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CLINICAL RESEARCH ARTICLE

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

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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 monotherapy, 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 farmacologico para el trastorno de estres postraumatico: una revision sistematica y metanalisis de monoterapia, potenciacion 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.

创伤后应激障碍的药物治疗：单一疗法、增强疗法和头对头方法的系统综述和元分析

背景: 尽管疗效不确定, 药理学方法被广泛用于创伤后应激障碍 (PTSD) 。
目的: 确定包括单一疗法, 增强疗法和头对头疗法 (药物对比药物, 药物对比心理治疗) 的所有药理学方法在降低PTSD症状严重程度方面的效果。

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PTSD; pharmacological therapy; medication; systematic review; meta-analysis

PALABRAS CLAVE
TEPT; terapia farmacológica; medicamento; revisión sistemática; metanálisis

关键词
PTSD; 药物治疗; 药物

HIGHLIGHTS

- Our review found evidence of asmall positive effect for ahandful of medications, which can reduce the symptom severity in post-traumatic stress disorder.
- These were fluoxetine, paroxetine, sertraline, venlafaxine and the antipsychotic quetiapine when used as monotherapy, prazosin and risperidone for augmentation.

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方法: 对随机对照试验进行系统综述和元分析。纳入了115项研究。结果:发现在降低PTSD症状上, 选择性5-羟色胺再摄取抑制剂 (SSRIs) 在统计意义上优于安慰剂, 但效应量较小 (标准化平均差值为-0.28, 95%置信区间为0.39至-0.17) 。在两项或更多项研究中的单一疗法药剂对比安慰剂, 我们发现抗抑郁药氟西汀, 帕罗西汀, 舍曲林, 文拉法辛和抗精神病药物喹硫平的较小统计显著学证据。对于药物增强疗法, 我们发现哌唑嗪和利培酮具有较小统计显著证据。
结论: 一些药物对降低PTSD症状严重程度有较小的正性效果, 可以被认为是潜在的单一疗法;包括氟西汀, 帕罗西汀, 舍曲林, 文拉法辛和喹硫平。当用于增强单药疗法时, 哌唑嗪和利培酮这两种药物也有较小的正性效果。在少数的头对头比较研究中, 无证据表明某种干预优于另一种干预。

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-afflicted 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, Tupler, Malik, & Davidson, 1999; Davidson, 2004; Davidson et al., 2006; Davidson, Brady, Mellman, Stein, & Pollack, 2007; Davidson et al., 2005, 1990; Davidson, Rothbaum, & 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; Rasmusson 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; Baniasadi, 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;

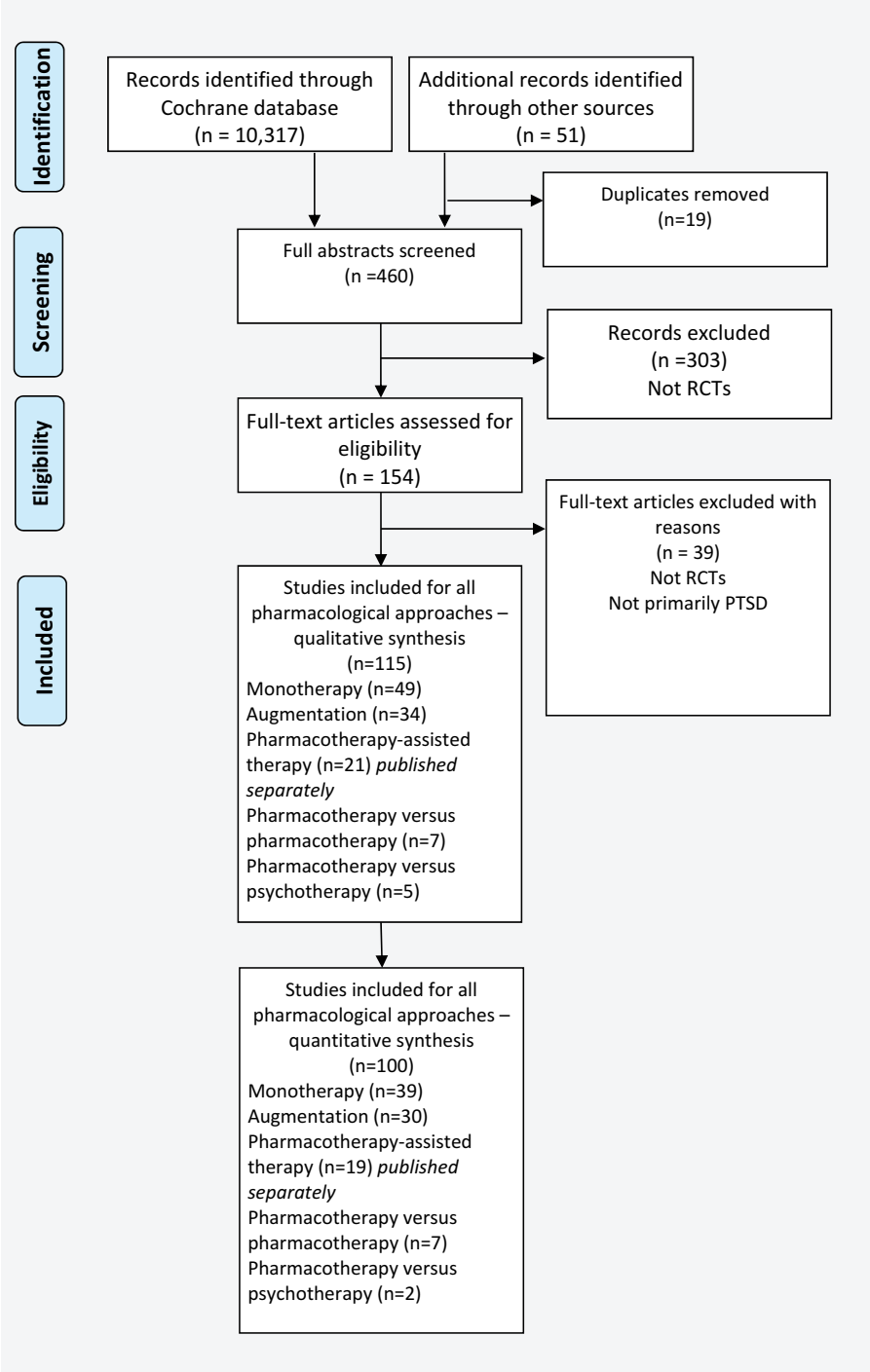

Figure 1. Flow diagram of included studies.

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., 2018, 2007; Raskind, Peskind, Kanter, Petrie, & Radant, 2003; 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; Frommberger 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; Martenyi 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 Noradrenalin Reuptake Inhibitors (SNRIs) (Davidson et al., 2006, 2006) and two assessed Monoamine Oxidase Inhibitors (MAOIs) (Baker et al., 1995; Kosten et al., 1991; Shestatzky 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; Rasmusson 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.,

Table 1. Characteristics of included monotherapy studies.

					Risk of bias (low/unclear/high)						
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: Baker 1995a USA Study type: Multicentre, randomised, double-blind, parallel, placebo controlled, flexible dose Duration: 12 weeks	*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	118 randomised 113 received one post-baseline blinded medication and efficacy measurement and counted as the author's modified ITT sample.	Unclear	Unclear	Unclear	Unclear	High	High	Unclear
Study ID: Brady 2000 USA Study type: Multicentre, randomised, double-blind, parallel, placebo controlled, flexible dose Duration: 12 weeks	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	Industry support for author.	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High
Study ID: Brady 2005 USA Study type: single centre, randomised, double-blind, parallel, placebo controlled, fixed dose Duration: 12 weeks	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	Industry support	Low	Unclear	Unclear	Unclear	High	Unclear	High
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	N = 16 Mean age: 37.7 years Sex: uclear 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: Alrpazolam 1.5–6 mg (mean dose 4.65 mg) *n* = 7 Group 2: placebo *n* = 9		Unclear	Unclear	Unclear	Unclear	High	Unclear	High
Study ID: Butterfield 2001 USA Study type: Randomised, double-blind, parallel, placebo controlled, flexible dose Duration: 10 weeks	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	Industry funded.	Unclear	Unclear	Unclear	Unclear	High	Unclear	High

(*Continued*)

Table 1. (Continued).

Methods	Participants	Outcomes	Interventions	Notes	Risk of bias (low/unclear/high)						
					Sequence generation	Allocation concealment	Blinding participants/ personnel	Blinding outcome assessors	Incomplete outcome data	Free of selective reporting	Any other bias
Study ID: Carey 2012	N = 34	CAPS	Group 1: Olanzapine 5–15 mg (mean dose	Industry funded	Unclear	Unclear	Low	Unclear	High	Unclear	High
South Africa	Mean age: 40.5 years	DTS	9.2 mg)								
Study type: Single centre, randomised, double-blind, parallel, placebo controlled, flexible dose	Sex: 60% feamle	MADRS	*n* = 14								
	Diagnosis: DSM-IV	CGI	Group 2: placebo								
	Predominant trauma type: mixed domestic and criminal violence	SDS	*n* = 14								
Duration: 8	Mean duration of Sx: unknown										
Study ID: Connor 1999	N = 54	DGRS	Group 1: Fluoxetine 10–60 mg (mean		Low	Low	Low	Unclear	Unclear	Unclear	Unclear
USA	Mean age: 32 years	SIP	dose 30 mg)								
Study type: Randomised, double-blind, parallel, placebo controlled, flexible dose	Sex: 91% female	DTS	*n* = 27								
	Diagnosis: DSM-III-TR	SDS	Group 2: placebo								
	Predominant trauma type: rape	VS	*n* = 27								
	Mean duration of Sx: 6 years										
Duration: 12 weeks											
Study ID: Davidson 1990	N = 46	CGI-I	Group 1: Amitriptyline 50–300 mg (mean	Author supported by industry	Unclear	Unclear	Unclear	Unclear	High	Unclear	High
USA	Mean age: unknown	SI-PTSD	dose 169 mg)								
Study type: Randomised, double-blind, parallel, placebo-controlled, flexible dose	Sex: unknown	CGI-S	*n* = 25								
	Diagnosis: DSM-III	HAM-D	Group 2: placebo								
	Predominant trauma type: combat	HAM-A	*n* = 21								
	Mean duration of Sx: unknown	IES									
Duration: 8		NI									
Study ID: Davidson 2001a	N = 208	CAPS	Group 1:	1-week placebo run-in	Low	Unclear	Unclear	Unclear	Unclear	Unclear	High
USA	Mean age: 37.1 years	CGI-I	*n* =	Unclear if dropout percentages refer							
Study type: Multicentre, randomised, double-blind, parallel, placebo-controlled, flexible dose	Sex: 22% female	CGI-S	Group 2:	to randomised or mITT sample.							
	Diagnosis: DSM-III-R	IES	*n* =								
	Predominant trauma type: physical/ sexual assault										
Duration: 12 weeks	Mean duration of Sx: 12.2 years										
Study ID: Davidson 2003	N = 29	SPRINT	Group 1: mirtazapine 15–45 mg (mean	1-week placebo run-in	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High
USA	Mean age: 36.5 years	CGI-I	dose 38.8 mg)	Author supported by industry							
Study type: Single centre, randomised, double-blind, parallel, placebo-controlled, fixed dose	Sex: unknown		*n* = 17								
	Diagnosis: DSM-IV		Group 2: placebo								
	Predominant trauma type: mixed		*n* = 9								
	Mean duration of Sx: unknown										
Duration: 8 weeks											
Study ID: Davidson 2004	N = 384	CGI-S	Group 1: sertraline	Insufficient data reported	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
USA	Mean age: 38 years	CGI-I	*n* = 190								
Study type: Multicentre, randomised, double blind, placebo controlled, flexible dose	Sex: 75.5% female	DTS	Group 2: fluoxetine								
	Diagnosis: DSM-III-R	IES	*n* = 194								
	Predominant trauma type: physical/ sexual assault	CAPS-2									
Duration: 12	Mean duration of Sx: 12.1 years										

(*Continued*)

Table 1. (Continued).

Methods	Participants	Outcomes	Interventions	Notes	Risk of bias (low/unclear/high)						
					Sequence generation	Allocation concealment	Blinding participants/ personnel	Blinding outcome assessors	Incomplete outcome data	Free of selective reporting	Any other bias
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	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) *n* = Group 2: placebo *n* =	Insufficient data reported	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear
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 dose110.2 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: Davidson 2006 USA Study type: Multicentre, randomised, double blind, parallel, placebo controlled, flexible dose Duration: 24 weeks	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 SVS Q-LES-Q-SF SDS	Group 1: Venlafaxine 37.5–300 mg (181.7 mg) *n* = 161 Group 2: placebo *n* = 168	Author supported by industry	Low	Low	Unclear	Unclear	Low	Unclear	High
Study ID: Davidson 2007 USA Study type: Multicentre, randomised, double blind, parallel, placebo controlled, flexible dose Duration: 12	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	Author supported by industry	Unclear	Unclear	Unclear	Unclear	Unclear	High	High
Study ID: Davis 2004 USA Study type: Randomised, double-blind, parallel, placebo-controlled, flexible dose Duration: 12	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	Industry funded	Unclear	Unclear	Low	Unclear	High	Unclear	High
Study ID: Davis 2008 USA Study type: Randomised, double-blind, parallel, placebo-controlled, flexible dose Duration: 8	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	Industry funded	Low	Low	Low	Low	Low	Unclear	High

(*Continued*)

Table 1. (Continued).

Methods	Participants	Outcomes	Interventions	Notes	Risk of bias (low/unclear/high)						
					Sequence generation	Allocation concealment	Blinding participants/ personnel	Blinding outcome assessors	Incomplete outcome data	Free of selective reporting	Any other bias
Study ID: Dunlop 2017 USA Study type: Mulitcentre, 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	CAPS PDS PSS-SR CTQ MADRS QIDS-SR CGI-S SDS CSSRS	Group 1: GSK561679 (350 mg) *n* = 63 Group 2: placebo *n* = 65	Insufficient data reported							
Study ID: Feder 2014 USA Study type: Single centre, randomised, double blind, placebo controlled, fixed dose, crossover single ketmaine 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	IESR CAPS at 7 days post-infusion MADRAS CGI-SI BPRS YMRS	Group 1: IV ketamine hydrochloride (0.5 mg/kg over 40 mins) *n* = 22 Group 2: midazolam (0.045 mg/kg over 40 mins) *n* = 19 Groups crossed over after 2 weeks	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.	Unclear	Unclear	Low	Low	Low	Unclear	High
Study ID: Friedman 2007 USA Study type: Multicentre, randomised, double-blind, parallel, 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	CAPS IES CGI-I CGI-S DTS HAM-A HAM-D PSQI DES	Group 1: Sertraline 50–200 mg (135 mg) *n* = 86 Group 2: placebo *n* = 83	Editorial assistant has received consulting income from drug company	Low	Low	Unclear	Unclear	Unclear	Unclear	High
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	SIP DGRP	Group 1: Lamotrigine 25–500 mg (380 mg) *n* = 10 Group 2: placebo *n* = 4	Industry funded	Unclear	Unclear	Unclear	Unclear	High	High	High

(*Continued*)

Table 1. (Continued).

Methods	Participants	Outcomes	Interventions	Notes	Risk of bias (low/unclear/high)						
					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 Study type: Randomised, double-blind, parallel, placebo-controlled, flexible dose Duration: 12 weeks	N = 12 Mean age: 46 years Sex: 100% male Diagnosis: DSM-III-R Predominant trauma type: combat Mean duration of Sx: unknown	DGRP DTS SDS SIP	Group 1: Fluoxetine 10–60 mg (48 mg) *n* = 6 Group 2: placebo *n* = 6		Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High
Study ID: Katz 1994 USA Study type: Multicentre, randomised, double-blind, parallel, placebo-controlled, flexible dose Duration: 14 weeks	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: Brofaromine 50–150 mg *n* = 33 Group 2: placebo *n* = 31	Industry funded	Unclear	Unclear	Unclear	Unclear	Low	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		Unclear	Unclear	Unclear	Unclear	High	Unclear	High
Study ID: Kwako 2015 USA Study type: Single centre, randomised, double blind, placebo controlled, parallel arm, fixed dose Duration: 4 weeks	N = 53 Mean age: 40.8 years Sex: 45.3% female Diagnosis: DSM-IV Predominant trauma type: unknown Mean duration of Sx: unknown		Group 1: aprepitant 125 mg *n* = 26 Group 2: placebo *n* = 27	Co-morbid alcohol Insufficient data reported	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Study ID: Li 2017 China Study type: Multicentre, randomised, double blind, placebo controlled, parallel arm, fixed dose Duration: 12 weeks	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 Group 2: placebo *n* = 36		Low	Low	Low	Low	Low	Unclear	Low
Study ID: Marshall 2001 USA Study type: Multicentre, randomised, double-blind, three parallel arms, placebo-controlled, fixed dose Duration: 12 weeks	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-I DTS TOP-8 SDS MADRS	Group 1: Paroxetine 20 mg *n* = 188 Group 2: Paroxetine 40 mg *n* = 187 Group 3: placebo *n* = 188	Industry funded	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High

(*Continued*)

Table 1. (Continued).

Methods	Participants	Outcomes	Interventions	Notes	Risk of bias (low/unclear/high)						
					Sequence generation	Allocation concealment	Blinding participants/ personnel	Blinding outcome assessors	Incomplete outcome data	Free of selective reporting	Any other bias
Study ID: Marshall 2007 USA Study type: Single centre, randomised, double-blind, parallel, placebo-controlled, flexible dose Duration: 10 weeks	N = 63 Mean age: 39.8 years Sex: 100% male Diagnosis: DSM-IV Predominant trauma type: physical assault or abuse Mean duration of Sx: unknown	CAPS CGI DES HAM-A HAM-D	Group 1: Paroxetine 10–60 mg *n* = 25 Group 2: placebo *n* = 27	1-week placebo run-in	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High
Study ID: Martenyi 2002a International Study type: Multicentre, randomised, double-blind, parallel, placebo-controlled, flexible dose Duration: 12 weeks	N = 301 Mean age:37.9 years Sex: 19% female Diagnosis: DSM-IV Predominant trauma type: combat Mean duration of Sx: unknown	TOP-8 CAPS CGI-S CGI-I MADRS HAM-A SCL-90-R DES	Group 1: Fluoxetine 20–80 mg (57.8 mg) *n* = 226 Group 2: placebo *n* = 75	Industry funded	Unclear	Unclear	Unclear	Unclear	High	Unclear	High
Study ID: Martenyi 2007 USA Study type: Multicenter, randomized, double-blind, parallel, placebo-controlled, fixed dose Duration: 12 weeks	N = 411 Mean age: 40.7 years Sex: 71.5% female Diagnosis: DSM-IV Predominant trauma type: sexual assault Mean duration of Sx: unknown	TOP-8 CAPS DTS CGI-S MADRS HAM-A DES	Group 1: Fluoxetine 20 mg *n* = 163 Group 2: Fluoxetine 40 mg *n* = 160 Group 3: placebo *n* = 88	Industry funded	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High
Study ID: Matthew 2011 USA Study type: Multicenter, randomized, double blind, parallel, placebo controlled, fixed dose Duration: 8 weeks	N = 47 Mean age: 41 years Sex: 59% female Diagnosis: DSM-IV Predominant trauma type: physical/ sexual assault Mean duration of Sx:	CAPS DTS CGI-I MADRS CGI-S SDS	Group 1: GR205171 5 mg *n* = 22 Group 2: placebo *n* = 25	2-week placebo lead-in Industry funded	Unclear	Unclear	Unclear	Low	High	Unclear	High
Study ID: Padala 2006 USA Study type: Single centre, randomised, double blind, parallel, placebo controlled, flexible dose Duration: 12 weeks	N = 20 Mean age: 41.3 years Sex: 100% male Diagnosis: unknown Predominant trauma type: unknown Mean duration of Sx: 24.1 years	CAPS TOP-8 HAM-D HAM-A	Group 1: Risperidone 4–6 mg (2.62 mg) *n* = 11 Group 2: placebo *n* = 9	Insufficient data reported	Unclear	Unclear	Unclear	Unclear	High	High	Unclear
Study ID: Panahi 2011 Iran Study type: Single centre, randomised, double blind, parallel, placebo controlled, flexible dose Duration: 10 weeks	N = 70 Mean age: 45.6 years Sex: 100% male Diagnosis: DSM-IV-TR Predominant trauma type: combat Mean duration of Sx: 24.1 years	IES-R CGI-S	Group 1: Sertraline 50–200 mg (140 mg) *n* = 35 Group 2: placebo *n* = 35		Low	Unclear	Unclear	Low	Low	Unclear	High

(*Continued*)

Table 1. (Continued).

Methods	Participants	Outcomes	Interventions	Notes	Risk of bias (low/unclear/high)						
					Sequence generation	Allocation concealment	Blinding participants/ personnel	Blinding outcome assessors	Incomplete outcome data	Free of selective reporting	Any other bias
Study ID: Pfizer 588 Unknown location Study type: Multicentre, randomised placebo-controlled, double-blind, parallel, flexible dose Duration: 74 days	N = 193 Mean age: 37 years Sex: 74.65 female Diagnosis: DSM- Predominant trauma type:physical/sexual assault Mean duration of Sx: 10.5 years	CAPS-2 CGI-I CGI-S IES DTS	Group 1: Sertraline (156 mg) *n* = 94 Group 2: placebo *n* = 94	Industry funded, unpublished	Unclear	Unclear	Unclear	Unclear	Unclear	High	High
Study ID: Rasmusson 2017 USA Study type: Muliti-centre, randomised, double blind, placebo controlled, parallel arm, flexible dose Duration: 6 weeks	N = 112 Mean age: 38.3 years Sex: 21% female Diagnosis: DSM-IV Predominant trauma type: combat Mean duration of Sx: unknown	CAPS CGI-I PCL POMS PHQ-9 ISI CD-RISC CSSRS	Group 1: Ganaloxone 200–600 mg (unknown mean dose) *n* = 59 Group 2: placebo *n* = 53	Several authors have industry ties	Low	Low	Low	Unclear	Unclear	Low	High
Study ID: Reist 1989 USA Study type: Multicentre, randomised, double blind, crossover, placebo controlled, flexible dose Duration: 8 weeks	N = 27 Mean age: 38.4 years Sex: 100% male Diagnosis: DSM-III-R Predominant trauma type: combat Mean duration of Sx: unknown	IES HAM-D HAM-A BDI	Group 1: Desipramine 50–200 mg (165 mg) *n* = unclear Group 2: placebo *n* = unclear	Insufficient data reported	Unclear	Unclear	Unclear	Unclear	High	Low	Unclear
Study ID: Shalev 2011 Israel Study type: Single centre, randomised, double-blind, parallel, placebo-controlled, fixed dose Duration: 20 weeks	N = 46 Mean age: 38.6 years Sex: 44.2% female Diagnosis: DSM-IV Predominant trauma type: road traffic accident Mean duration of Sx: 144 days	CAPS PSS-SR	Group 1: Escitalopram 10–20 mg *n* = 23 Group 2: placebo *n* = 23	Industry funded	Low	Unclear	Low	Low	High	Unclear	High
Study ID: Shestatzky 1986 Israel Study type: Single centre, randomised, double blind, parallel arm, 5 week crossover Duration: 12 weeks	N = 13 Mean age: unknown Sex: Diagnosis: DSM-III Predominant trauma type: combat Mean duration of Sx: 5.6 years		Group 1: Phelezine 45–75 mg (mean dose) *n* = 7 Group 2: placebo *n* = 5	Insufficient data reported	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Study ID: SKB627 Unknown location Study type: Randomised, double-blind, parallel, placebo-controlled, flexible dose Duration: 84 days	N = 322 Mean age: unknown Sex: 53.7% female Diagnosis: DSM-IV Predominant trauma type: unknown Mean duration of Sx: unknown	CAPS-2 CGI-I	Group 1: Paroxetine 20–50 mg *n* = 109 Group 2: placebo *n* = 103	Industry funded Unpublished	Unclear	Unclear	Unclear	Unclear	High	High	High

(*Continued*)

Table 1. (Continued).

					Risk of bias (low/unclear/high)						
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: SKB650 Unknown location Study type: Randomised, double-blind, placebo-controlled, flexible dose Duration: 252 days	N = 176 Mean age: unknown Sex: 66% female Diagnosis: DSM-IV Predominant trauma type: unknown Mean duration of Sx: unknown	CAPS-2 DTS MADRS SDS	Group 1: Paroxetine up to 50 mg (mean dose unknown) *n* = unknown Group 2: placebo *n* = unknown	Relapse prevention Insufficient data reported	Unclear	Unclear	Unclear	Unclear	High	High	High
Study ID: Sonne 2006 Unknown location Study type: Randomised, double-blind, parallel, placebo controlled, Duration: 12 weeks	N = 25 Mean age: 35.5 years Sex: unknown Diagnosis: DSM-IV Predominant trauma type: unknown Mean duration of Sx: unknown	CAPS-2 DTS	Group 1: paroxetine (mean dose42.3 mg) *n* = 13 Group 2: *n* = 12	Insufficient data reported Full report unpublished	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Study ID: Tucker 2001 USA and Canada Study type: Multicentre, randomised, double blind, parallel arm, placebo controlled, flexible dose Duration: 12 weeks	N = 323 Mean age: 40.8 years Sex: 66% female Diagnosis: DSM-IV Predominant trauma type: unknown Mean duration of Sx: 14.9 years	CAPS-2 CGI-I DTS TOP-8 SDS MADRS	Group 1: *n* = Group 2: *n* =	Industry funded	Unclear	Unclear	Unclear	Unclear	High	Unclear	High
Study ID: Tucker 2003 USA Study type: Multicentre, randomised, double blind, parallel, placebo controlled, flexible dose Duration: 10 weeks	N = 59 Mean age: 38.5 years Sex: 72% female Diagnosis: DSM-IV Predominant trauma type: physical abuse/assault Mean duration of Sx: unknown	CAPS IES BDI	Group 1: Citalopram 20–50 mg (36.2 mg) *n* = 25 Group 2: Sertraline 50–200 mg (134.1 mg) *n* = 23 Group 3: placebo *n* = 10	Industry funded							
Study ID: Tucker 2007 USA Study type: Single centre, double blind, randomised, parallel arm, placebo controlled Duration: 12 weeks	N = 40 Mean age: 41.5 years Sex: 79% female Diagnosis: DSM-IV Predominant trauma type: childhood sexual abuse Mean duration of Sx: unknown	CAPS HAM-A HAM-D CGI-S CGI-I DTS SDS CDRS	Group 1: Topiramate (25–400 mg, mean dose 150 mg) *n* = 19 Group 2: placebo *n* = 19	Authors affiliated with the industry	Low	Unclear	Unclear	Unclear	Low	Unclear	High
Study ID: van der Kolk 1994 USA Study type: Multicentre, randomised, double-blind, parallel arm, placebo-controlled, flexible dose Duration: 5 weeks	N = 64 Mean age: unknown Sex: 34.3% female Diagnosis: DSM-II-R Predominant trauma type: combat Mean duration of Sx: unknown	CAPS HAM-D DES DESI	Group 1: Fluoxetine 20–60 mg (mean dose 40 mg) *n* = Group 2: *n* =	Insufficient data reported	Unclear	Unclear	Unclear	Unclear	High	Low	High

(*Continued*)

Table 1. (Continued).

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

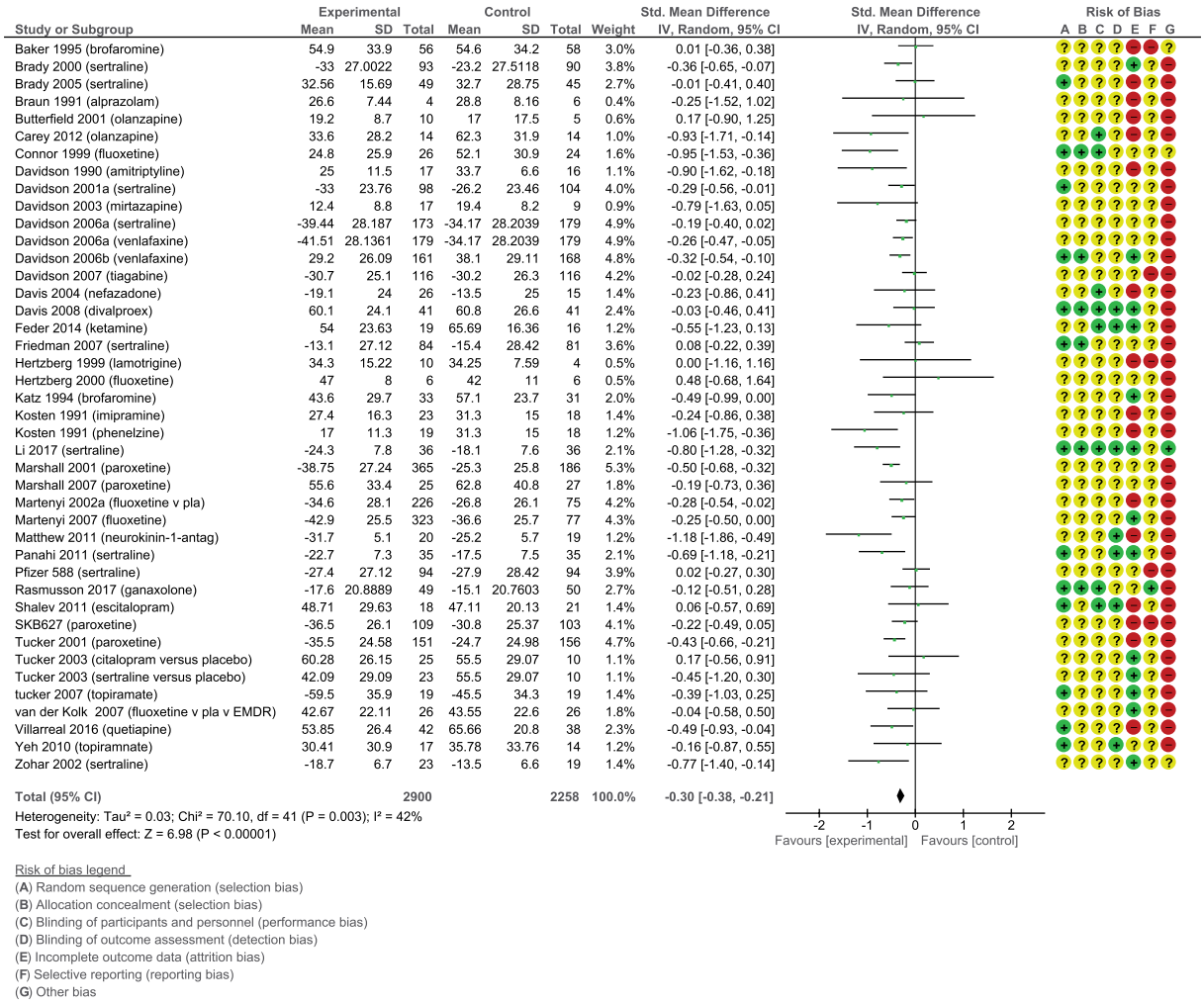

Figure 2. Any agent versus placebo.

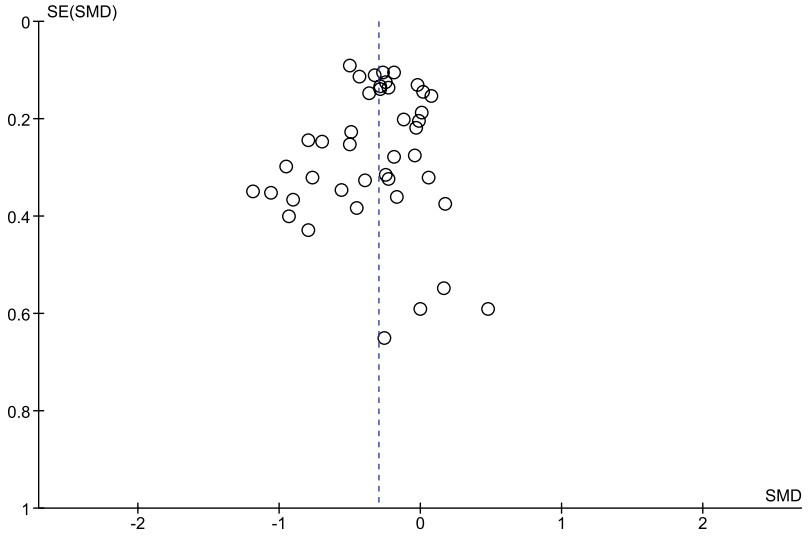

Figure 3. Funnel plot of all monotherapy studies.

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

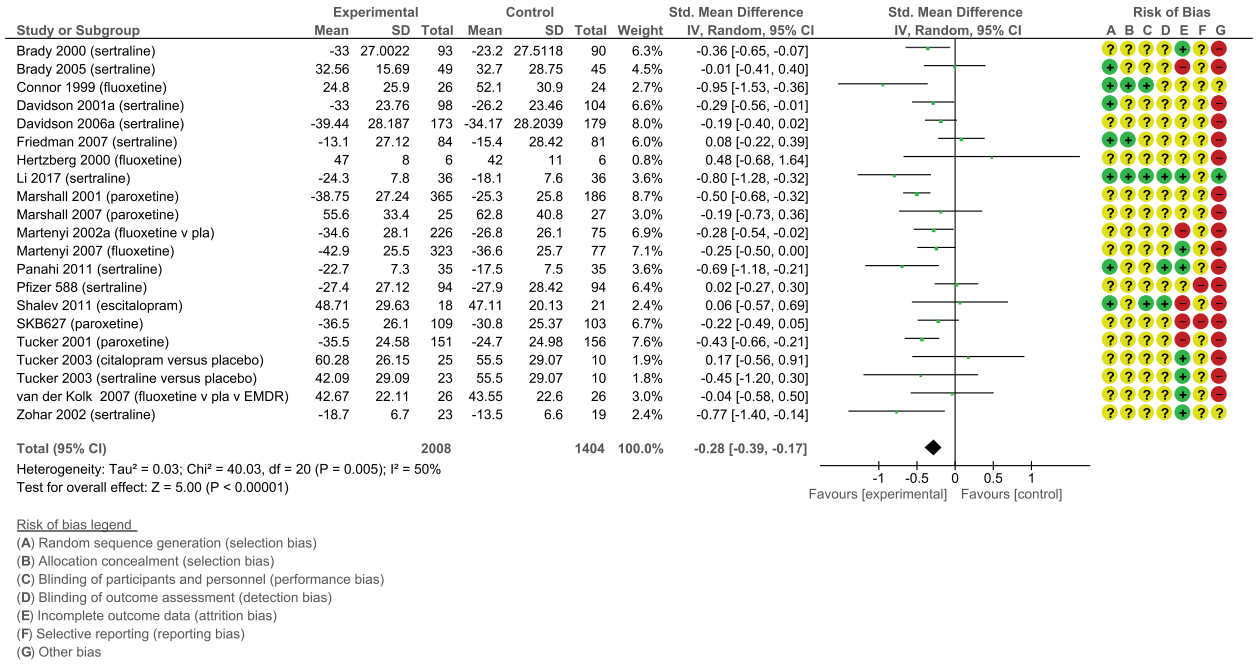

Figure 4. SSRIs versus placebo.

Table 2. Individual agents versus placebo.

Active drug	PTSD symptoms
SSRIs Paroxetine Fluoxetine Sertraline	Four studies (Marshall et al., 2001; Marshall et al., 2007; SKB627 et al., unpublished; Tucker et al., 2001), *n* = 1,122, SMD = −0.41 (95% CI −0.53 to −0.29) I^2 = 16% 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) I^2 = 46% 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; Pfizer588 – sertraline; Tucker et al., 2003; Zohar et al., 2002), *n* = 1,401, SMD = −0.28 (95% CI −0.45 to −0.10) I^2 = 57%
SNRIs Venlafaxine	Two studies (Davidson et al., 2006; Davidson et al., 2006), *n* = 687, SMD = −0.29 (95% CI −0.44 to −0.14) I^2 = 0%
MAOIs Brofaromine	Two studies (Baker et al., 1995; Katz et al., 1994), *n* = 159, SMD = −0.24 (95% CI −0.81 to 0.33) I^2 = 63%
Antipsychotics Olanzapine Quetiapine	Two studies (Butterfield et al., 2001; Carey et al., 2012), *n* = 43, SMD = −0.44 (95% CI −1.51 to 0.63) I^2 = 62% One study (Villarreal et al., 2016), *n* = 80, SMD = −0.49 (95% CI −0.93 to −0.04)
Other drugs Topiramate	Two studies (Tucker et al., 2007; Yeh et al., 2010), *n* = 69, SMD = −0.29 (95% CI −0.76 to 0.19) I^2 = 0%

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., 2000; 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 3. Characteristics of included augmentation studies.

Methods	Participants	Outcomes	Interventions	Notes	Risk of bias (low/unclear/high)						
					Sequence generation	Allocation concealment	Blinding participants/ personnel	Blinding outcome assessors	Incomplete outcome data	Free of selective reporting	Any other bias
Study ID: Ahmadpana 2014 Iran Study type: single centre, randomised, double blind, placebo controlled, three parallel arms Duration: 8 weeks	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	PSQI MINI	Group 1: Prazosin 1–15 mg ON (all participants remained on 15 mg after 10 days) *n* = 35 Group 2: Hydorxyzine 10–100 mg ON (all participants remained on 100 mg after 10 days) *N* = 35 Group 3: Placebo *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.	Low	Unclear	Low	Unclear	Low	Unclear	Low
Study ID: Akuchekian 2004 Iran Study type: single centre, outpatient, randomised, double blind, placebo controlled, parallel group, flexible dose Duration: 12 weeks	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 Group 2: Placebo *n* = 33	'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.	Unclear	Unclear	Low	Unclear	Low	Unclear	Unclear
Study ID: Attari 2014 Iran Study type: Single centre, outpatient, randomised, double blind, crossover, fixed dose Duration: 11 weeks	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 Group 2: Placebo *n* = 32 First period – 4 weeks Crossover washout – 2 weeks Second period – 4 weeks	CAPS was performed at baseline and treatment endpoints but only a subscale was repoted. 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	Low	Low	Low	Low	Low	High	Low
Study ID: Baniasadi 2014 Iran Study type: Single centre, inpatient, randomised, double blind, placebo controlled, fixed dose, parallel group Duration: 6 weeks	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 HAM-D HAM-A SQLI	Group 1: Pregabalin 300 mg *n* = 18 Group 2: Placebo *n* = 19	Poorly reported study, with no descriptions that can aid ROB assessment 'All patients recruited into the study were treated with SSRIs (citalopram 20–40 mg/ day or sertraline 50–200 mg/day) and sodium valproate (1000–1800 mg/day) for at least 1 month.'	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High

(*Continued*)

Table 3. (Continued).

Methods	Participants	Outcomes	Interventions	Notes	Risk of bias (low/unclear/high)						
					Sequence generation	Allocation concealment	Blinding participants/ personnel	Blinding outcome assessors	Incomplete outcome data	Free of selective reporting	Any other bias
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 *n* = 33 Group 2: Placebo *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, paralel 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 Group 2: Placebo *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	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 PANSS PSQI CGI-I	Group 1: Bupropion SR 100–150 mg BD max 300 mg daily (mean dose 180 mg) *n* = 18 Group 2: Placebo *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 Group 2: Behavioural Sleep Intervention *n* = 17 Group 3: Placebo *n* = 16	13/18 in prazosin group and 9/16 in placebo had PTSD	Unclear	Unclear	Low	Unclear	High	Unclear	High

(*Continued*)

Table 3. (Continued).

Methods	Participants	Outcomes	Interventions	Notes	Risk of bias (low/unclear/high)						
					Sequence generation	Allocation concealment	Blinding participants/ personnel	Blinding outcome assessors	Incomplete outcome data	Free of selective reporting	Any other bias
Study ID: Golier 2012 USA Study type: Single centre, outpatient, randomised, double blind, placebo controlled, fixed dose, parallel arm Duration: 1 week	N = 9 Mean age: 48.8 years Sex: 100% male Diagnosis: DSM-IV Predominant trauma type: combat Mean duration of Sx: "chronic)	CAPS PCL BDI Neuroendocrine variable	Group 1: mifepristone 600 mg *n* = 4 Group 2: Placebo *n* = 4	No description of primary pharmacotherapy No description of single dropout (group or reason) – potential for reporting bias in such a small study	Low	Low	Low	Unclear	High	Low	High
Study ID: Hamner 2003 USA Study type: Single centre, outpatient, randomised, placebo controlled, flexible dose, parallel arm Duration: 5 weeks	N = 40 Mean age: 52 years Sex: 100% male Diagnosis: DSM-IV and current psychosis Predominant trauma type: combat Mean duration of Sx: 'chronic'	CAPS PANSS HAM-D	Group 1: Risperidone 1–6 mg (mean 2.5 ± 1.25 mg) *n* = 20 Group 2: Placebo *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	Unclear	Unclear	Low	Unclear	High
Study ID: Hamner 2009 USA Study type: Single centre, randomised, double blind, placebo controlled, parallel arm, flexible dose Duration: 10 weeks	N = 29 Mean age: 52.3 years Sex: 3% female Diagnosis: DSM-IV Predominant trauma type: combat Mean duration of Sx: unknown	CAPS CGI HAM-D IES LSAC PSQI	Group 1: Divalproex 500–1500 mg (mean dose 1196 mg) *n* = 16 Group 2: Placebo *n* = 13	Industry support for lead author	Unclear	Unclear	Low	Unclear	High	Unclear	High
Study ID: Heresco-Levy Israel Study type: Single centre, randomised, double blind, placebo controlled, crossover, fixed dose Duration: 12 weeks	N = 11 Mean age: 38.5 years Sex: 18% female Diagnosis: DSM-IV Predominant trauma type: mixed Mean duration of Sx: 7.7 years	CAPS Wisconsin Card Sorting Test	Group 1: d-cycloserine 25 mg BD *n* = Group 2: Placebo *n* = First period: 4 weeks Crossover washout: 2 weeks Second period: 4 weeks	Insufficient data reported	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High

(*Continued*)

Table 3. (Continued).

Methods	Participants	Outcomes	Interventions	Notes	Risk of bias (low/unclear/high)						
					Sequence generation	Allocation concealment	Blinding participants/ personnel	Blinding outcome assessors	Incomplete outcome data	Free of selective reporting	Any other bias
Study ID: Jetly 2015 Canada Study type: Single centre, outpatient, randomised, double blind, placebo controlled, crossover, flexible dose Duration: 16 weeks	N = 10 Mean age: 43.6 years Sex: 100% male Diagnosis: DSM-IV Predominant trauma type: combat Mean duration of Sx: unknown	CAPS CGI-C GWBQ	Group 1: nabilone 0.5–3 mg (mean 1.95 mg) *n* = 10 Group 2: Placebo *n* = 9 First period – 7 weeks Crossover washout – 2 weeks Second period – 7 weeks	'subjects were allowed to continue any other medicationsand psychotherapy present at time of study entry. If on anantidepressant, subjects were required to be on a stabledose for at least four weeks prior to study entry.'	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
Study ID: Krystal 2011 USA Study type: Multicentre, outpatient, randomised, double blind, placebo controlled, parallel group, flexible dose Duration: 24 weeks	N = 296 Mean age: 54.4 years Sex: 3.6% female Diagnosis: DSM-IV Predominant trauma type: combat Mean duration of Sx: un known		Group 1: Risperidone 1–4 mg (mean dose 2.74 mg) *n* = 147 Group 2: Placebo *n* = 149	100% treatment resistance, defined as 'a clinical history of intolerance of or nonresponse to 2 or more antidepressants, and had an inadequate response to 2 adequate SRI treatments (minimum of 4 weeks of pharmacotherapy each)' Industry supported	Low	Low	Low	Low	High	Low	High
Study ID: Lindley 2007 USA Study type: Single centre, randomised, double blind, placebo controlled, parallel group, flexible dose Duration: 7 weeks	N = 40 Mean age: 53.4 years Sex: 100% male Diagnosis: DSM-IV Predominant trauma type: combat Mean duration of Sx: unknown	CAPS BDI CGI-S	Group 1: topiramate 50–200 mg *n* = 20 Group 2: Placebo *n* = 20	Insufficient data reported	Unclear	Unclear	Unclear	Unclear	High	High	High
Study ID: Ludascher 2015 Germany Study type: Single centre, inpatient, randomised, double blind, placebo controlled, crossover, fixed dose Duration: 4 weeks	N = 30 Mean age: 30.7 years Sex: 100% female Diagnosis: DSM- Predominant trauma type: childhood sexual abuse Mean duration of Sx: unknown	CAPS IES-R	Group 1: hydrocortisone (HC) 10–30 mg *n* = 15 Group 2: Placebo *n* = 15 Group 1: HC 30 mg 1 week placebo 1 week HC 10 mg 1 week placebo 1 week Group 2: placebo 1 week HC 10 mg 1 week placebo 1 week HC 30 mg 1 week	Insufficient data reported	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear

(*Continued*)

Table 3. (Continued).

Methods	Participants	Outcomes	Interventions	Notes	Risk of bias (low/unclear/high)						
					Sequence generation	Allocation concealment	Blinding participants/ personnel	Blinding outcome assessors	Incomplete outcome data	Free of selective reporting	Any other bias
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	High	High

(*Continued*)

Table 3. (Continued).

Methods	Participants	Outcomes	Interventions	Notes	Risk of bias (low/unclear/high)						
					Sequence generation	Allocation concealment	Blinding participants/ personnel	Blinding outcome assessors	Incomplete outcome data	Free of selective reporting	Any other bias
Study ID: Petrakis 2016 USA Study type: Multicentre, outpatient, randomised, double blind, placebo controlled, parallel arm, flexible dose Duration: 13 weeks	N = 96 Mean age: 44.5 years Sex: 100% male Diagnosis: DSM-IV PTSD and Alcohol Dependence Predominant trauma type: combat Mean duration of Sx: unknown	CAPS OCDS TLFB	Group 1: Prazosin 2–16 mg BD (mean dose 14.5 mg) *n* = 50 Group 2: Placebo *n* = 46	Lead author ties to industry	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
Study ID: Pollack 2011 USA Study type: Single centre, outpatient, randomised, double blind, placebo controlled, crossover, fixed dose Duration: 7	N = 27 Mean age: 42 years Sex: 70.8% female Diagnosis: DSM-IV PTSD and comorbid sleep disturbance Predominant trauma type: unknown Mean duration of Sx: 19 years	CAPS SPRI PSQI	Group 1: Eszopiclone 3 mg *n* = 24 Group 2: Placebo *n* = 24	Lead author ties to industry	Unclear	Unclear	Unclear	Unclear	Low	Low	High
Study ID: Ramaswamy 2015 USA Study type: Single centre, outpatient, randomised, double blind, placebo controlled, parallel arm, flexible dose Duration: 9	N = 30 Mean age: 38.9 years Sex: 87% female Diagnosis: DSM-IV PTSD and comorbid depression Predominant trauma type: unknown Mean duration of Sx: unknown	CAPS HAM-D HAM-A CGI TOPS	Group 1: Ziprasidone 20–80 mg BD (mean dose unknown) *n* = 15 Group 2: Placebo *n* = 15	Industry funded. Published 10 years after completion.	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Study ID: Raskind 2003 USA Study type: Single centre, outpatient, randomised, double blind, placebo controlled, crossover, flexible dose Duration: 20	N = 10 Mean age: 53 years Sex: 100% male Diagnosis: DSM-IV PTSD and severe trauma-related nightmares Predominant trauma type: combat Mean duration of Sx: 25 years	CAPS CGI-C	Group 1: Prazosin 1–10 mg divided dose (mean dose 9.5 mg) *n* = 5 Group 2: Placebo *n* = 5 First period – 9 weeks Crossover washout – 2 weeks Second period – 9 weeks	Very small study.	Unclear	Unclear	Unclear	Low	Low	Unclear	High

(*Continued*)

Table 3. (Continued).

Methods	Participants	Outcomes	Interventions	Notes	Risk of bias (low/unclear/high)						
					Sequence generation	Allocation concealment	Blinding participants/ personnel	Blinding outcome assessors	Incomplete outcome data	Free of selective reporting	Any other bias
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	Group 1: Prazosin 1–15 mg ON (mean dose 13.3 mg) *n* = 20 Group 2: Placebo *n* = 20	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 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 divided dose (mean daily dose 14.8 mg in men and 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 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*)

Table 3. (Continued).

Methods	Participants	Outcomes	Interventions	Notes	Risk of bias (low/unclear/high)						
					Sequence generation	Allocation concealment	Blinding participants/ personnel	Blinding outcome assessors	Incomplete outcome data	Free of selective reporting	Any other bias
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	Unclear	Unclear	Unclear	Unclear	High	Unclear	High
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 QLESQ SF12 PSQI	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	Low	Low	Low	Low	High	High	Low
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	PSS-I PACS PCL-C	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	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	Unclear	Unclear	Unclear	Unclear	Low	Low	Low

(*Continued*)

Table 3. (Continued).

Methods	Participants	Outcomes	Interventions	Notes	Risk of bias (low/unclear/high)						
					Sequence generation	Allocation concealment	Blinding participants/ personnel	Blinding outcome assessors	Incomplete outcome data	Free of selective reporting	Any other bias
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	PDRS PCL-C CGI-I	Group 1: Prazosin 2–5 mg (mean dose 3.2 mg) *n* = Group 2: Placebo *n* = First period: 3 weeks Crossover washout: 1 week Second period: 3 weeks	All participants received ongoing psychotherapy, 8 were on sertraline, 2 on duloxetine, and 3 on alprazolam.	Unclear	Unclear	Low	Unclear	Low	Unclear	Unclear
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	CAPS PSQI	Group 1: Prazosin 2–5 mg ON (mean dose 3.2 mg) *n* = 13 Group 2: Placebo *n* = 13		Unclear	Unclear	Low	Unclear	Low	Unclear	Unclear

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[105], one study assessed venlafaxine

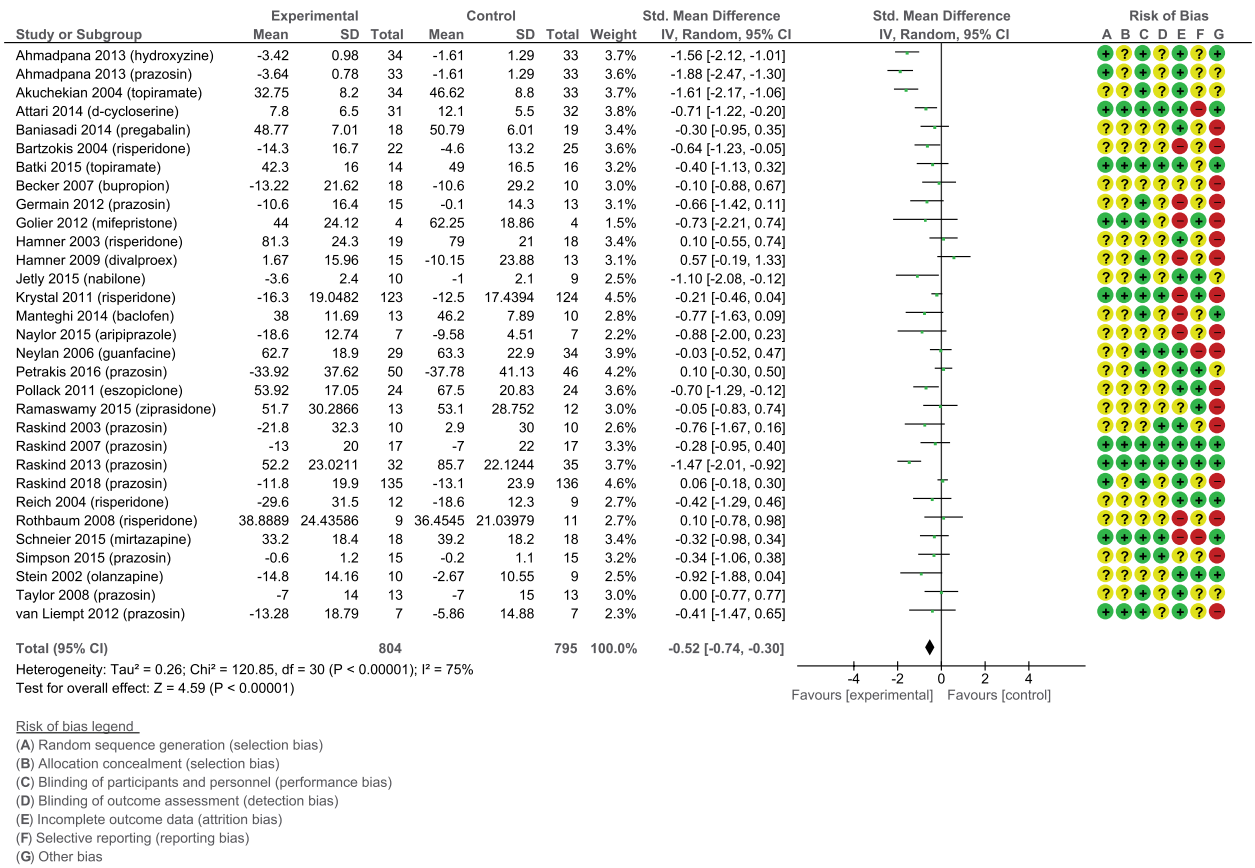

Figure 5. All agents versus placebo augmentation.

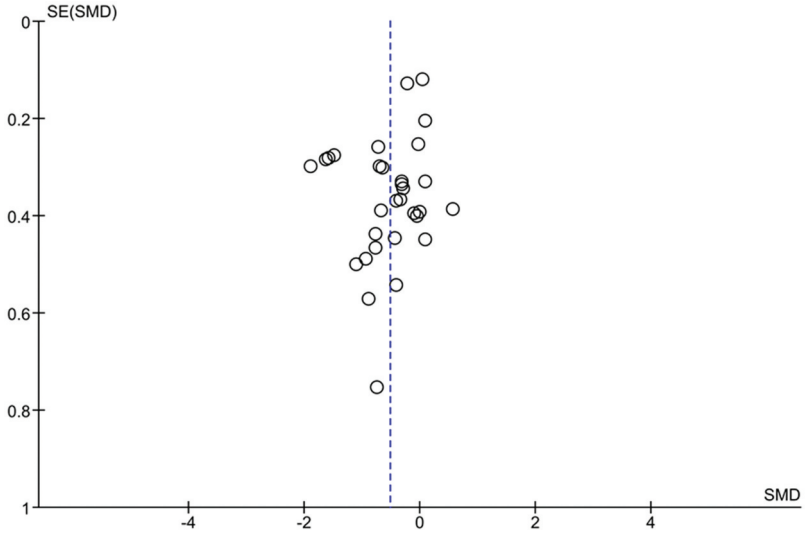

Figure 6. Funnel plot of augmentation studies.

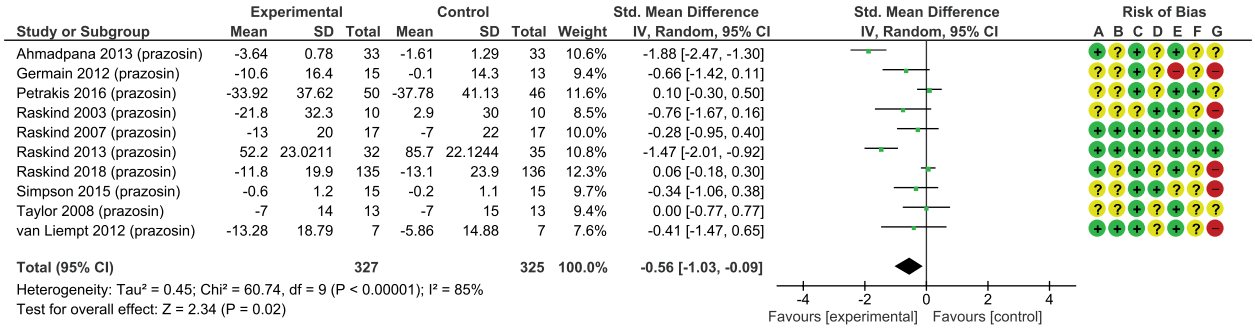

Figure 7. Prazosin versus placebo augmentation.

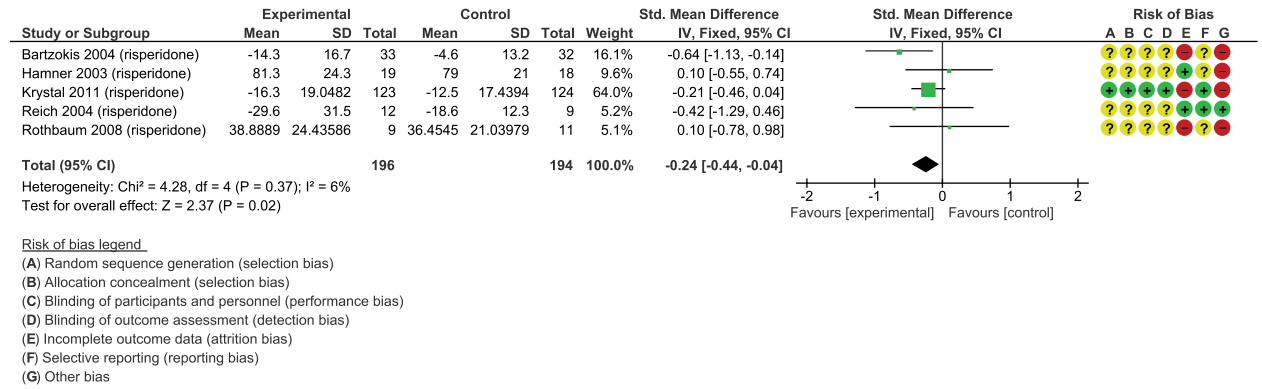

Figure 8. Risperidone versus placebo.

(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

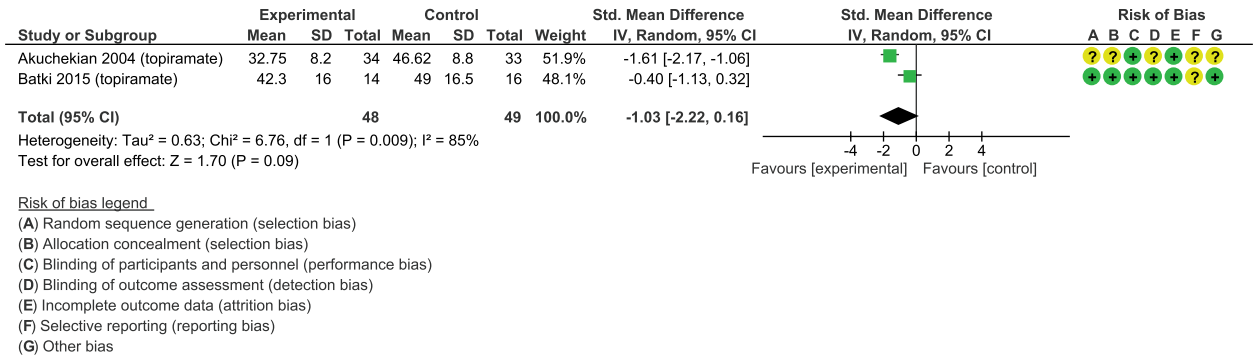

Figure 9. Topiramate versus placebo augmentation.

Table 4. Individual augmentation agents versus placebo.

Active drug	PTSD symptoms
Prazosin	10 studies (Ahmadpanah et al., 2014; Germain et al., 2012; Petrakis et al., 2016; Raskind et al., 2003; Raskind et al., 2007; Raskind et al., 2013; Raskind et al., 2018; Simpson et al., 2015; Taylor et al., 2008; Van Liempt et al., 2012), *n* = 652, SMD = −0.56, 95% CI = −1.03 to −0.09 I^2= 79%
Risperidone	Five studies (Bartzokis et al., 2005; Hamner et al., 2000; Krystal et al., 2011; Reich et al., 2004; Rothbaum et al., 2008), *n* = 390, SMD = −0.24, 95%CI = −0.44 to −0.04 I^2=0%
Topiramate	Twostudies (Akuchekian & Amanat, 2004; Batki et al., 2014)*n* = 97, SMD = −1.03, 95%CI = −2.22 to 0.16 I^2=83%
Eszopiclone	One study (Pollack et al., 2011), *n* = 48, SMD = −0.70, 95%CI = −1.29 to −0.12
D-Cycloserine	One study (Attari et al., 2014), *n* = 63, SMD = −0.71, 95% CI = −1.22 to −0.20

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.

					Risk of bias (low/unclear/high)						
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: 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 dose110.2 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	High

(*Continued*)

Table 5. (Continued).

Methods	Participants	Outcomes	Interventions	Notes	Risk of bias (low/unclear/high)						
					Sequence generation	Allocation concealment	Blinding participants/ personnel	Blinding outcome assessors	Incomplete outcome data	Free of selective reporting	Any other bias
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	CAPS HAM-D	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).	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	TOP-8 CGI-I CGI-S CGI-SE	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		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	CAPS TOP-8 HAM-D HAM-A	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	Insufficient data reported. Industry funded	Unclear	Unclear	Unclear	Unclear	High	Unclear	Unclear

(*Continued*)

Table 5. (Continued).

Methods	Participants	Outcomes	Interventions	Notes	Risk of bias (low/unclear/high)						
					Sequence generation	Allocation concealment	Blinding participants/ personnel	Blinding outcome assessors	Incomplete outcome data	Free of selective reporting	Any other bias
Study ID: Tucker 2003 USA Study type: Multicentre, randomised, double blind, parallel, placebo controlled, flexible dose Duration: 10 weeks	*N* = 59 Mean age: 38.5 years Sex: 72% female Diagnosis: DSM-IV Predominant trauma type: physical abuse/ assault Mean duration of Sx: unknown	CAPS IES BDI	Group 1: Citalopram 20–50 mg (36.2 mg) *n* = 25 Group 2: Sertraline 50–200 mg (134.1 mg) *n* = 23 Group 3: placebo *n* = 10	Industry funded							

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 MOAI 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.

					Risk of bias (low/unclear/high)						
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: Buhman 2018 Denmark Study type: Multicentre, pragmatic, randomised controlled trial with 2 × 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 HRSA SCL-90 VAS SDS WHO-5	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	54% of sessions were translated. 25% in therapy actually received exposure treatment. Additionally, 27% of the therapy group received another antidepressant.	Low	Low	High	Low	Unclear	Low	High
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.	Unclear	High	High	High	High	Unclear	High
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.	Unclear	High	High	Unclear	High	High	High
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 BDI-II	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.	Unclear	High	High	Low	High	Unclear	Low

(*Continued*)

Table 6. (Continued).

Methods	Participants	Outcomes	Interventions	Notes	Risk of bias (low/unclear/high)						
					Sequence generation	Allocation concealment	Blinding participants/ personnel	Blinding outcome assessors	Incomplete outcome data	Free of selective reporting	Any other bias
Study ID: van der Kolk 2007 USA Study type: Multicentre, randomised, three parallel arms, placebo-controlled, flexible dose Duration: 5 weeks	*N* = 59 Mean age: 34.9 years Sex: 86.4% female Diagnosis: DSM-IV Predominant trauma type: interpersonal victimisation Mean duration of Sx: 13.1 years	CAPS BDI	Group 1: Fluoxetine 20–60 mg (mean dose 40 mg) *n* = 30 Group 2: EMDR *n* = 29 Group 3: placebo *n* = 29	Authors affiliated with one of the interventions being tested	Unclear	Unclear	High	Unclear	Low	Unclear	High

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 benefitting 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

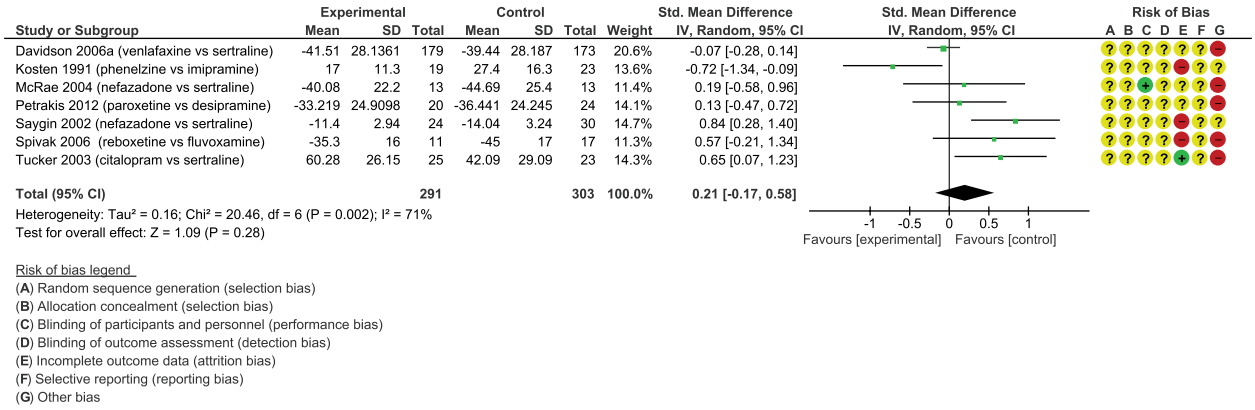

Figure 10. Pharmacotherapy versus pharmacotherapy.

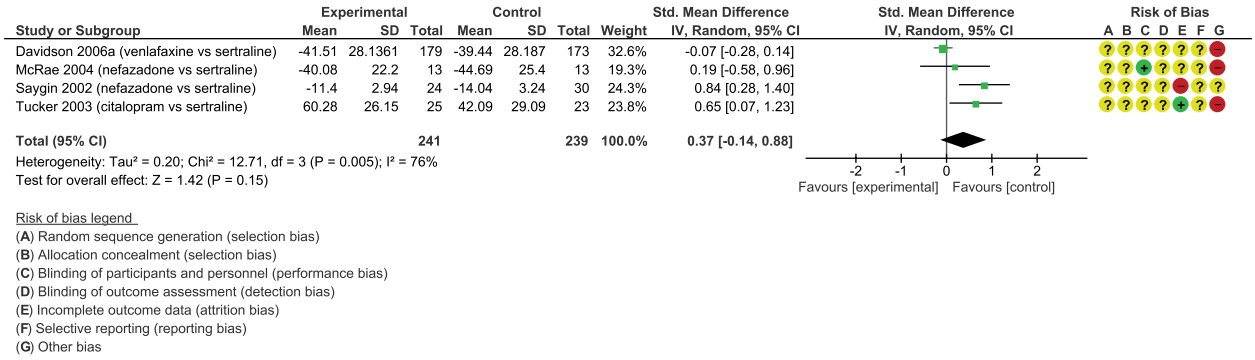

Figure 11. Pharmacotherapy versus sertraline.

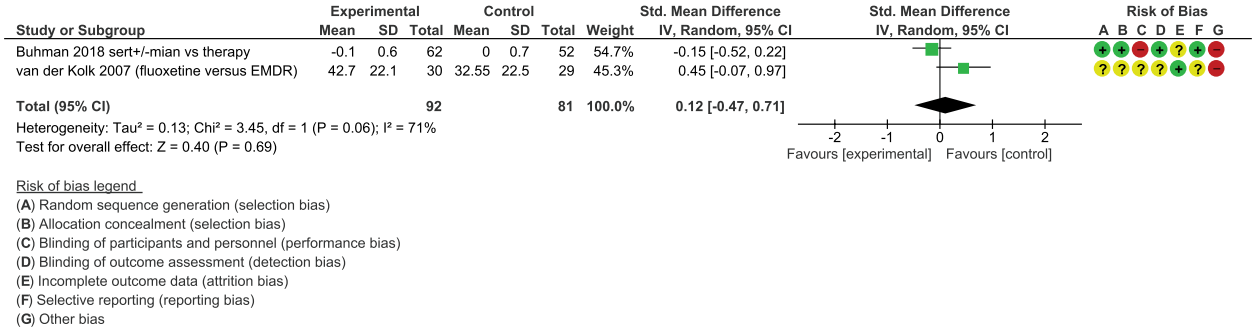

Figure 12. Pharmacotherapy versus psychological therapy.

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 benefitted 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-sided 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 benefitted 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 citalopram 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 placeboes and active comparator arms will further bolster the ability to perform hierarchical analysis of efficacy and tolerability via NMAs. 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.

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