problem is faced with other unlicensed psychotropic medications with evidence for helping to reduce PTSD symptom severity (fluoxetine, venlafaxine, quetiapine), but we are able to look at their prescribing regimens in other psychiatric conditions in addition to the doses used in RCTs to inform prescribing for people with PTSD.

Prazosin is prescribed up to 20 mg daily in divided doses for hypertension and congestive heart failure and this, coupled with the fact participants in flexible dosing studies required up to 25 mg, suggests that cautious prescribing up to 20 mg can be justified and offer people with PTSD the best chance of improvement. The recognised side effects from prazosin include hypotension (especially severe first-dose hypotension), syncope, drowsiness, dizziness, asthenia and depression, and particular caution is required for patients with a history of hypotension or micturition syncope (Taylor, Barnes, & Young, 2018). Prazosin represents a choice for the many patients with PTSD who have not fully benefited from an evidence-based pharmacological monotherapy.

Risperidone is an atypical antipsychotic which is commonly prescribed for acute and chronic psychoses, mania, and the short-term management of persistent aggression in patients with dementia and conduct disorder (Taylor et al., 2018). The recognised side effects of risperidone include commonly causing sedating, increased appetite, blurred vision, constipation and postural hypotension. More notable side effects include the increased risk of metabolic syndrome, sexual dysfunction, and, because risperidone is the most typical of the atypical antipsychotics there is a comparatively higher chance of causing extra-pyramidal-sid effects. Serious side effects include hyperglycaemia, arrhythmias, cerebrovascular events in the elderly, rare neuroleptic malignant syndrome and rare seizures (Li et al., 2017). Risperidone augmentation may be of benefit to patients with PTSD, who have not fully benefited from pharmacological monotherapy. A careful clinical appraisal of the potential benefits should be weighed against the risk of side effects, with the guidelines for prescribing in other conditions followed (including ECG and blood tests prior to initiation with ongoing metabolic and cardiac monitoring).

This review did not find evidence to recommend the use of topiramate augmentation, in contrast with other reviews (Matthew et al., 2011), for several reasons; we have delineated monotherapy and augmentation studies and excluded studies from the quantitative analysis that suffered from a lack of sufficient data reporting. There are five studies that assess the use of topiramate for PTSD in the literature; Akuchekian et al., 2004 (McHugh et al., 2013), Batki et al., 2014 (Review Manager (RevMan), 2014), Lindley et al., 2007 (Davidson et al., 2005), Tucker et al., 2007 (Matthew et al., 2011) and Yeh et al., 2010 (Padala et al., 2006). The latter two (Tucker and Yeh) are the only RCTs that prohibited the use of concomitant psychotropics during the course of the trial and were included in our monotherapy meta-analysis. The remainder allowed topiramate to be added to existing pharmacological treatment and were included for qualitative assessment in this review. Lindley et al. (Butterfield et al., 2001) was deemed to be at a high risk of selection and attrition bias, with insufficient data reported that could not be usefully meta-analysed.

4.3. Head-to-head studies

There is a sparse literature of head-to-head pharmacotherapy trials. This review did not find evidence of superiority for the small number of included agents
over one another, although it is noteworthy that the general trend appears to favour sertraline over citilopram and nefazodone. It is also interesting that there are similar effect sizes seen when comparing venlafaxine and sertraline directly in a large study \((n = 352)\) (Davidson et al., 2006). Unfortunately, this is the only RCT which directly compares two evidence-based pharmacological interventions; future head-to-head RCTs would do well to compare interventions where there is already an evidence base.

The use of nefazodone as a comparator in two studies (McRae et al., 2004; Saygin et al., 2002) is curious; nefazodone was first marketed in 1994 and there has been only one other PTSD RCT (Davis et al., 2004), where it was compared to placebo and failed to demonstrate efficacy. It was taken off the market by the manufacturer across Europe by 2004, but is still marketed in countries across the world; it carries a black box warning in the USA due to the serious risk of hepatobiliary reactions, including irreversible liver failure. In at least one study (McRae et al., 2004), the pharmaceutical industry sponsored the trial. It is not clear whether they did it in the other study (Saygin et al., 2002) due to poor reporting.

There is also a sparse literature of RCTs which compare pharmacotherapy to psychotherapy and this review does not find evidence to recommend this approach; just two studies had usable data. Buhman and colleagues (Buhmann et al., 2016) conducted a pragmatic randomised trial in an asylum seeker population; four conditions were compared, including sertraline plus mianserin, sertraline plus mianserin plus therapy, therapy alone, and wait list control. However, perhaps owing to the flexible pragmatic nature of the trial, participants in each arm actually received a variety of treatments, making it difficult to establish the effect of any in isolation. For instance, only 25% of participants in the therapy group received exposure treatment, and 27% in the therapy group also received another antidepressant.

There are many difficulties inherent to conducting RCTs of pharmacotherapy versus psychotherapy, most notably the ability to blind participants and personnel. The study by Buhmann et al. (2016) was commendable for the use of blinded outcome assessors.

The study by van der Kolk et al. (2007) employed three parallel arms in their RCT, comparing fluoxetine to EMDR and pill placebo, to 88 participants over 8 weeks of treatment. This study design is close to optimal for comparing the efficacy of pharmacotherapy versus psychotherapy, but would likely be more expensive to run.

It is interesting that there was no statistically significant difference between EMDR and sertraline in this small study, although there was an unclear risk of bias across five out of seven assessed domains, and a high risk of bias related to one of the authors being affiliated with one of the interventions being tested.

### 4.4. Study limitations

This review was strict in its approach to assessing risk of bias. Most studies did not adhere to the CONSORT 2010 Statement (Schulz et al., 2010); studies described themselves as being randomised and double blind, but the vast majority did not describe the process to achieve adequate randomisation, allocation concealment, nor steps taken to ensure the blinding of participants, personnel or outcome assessors. Where there was missing information around methodology, we contacted authors via email to ask additional questions. Unfortunately, we rarely received an adequate response. For these reasons, this study is limited in terms of our uncertainty around the true risk of bias. However, it is notable that many of the included studies were over a decade old, and those studies published more recently were generally of a higher quality with regards to reporting.

Another limitation of this study relates to the inclusion of studies which chose to use a modified definition of their intention to treat (ITT) population. The most accurate approach is ‘once randomised, always analysed’ and using an appropriate imputation method to account for dropouts at any stage after randomisation. Some studies defined their modified ITT population as those participants who were randomised and received at least one post-baseline assessment. The difficulty in accepting this approach is the vagueness. Some studies may have chosen to perform the first post-baseline assessment prior to receiving the medication or placebo, which is preferable and closer in definition to the ITT, whilst others would perform the first post-baseline assessment after a period of receiving the intervention. Whilst adhering to an analysis of an accurate ITT may lead to a more conservative underestimation of effect in an arm with higher attrition rates, it represents the most statistically rigorous approach and limits the risk of attrition bias.

This study did not include a network meta-analysis (NMA) of included studies, a limitation which precludes an ability to rank interventions based on efficacy; we would direct readers to a recently published NMA by Cipriani et al. (2018). For our augmentation review, the quality of the included studies was relatively high and higher overall than the monotherapy studies. This may be because augmentation studies have tended to be published more recently, and awareness over rigorous scientific reporting has likely increased over time. As mentioned, the vast majority of studies included...
here were assessing populations who had suffered from combat trauma, and it is unclear if these results would be seen across other trauma types. There was significant statistical heterogeneity in the prazosin and topiramate meta-analyses but this was not an issue for the risperidone meta-analysis.

An ideal RCT of pharmacological augmentation would have required all participants to first be stabilised on one pharmacological agent before being randomised to either the augmentation drug or placebo. In practice, most RCTs allowed participants to be on a wider variety of monotherapy drugs prior to randomisation, and the interactions between different agents would likely be a confounding factor.

For our head-to-head review, there was a paucity of RCTs both for pharmacotherapy versus pharmacotherapy, and for pharmacotherapy versus psychotherapy, with seven and two studies having acceptable data for extraction, respectively.

4.5. Implications

This review found evidence to recommend the monotherapy use of paroxetine, fluoxetine, sertraline and venlafaxine in treating PTSD. We also found emerging evidence to suggest quetiapine as monotherapy. Unfortunately, the effect sizes for these medications is small, but they would be likely to offer clinically significant benefits in patients who take them.

Further research should be directed towards the comparison of these medications, as well as amitriptyline, GR205171 (a neurokinin-1 antagonist), mirtazapine and phenelzine, and studies that employ several placebos and active comparator arms will further bolster the ability to perform hierarchical analysis of efficacy and tolerability via NMA.s. Further research using ketamine of differing doses and rates of administration may also yield more promising results in the future.

The use of medication in treating serious mental illnesses may often be suboptimal and efforts to improve this have included the use of prescribing algorithms (van der Kolk et al., 2007). Using the findings of this review alongside the ISTSS treatment recommendations, the Cardiff Traumatic Stress Research Group has developed the Cardiff PTSD Algorithm; this prescribing algorithm will guide clinicians through a number of evidence-based steps and is available on request.

In terms of augmentation, this review found evidence for the use of prazosin and risperidone as augmentation agents in the treatment of PTSD, although the effect size for both medications is small. Prazosin and risperidone may be considered for use in patients with PTSD who have not fully benefitted from evidence-based pharmacological monotherapy, although both of these agents are associated with significant adverse events and may not be tolerated by everyone.

Future research may be best directed towards studies of prazosin comparing a single night time or divided twice-daily doses, to examine where the strongest beneficial effect and highest tolerability might lie. Further studies of atypical antipsychotics are also needed and should include those drugs with more favourable side effect profiles, such as quetiapine and aripiprazole.

This review did not find any current evidence to support the use of one evidence-based pharmacotherapy over another in direct head-to-head comparisons. A network meta-analysis was beyond the scope of this review, but has recently been performed elsewhere and can be (Cipriani et al., 2018) a useful analysis for clinicians to rank the efficacy of interventions, provided there are adequate bilateral comparisons to input. Further research is needed that would elucidate the comparative efficacy of evidence-based interventions, such as those cited above for monotherapy and augmentation, and an RCT design that employs multiple comparator arms (which would include another medication, placebo and trauma therapy) would be of great interest.

Acknowledgments

We wish to thank the ISTSS and the Cochrane Collaboration for their support.

Disclosure statement

Dr Hoskins has received MDMA-assisted psychotherapy training and travel expenses from MAPS. Professor Bisson and Dr Hoskins are co-applicants on a MAPS-sponsored Phase 2 clinical trial of MDMA-assisted psychotherapy taking place with Cardiff University and Cardiff and Vale University Health Board (NHS).

Funding

The International Society for Traumatic Stress Studies supported this work to inform the development of their pharmacological treatment guidelines. The views expressed in this article are those of the authors solely and do not necessarily reflect the views, policies or decisions of their employers.

ORCID

Neil P. Roberts https://orcid.org/0000-0002-6277-0102
Jonathan I. Bisson https://orcid.org/0000-0001-5170-1243

References

Ahmadpanah, M., Sabzeiee, P., Hosseini, S. M., Torabian, S., Haghighi, M., Jahangard, L., ... Brand, S. (2014). Comparing the effect of prazosin and
hydroxyzine on sleep quality in patients suffering from posttraumatic stress disorder. *Neuropsychobiology*, 69(4), 235–242. doi:10.1159/000362243

Akuchekian, S., & Amanat, S. (2004). The comparison of topiramate and placebo in the treatment of posttraumatic stress disorder: A randomized, double-blind study. *Journal of Research in Medical Sciences*, 9(5), 240–244. doi:10.1186/1744-859X-5-S1-S225

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). doi:10.1176/appi.books.9780890425966.dsm05

Attari, A., Rajabi, F., & Maracy, M. R. (2014). D-cycloserine for treatment of numbing and avoidance in chronic post traumatic stress disorder: A randomized, double blind, clinical trial. *Journal of Research in Medical Sciences: The Official Journal of Isfahan University of Medical Sciences*, 19(7), 592–598. PMCID: PMC4214015 PMID: 25364356.

Baker, D. G., Diamond, B. I., Gillette, G., Hamner, M., Katzelnick, D., & Keller, T. (1995). A double-blind randomized placebo-controlled multi-center study of brofaromine in the treatment of posttraumatic stress disorder. *Psychopharmacology*, 122(4), 386–389. doi:10.1007/bf02246271

Baniasadi, M., Hosseini, G., Fayyazi Bordbar, M. R., Rezaei Ardani, A., & Mostafavi Toroghi, H. (2014). Effect of pregabalin augmentation in treatment of patients with combat-related chronic posttraumatic stress disorder: A randomized controlled trial. *Journal of Psychiatric Practice*, 20(6), 419–427. doi:10.1097/JOP.0b013e3182998a41

Bartzokis, G., Lu, P. H., Turner, J., Mintz, J., & Saunders, C. S. (2005). Adjunctive risperidone in the treatment of chronic combat-related posttraumatic stress disorder. *Biological Psychiatry*, 57(5), 474–479. doi:10.1016/j.biopsyc.2004.11.039

Batki, S. L., Pennington, D. L., Lasher, B., Neylan, T. C., Metzler, T., Waldrop, A., … Herbst, E. (2014). Topiramate treatment of alcohol use disorders in veterans with PTSD: A randomized controlled pilot study. *Alcoholism: Clinical and Experimental Research*, 8(8), 2169–2177. doi:10.1111/acer.12496

Becker, M., Hertzberg, M., Moore, S., Dennis, M., Bukenya, D., & Beckham, J. (2007). A placebo-controlled trial of bupropion SR in the treatment of chronic posttraumatic stress disorder. *Journal of Clinical Psychopharmacology*, 27(2), 193–197. doi:10.1097/JCP.0b013e318302eacd

Bisson, J. I., Roberts, N. P., Andrew, M., Cooper, R., & Lewis, C. (2013). Psychological therapies for chronic post-traumatic stress disorder (PTSD) in adults. *The Cochrane Database of Systematic Reviews*. doi:10.1002/14651858.CD003388.pub4

Blanchard, E. B., Hickling, J. H., Malta, L. S., Jaccard, J., Devineni, T., Vezay, C. H., & Galovski, T. E. (2003). Prediction of response to psychological treatment among motor vehicle accident survivors with PTSD. *Behavior Therapy*, 34(3), 351–363. doi:10.1016/s0005-7894(03)80005-9

Brady, K., Pearlstein, T., Asnis, G. M., Baker, D., Rothbaum, B., & Sikes, C. R. (2000). Efficacy and safety of sertraline treatment of posttraumatic stress disorder. *Archives of General Psychiatry*, 283, 1837–1844. doi:10.1016/j.jama.283.14.1837

Brady, K. T., Sonne, S., Anton, R. F., Randall, C. L., Back, S. E., & Simpson, K. (2005). Sertraline in the treatment of co-occurring alcohol dependence and post-traumatic stress disorder. *Alcoholism: Clinical & Experimental Research*, 29(3), 395–401. doi:10.1097/01.ALC.0000156129.98265.57

Braun, P., Greenberg, D., Dasberg, H., & Lerer, B. (1991). Core symptoms of posttraumatic stress disorder unimproved by alprazolam treatment. *Journal of Clinical Psychiatry*, 51, 236–238.

Buhmann, C. B., Nordentoft, M., Ekstroem, M., Carlsson, J., & Mortensen, E. L. (2016). The effect of flexible cognitive-behavioural therapy and medical treatment, including antidepressants on post-traumatic stress disorder and depression in traumatised refugees: Pragmatic randomised controlled clinical trial. *British Journal of Psychiatry*, 208(3), 252–259. doi:10.1192/bjp.bp.114.150961

Butterfield, M. I., Becker, M. E., Connor, K. M., Sutherland, S., Churchill, L. E., & Davidson, J. R. (2001). Olanzapine in the treatment of post-traumatic stress disorder: A pilot study. *International Clinical Psychopharmacology*, 16(4), 197–203. doi:10.1007/0004850-20010700-00003

Carey, P., Suliman, S., Ganesan, K., Seedat, S., & Stein, D. J. (2012). Olanzapine monotherapy in posttraumatic stress disorder: Efficacy in a randomized, double-blind, placebo-controlled study. *Human Psychopharmacology: Clinical and Experimental*, 27(4), 386–391. doi:10.1002/hup.2238

Cipriani, A., Williams, T., Nikolakopoulou, A., Salanti, G., Chaimani, A., Ipser, J., … Stein, D. J. (2018). Comparative efficacy and acceptability of pharmacological treatments for post-traumatic stress disorder in adults: A network meta-analysis. *Psychological Medicine*, 48(12), 1975–1984. doi:10.1017/S003329171700349X

Connor, K. M., Sutherland, S. M., Tuner, L. A., Malik, M. L., & Davidson, J. R. (1999). Fluoxetine in post-traumatic stress disorder: Randomized, double-blind study. *British Journal of Psychiatry*, 175(1), 17–22. doi:10.1192/bjp.175.1.17

Davidson, J., Baldwin, D., Stein, D. J., Kuper, E., Benattia, I., & Ahmed, S. (2006). Treatment of posttraumatic stress disorder with venlafaxine extended release: A 6 month randomized controlled trial. *Archives of General Psychiatry*, 63(10), 1158–1160. doi:10.1001/archpsyc.63.10.1158

Davidson, J., Brady, K., Bellman, T. A., Stein, M. B., & Pollack, M. H. (2007). The efficacy and tolerability of tiagabine in adult patients with post traumatic stress disorder. *The Journal of Clinical Psychiatry*, 27, 85–88. doi:10.1192/bjp.0b013e318102e5115

Davidson, J., Rothbaum, B. O., & Tucker, P. (2006). Venlafaxine extended release in posttraumatic stress disorder: A sertraline and placebo controlled study. *Journal of Clinical Psychopharmacology*, 26(3), 259–267. doi:10.1097/01.jcp.0000222514.71390.c1

Davidson, J. R. (2004). Remission in post-traumatic stress disorder (PTSD): Effects of sertraline as assessed by the Davidson trauma scale, clinical global impressions and the clinician-administered PTSD scale. *International Clinical Psychopharmacology*, 19(2), 85–87. doi:10.1097/00004850-200403000-00005

Davidson, J. R., Connor, K. M., Hertzberg, M. A., Weisler, R. H., Wilson, W. H., & Payne, V. M. (2005). Maintenance therapy with fluoxetine in posttraumatic stress disorder: A randomized, double-blind study. *Archives of General Psychiatry*, 62(3), 259–267. doi:10.1001/archpsyc.62.3.259

---

*Note: The above text includes references that are not formatted consistently, which may affect readability and comprehension.*

---

*European Journal of Psychotraumatology*
posttraumatic stress disorder with amitriptyline and placebo. Archives of General Psychiatry, 47(3), 259–266. doi:10.1001/archpsyc.1990.01810150059010

Davidson, J. R., Rothbaum, B. O., van der Kolk, B. A., Sikes, C. R., & Farfel, G. M. (2001). Multicenter, double-blind comparison of sertraline and placebo in the treatment of posttraumatic stress disorder. Archives of General Psychiatry, 58(5), 485–492. doi:10.1001/archpsyc.58.5.485

Davidson, J. R., Weisler, R. H., Butterfield, M. L., Casat, C. D., Connor, K. M., & Barnett, S. (2003). Mirtazapine vs. placebo in posttraumatic stress disorder: A pilot trial. Biological Psychiatry, 53(2), 188–191. doi:10.1016/s0006-3223(02)01411-7

Davis, L. L., Davidson, J. R., Ward, L. C., Bartolucci, A., Bowden, C. L., & Petty, F. (2008). Divalproex in the treatment of posttraumatic stress disorder. The Journal of Clinical Psychiatry, 281, 84–88. doi:10.1097/JCP.0b013e318160f83b

Davis, L. L., Jewell, M. E., Ambrose, S., Farley, J., English, B., & Bartolucci, A. (2004). A placebo-controlled study of nefazodone for the treatment of chronic posttraumatic stress disorder. Journal of Clinical Psychopharmacology, 24(3), 291–297. doi:10.1097/01.jcp.0000125685.82219.1a

Dunlop, B. W., Binder, E. B., Losiescu, D., Mathew, S. J., Neylan, T. C., Pape, J. C., … Mayberg, H. S. (2017). Corticotropin-releasing factor receptor 1 Antagonism is ineffective for women with posttraumatic stress disorder. Biological Psychiatry, 82(12), 866–874. doi:10.1016/j.biopsych.2017.06.024

Feder, A., Parides, M. K., Murrough, J. W., Perez, A. M., Morgan, J. E., Saxena, S., … Charney, D. S. (2014). Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: A randomized clinical trial. JAMA Psychiatry, 71(6), 681–688. doi:10.1001/jamapsychiatry.2014.62

Ferry, F., Bolton, D., Bunting, B., Devine, B., McCann, S., & Murphy, S. (2008). Trauma, health and conflict in Northern Ireland: A study of the epidemiology of trauma related disorders and qualitative investigation of the impact of trauma on the individual. Ireland: Psychology Research Institute, University of Ulster.

Forbes, D., Creamer, M., Bissell, J. I., Cohen, J. A., Crow, B. E., Foa, E. B., … Ursano, R. J. (2010). A guide to guidelines for the treatment of PTSD and related conditions. Journal of Traumatic Stress, 23(5), 537–552. doi:10.1002/jts.20565

Forman-Hoffman, V., Middleton, J. C., Feltner, C., Gaynes, B. N., Weber, R. P., Bann, C., … Green, J. (2018a). Psychological and pharmacological treatments for adults with posttraumatic stress disorder: A systematic review update (Internet) (Comparative Effectiveness Review, No. 207). Rockville, MD: Agency for Healthcare Research and Quality.

Forman-Hoffman, V., Middleton, J. C., Feltner, C., Gaynes, B. N., Weber, R. P., Bann, C., … Green, J. (2018b). Psychological and pharmacological treatments for adults with posttraumatic stress disorder: A systematic review update, agency for healthcare research and quality, PMID: 30204376.

Friedman, M. J., Marmar, C. R., Baker, D. G., Sikes, C. R., & Farfel, G. M. (2007). Randomized, double blind comparison of sertraline for posttraumatic stress disorder in a department of veterans affairs setting. The Journal of Clinical Psychiatry, 68(5), 711–720. doi:10.4088/jcp.v68n0508

Fromberger, U., Stieglitz, R. D., Nyberg, E., Richter, H., Novelli, F. U., & Angenendt, J. (2004). Comparison between paroxetine and behaviour therapy in patients with posttraumatic stress disorder (PTSD): A pilot study. International Journal of Psychiatry in Clinical Practice, 8(1), 19–23. doi:10.1080/1365100310004803

Germain, A., Richardson, R., Moul, D. E., Mammen, O., Haas, G., Forman, S. D., … Nozflinger, E. A. (2012). Placebo-controlled comparison of prazosin and cognitive-behavioral treatments for sleep disturbances in US military veterans. Journal of Psychosomatic Research, 72(2), 89–96. doi:10.1016/j.jpsychores.2011.11.010

Golier, J. A., Caramanica, K., Demaria, R., & Yehuda, R. (2012). A pilot study of mifepristone in combat-related PTSD. Depression Research and Treatment, 2012, 393251. doi:10.1155/2012/393251

Hamner, M. B., Faldowski, R. A., Robert, S., Ulmer, H. G., Horner, M. D., & Lorberbaum, J. P. (2009). A preliminary controlled trial of divalproex in posttraumatic stress disorder. Annals of Clinical Psychiatry: Official Journal of the American Academy of Clinical Psychiatrists, 21(2), 89–94. PMID: 19439158.

Hamner, M. B., Faldowski, R. A., Ulmer, H. G., Frueh, B. C., Huber, M. G., & Arana, G. W. (2000). A randomized, controlled trial of risperidone for psychotic features in PTSD. Biological Psychiatry, 8(1), 158–159. doi:10.1007/s00018-200031000-00001

Heresco-Levy, U., Kremer, I., Javitt, D. C., Goichman, R., Reshef, A., Blanaru, M., & Cohen, T. (2002). Pilot-controlled trial of D-cycloserine for the treatment of post-traumatic stress disorder. The International Journal of Neuropsychopharmacology, 5(4), 301–307. doi:10.15031/jnpsychores.2011.11.010

Hertzberg, M. A., Butterfield, M. L., Feldman, M. E., Beckham, J. C., Sutherland, S. M., & Connor, K. M. (1999). A preliminary study of lamotrigine for the treatment of posttraumatic stress disorder. Biological Psychiatry, 45(9), 1226–1229. doi:10.1016/s0006-3223(99)00011-6

Hertzberg, M. A., Feldman, M. E., Beckham, J. C., Kudler, H. S., & Davidson, J. R. (2000). Lack of efficacy for fluoxetine in PTSD: A placebo controlled trial in combat veterans. Annals of Clinical Psychiatry, 12(2), 101–105. doi:10.1230/a167009706231175

Higgins, J. P. T., & Green, S. (2011). Cochrane handbook for systematic reviews of interventions version 5.1.0. UK: The Cochrane Collaboration and John Wiley and Sons Ltd.

Hoskins, M., Pearce, J., Bethell, A., Dankova, L., Barbui, C., Tol, W., & Bisson, J. (2015). Pharmacotherapy for post-traumatic stress disorder: Systematic review and meta-analysis. British Journal of Psychiatry, 206(2), 93–100. doi:10.1192/bjp.bp.114.148551

Jerd, A. B., Pruitt, L. D., Zoeliner, L. A., & Feeny, N. C. (2016). The effects of prolonged exposure and sertraline on emotion regulation in individuals with posttraumatic stress disorder. Behaviour Research and Therapy, 77, 62–67. doi:10.1016/j.brat.2015.12.002

Jely, R., Heber, A., Fraser, G., & Boisvert, D. (2015). The efficacy of nabulone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: A preliminary randomized, double-blind, placebo-controlled cross-over design study. Psychoneuroendocrinology, 51, 585–588. doi:10.1016/j.psyneuen.2014.11.002
Petrakis, I. L., Ralevski, E., Desai, N., Trevisan, L., Gueorguiva, R., Rounsaville, B., & Krystal, J. H. (2012). Noradrenergic vs serotoninergic antidepressant with or without naltrexone for veterans with PTSD and comorbid alcohol dependence. *Neuropsychopharmacology*, 37(4), 996–1004. doi:10.1038/npp.2011.283

Pfizer588 – sertraline (Unpublished).

Pietrzak, R. H., Goldstein, R. B., Southwick, S. M., & Grant, B. F. (2011). Prevalence and axis I comorbidity of full and partial posttraumatic stress disorder in the United States: Results from wave 2 of the national epidemiologic survey on alcohol and related conditions. *Journal of Anxiety Disorders*, 25(3), 456–465. doi:10.1016/j.janxdis.2010.11.010

Pollack, M. H., Hoge, E. A., Worthington, J. J., Mosher, S. J., Wechsler, R. S., Brandes, M., & Simon, N. M. (2011). Eszopiclone for the treatment of posttraumatic stress disorder and associated insomnia: A randomized, double-blind, placebo-controlled trial. *The Journal of Clinical Psychiatry*, 72(7), 892–897. doi:10.4088/JCP.09m05607gry

Popiel, A., Zawadzki, B., Pragelowska, E., & Teichman, Y. (2015). Prazosin for post-traumatic stress disorder in military veterans. A randomized clinical trial - The tRAKT study. *Journal of Behavior Therapy and Experimental Psychiatry*, 48, 17–26. doi:10.1016/j.jbtep.2015.01.002

Ramaswamy, S., Driscoll, D., Smith, L. M., Bhatia, S. C., & Popiel, A., Zawadzki, B., Pragelowska, E., & Teichman, Y. (2002). Nefazodone versus sertraline in treatment of posttraumatic stress disorder. *Bulletin of Clinical Psychopharmacology*, 12, 1–5.

Schneier, F. R., Campeas, R., Carcamo, J., Glass, A., Lewis-Fernandez, R., Neria, Y., … Wall, M. M. (2015). Mirtazapine SR versus sertraline for the treatment of posttraumatic stress disorder. *American Journal of Psychiatry*, 172(6), 808–817. doi:10.1176/appi.ajp.2015.14020117

Shalev, A. Y., Ankri, Y., Israeli-Shalev, Y., Peleg, T., Adesky, R., & Freedman, S. (2011). Prevention of post-traumatic stress disorder by early treatment. *Archives of General Psychiatry*, 69(2), 166–176. doi:10.1001/archgenpsychiatry.2011.127

Shestatzky, M., Greenberg, D., & Lerrer, B. (1988). A controlled trial of phenerazine in posttraumatic stress disorder. *Psychiatric Research*, 24(2), 149–155. doi:10.1016/0165-1718(88)90057-1

Simpson, L., Malte, C. A., Dietel, B., Tell, D., Pocock, I., Lyons, R., … Saxon, A. J. (2015). A pilot trial of prazosin, an alpha-1 adrenergic antagonist, for comorbid alcohol dependence and posttraumatic stress disorder. *Alcoholism, Clinical and Experimental Research*, 39(5), 808–817. doi:10.1111/acer.12703

SKB627, Bryson, H., Lawrison, S., GJ, E., & KM, G. (unpublished). A 12 week, double-blind, placebo-controlled, parallel group study to assess the efficacy and tolerability of paroxetine in patients suffering from post-traumatic stress disorder.

SKB650, Bryson, H., KE, D., & Jeffery, P. J. (unpublished). A study of the maintained efficacy and safety of paroxetine versus placebo in the long-term treatment of post-traumatic stress disorder.

Sonnett, S. C., Waldrop, A., Back, S., Killeen, T., McRae, A., & Brady, K. (2006). Paxil CR versus placebo in the treatment of outpatients with comorbid PTSD and substance dependence, *Proceedings of the 68th Annual Scientific Meeting of the College on Problems of Drug Dependence*, June 17–22; Scottsdale, Arizona.

Spivak, B., Strous, R. D., Shaked, G., Shabash, E., Kotler, M., & Weizman, A. (2006). Reboxetine versus trial of desipramine in 18 men with posttraumatic stress disorder. *American Journal of Psychiatry*, 164, 513–516. doi:10.1176/ajp.164.4.513

Review Manager (RevMan) (2014) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, *The Cochrane Collaboration*. reviewed by M. D. Hoskins et al.
fluvoxamine in treatment of motor vehicle accident related posttraumatic stress disorder. Journal of Clinical Psychopharmacology, 26(2), 152–156. doi:10.1097/01.jcp.0000203195.65710.fo

Steel, Z., Choy, T., Silove, D., Marnane, C., Bryant, R. A., & van Ommeren, M. (2009). 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, 302 (5), 537–549. doi:10.1001/jama.2009.1132

Stein, M., Kline, N., & Matloff, J. (2002). Adjunctive olanzapine for SSRI-resistant combat-related PTSD: A double-blind placebo-controlled study. American Journal of Psychiatry, 159(10), 1777–1779. doi:10.1176/appi.ajp.159.10.1777

Strawbridge, R., Carter, B., Marwood, L., & Bandelow, B. (2019). Augmentation therapies for treatment-resistant depression: Systematic review and meta-analysis. The British Journal of Psychiatry: The Journal of Mental Science, 214(1), 42–51. doi:10.1192/bjp.2018.233

Taylor, D. M., Barnes, T. R. E., & Young, A. H. (2018). The maudsley prescribing guidelines in psychiatry (13th ed.). London: Wiley Blackwell. ISBN: 978-1-119-44260-8.

Taylor, F. B., Martin, P., Thompson, C., Williams, J., Mellman, T. A., Gross, C., ... Raskind, M. A. (2008). Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma posttraumatic stress disorder: A placebo-controlled study. Biological Psychiatry, 63(6), 629–632. doi:10.1016/j.biopsych.2007.07.001

Tucker, P., Potter-Kimball, R., Wyatt, D. B., Parker, D. E., Burgin, C., & Jones, D. E. (2003). Can physiologic assessment and side effects tease out differences in PTSD trials? A double-blind comparison of citalopram, sertraline, and placebo. General Psychopharmacology, 37, 135–149.

Tucker, P., Trautman, R. P., Wyatt, D. B., Thompson, J., Wu, S. C., & Capcece, J. A. (2007). Efficacy and safety of topiramate monotherapy in civilian posttraumatic stress disorder: A randomized, double blind, placebo controlled trial. The Journal of Clinical Psychiatry, 68(2), 201–206. doi:10.4088/jcp.v68n0204

Tucker, P., Zaninelli, R., Yehuda, R., Ruggiero, L., Dillingham, K., & Pitts, C. D. (2001). Paroxetine in the treatment of chronic posttraumatic stress disorder: Results of a placebo-controlled, flexible-dosage trial. Journal of Clinical Psychiatry, 62(11), 860–868. doi:10.4088/jcp.v62n1105

van der Kolk, B. A., Dreyfuss, D., Michaels, M., Shera, D., Berkowitz, R., Fisler, R., & Saxe, G. (1994). Fluoxetine in posttraumatic stress disorder. The Journal of Clinical Psychiatry, 55(12), 517–522.

van der Kolk, B. A., Spinazzola, J., Blaustein, M. E., Hopper, J. W., Hopper, E. K., & Korn, D. L. (2007). A randomized clinical trial of EMDR, fluoxetine and pill placebo in the treatment of posttraumatic stress disorder: Treatment effects and long-term maintenance. The Journal of Clinical Psychiatry, 68(1), 37–46. doi:10.4088/jcp.v68n0105

Van Liempt, S., Arends, J., Smulders, J., Westenberg, H. G. M., Kahn, R. S., & Vennetten, E. (2012) Prazosin treatment for sleep disturbances in veterans with a post-traumatic stress disorder; a placebo-controlled pilot study using polysomnography. PhD manuscript.

Villarruel, G., Hamner, M., Canive, J., Robert, S., Calais, L., Durklaski, V., ... Qualls, C. (2016). Efficacy of quetiapine monotherapy in posttraumatic stress disorder: A randomized, placebo-controlled trial. American Journal of Psychiatry, 173(12), 1205–1212. doi:10.1176/appi.ajp.2016.15070967

Wang, P. S., Aguilar-Gaxiola, S., Alonso, J., Angermeyer, M. C., Borges, G., Bromet, E. J., ... Haro, J. M. (2007). Use of mental health services for anxiety, mood, and substance disorders in 17 countries in the WHO world mental health surveys. The Lancet, 370(9590), 841–850. doi:10.1016/S0140-6736(07)61414-7

Yeh, M. S., Mari, J. J., Costa, M. C., Andreoli, S. B., Bressan, R. A., & Mello, M. F. (2010). A double blind, randomized controlled trial to study the efficacy of topiramate in a civilian sample of PTSD. CNS Neuroscience & Therapeutics, 175, 305–310. doi:10.1111/j.1755-5949.2010.00188.x

Zohar, J., Amital, D., Miodownik, C., Kotler, M., Bleich, A., & Lane, R. M. (2002). Double-blind placebo-controlled pilot study of sertraline in military veterans with post-traumatic stress disorder. Journal of Clinical Psychopharmacology, 22(2), 190–195. doi:10.1097/00004714-20020400-000013