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ROUND THE CORNER

Medication choice in post-traumatic stress disorder†

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SUMMARY

Post-traumatic stress disorder is a disabling condition resulting from a range of traumas and affecting many people worldwide. This month's Cochrane Corner review systematically searched and reported findings from 66 randomised controlled trials of pharmacotherapy for PTSD, 54 of which were included in a meta-analysis. Evidence was shown for the benefit of selective serotonin reuptake inhibitors, mirtazapine and amitriptyline in treatment response. This Round the Corner commentary critically appraises the review's findings, concluding that the summative evidence was of poor quality owing to the low number of studies, the high risk of bias and significant heterogeneity.

KEYWORDS

Post-traumatic stress disorder; pharmacology; statistical methodology; critical appraisal; trauma.

Post-traumatic stress disorder (PTSD) is a highly disabling condition, with recent estimates reporting a lifetime prevalence (Box 1) of 5.6% among trauma-exposed people worldwide (ranging from 0.5% to 14.5% between countries) (Koenen 2017a). The World Health Organization (WHO) further reported an age-standardised point prevalence of 15.3% specific to conflict settings (Charlson 2019).

PTSD can be associated with increased psychiatric comorbidities, including depression, anxiety, suicidality and substance misuse (Brady 2000; Debell 2014; Head 2016; Facer-Irwin 2019), and with higher risk of cardiovascular disease, type 2 diabetes, stroke, respiratory problems, pain and cancer (Buckley 2004; Kubzansky 2007; Possemato 2010; Asnaani 2014; Koenen 2017b). People with PTSD therefore have a high demand for specialised healthcare services. Furthermore, there is a significant economic burden. For example, Kessler (2000) showed a loss of 3.6 workdays/month (missing part or all of a workday or working less efficiently), with an annual productivity loss of $3 billion in the USA. More recent data have shown excess direct and indirect costs to be over $232 billion in 2018 in the USA (Davis 2022).

Given the impact, identifying effective pharmacotherapy for PTSD is vital, and this month's Cochrane Corner review (Williams 2022) offers beneficial guidance for clinicians. However, it is important that evidence from the literature is carefully analysed, as recommendations based on poor-quality evidence could have negative implications. This commentary intends to give a balanced view of the review, to further inform professionals on its usefulness in clinical practice.

What has been found before this?

National Institute for Health and Care Excellence (NICE) guidelines for PTSD recommend primarily psychological approaches, advising that drug therapy should not be used first line (NICE 2018a). When appropriate, selective serotonin reuptake inhibitors (SSRIs: sertraline and paroxetine) and venlafaxine are recommended. Antipsychotics can be considered in case of non-response or if arousal or psychotic symptoms are present. Some other studies reviewed for possible inclusion in the NICE guidelines also showed significant results for amitriptyline, imipramine, phenelzine, prazosin, hydroxyzine and eszopiclone (Davidson 1990; Kosten 1991; Raskind 2007; Pollack 2011; Ahmadpanah 2014). However, in these studies, the evidence base was found to be too small to be confident that the benefits were the true effects (NICE 2018b). Given the large impact of PTSD and the potential for effective pharmacological treatments, it is key to follow an evidenced-based treatment strategy to optimise recovery.

Previous reviews reported that SSRIs showed a small but significant effect size compared with placebo, especially fluoxetine, paroxetine, and venlafaxine (Hoskins 2015). Interestingly, no statistically significant evidence for sertraline, currently licensed for PTSD, was found. Others (Albucher 2002; Asnis 2004; Ipser 2012; Coventry 2020) also highlighted the promising therapeutic potential of venlafaxine, mirtazapine, nefazodone, trazodone, prazosin and antipsychotics.

This month's Cochrane Review (Williams 2022) is an update of previous versions (Stein 2000, 2006). The review authors acknowledge that several recent reviews have provided a helpful summary of pharmacotherapy for PTSD but they note that these had various methodological weaknesses. In the present review they therefore aimed

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BOX 1 What is prevalence?

Prevalence refers to the number/percentage of people with a disorder/risk factor/characteristic within a specific time period. It is calculated using the formula:

$$\text{Prevalence} = \frac{\text{No. of people in population/sample with disorder}}{\text{Total no. of people in population/sample}}$$

It is often reported using a percentage or number per 10 000/per 100 000.

Lifetime prevalence refers to the proportion of people who have ever had the disorder in their lifetime.

The point prevalence is the proportion of people who have the disorder at a specific time point.

The age-standardised prevalence allows a comparison of prevalence rates between populations, where the age ranges in the populations are different. For example, in a sample with an ageing population, the prevalence of a disease more common in older age would be higher than in a younger population group.

to assess the literature using improved methods and a systematic search strategy.

Is there a clear research question?

This Cochrane Review clearly specified its research question using the PICO model (patient, population or problem; intervention; comparison; outcome). Only randomised controlled trials (RCTs) were included. Participants included were diagnosed with PTSD (population). A PTSD diagnosis was 'as determined by the study author', with no mention of the specific diagnostic criteria used, symptom duration or severity, although these were then tabulated to look at their impact on the medication effect. No restrictions were made to exclude patients with comorbid disorders.

A wide range of medication was listed as the intervention. Polypharmacotherapy was allowed, but studies with participants undergoing psychotherapy were excluded. Interventions were compared with either placebo or another medication (comparison). There were no restrictions placed on timing, dosage or duration of treatment.

Primary outcomes focused on treatment efficacy, determined using the Clinical Global Impressions Scale – Improvement (CGI-I), and treatment tolerability (outcome). The review authors note that they chose the CGI-I because it is a widely used outcome measure in RCTs looking at PTSD and they therefore concluded that it was robust. There is little information given beyond this, and the reference (Davidson 1997) links to an article seemingly unrelated to the statement, so it is unclear what the evidence is for this.

It seems that the primary outcome measure (the CGI-I) is quite a simple, broad and generalised scale, whereas it might have been more helpful to have used a PTSD symptom-specific scale (such as the Clinically Administered PTSD Scale (CAPS), which they did use to assess the secondary outcome of PTSD symptom reduction). This would have perhaps fit better with the review's main objective, assessing the effects of medication in reducing PTSD symptoms. The review found that 36 of the 66 RCTs used the CGI-I (primary outcome) as their primary or secondary outcome whereas 47 of the 66 RCTs used the CAPS, indicating that perhaps the CAPS would have been better as a primary outcome measure as there were more data to examine. As the CGI-I is a subjective scale, there is likely to be an effect on the reliability and validity of this outcome measure.

This Round the Corner commentary will focus on the primary outcome of treatment efficacy, determined using the CGI-I; results for treatment tolerability and secondary outcomes will not be discussed in detail.

I used the PRISMA checklist (Box 2) to critically appraise this Cochrane Review.

How were the searches performed?

The review authors searched eight databases: the Cochrane Central Register of Controlled Trials, Cochrane Common Mental Disorders Controlled Trials Register, Embase, MEDLINE, PsycInfo, PTSDPubs Proquest, Clinicaltrials.gov and the WHO International Clinical Trials Registry Platform. As some lesser-known medications were also investigated, searches were performed for 'population only' (i.e. no search terms for interventions were included). These trials would probably have been missed otherwise – the search strategy was therefore evidence of good practice for trying to capture all the relevant literature. The review's appendix contains the search terms but does not mention whether searches were made in languages other than English, although this seems to be the case, as there was no language filter. The Cochrane Handbook (Higgins 2022: Box 1.5.a) states that removing language restrictions, which is what the authors seem to have done in this case, is not a good substitute for searching non-English databases.

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BOX 2 The PRISMA checklist

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist is an evidence-based list advising those writing systematic reviews and meta-analyses of the minimum information they need to include, to encourage transparency in reporting (Page 2021). The checklist can also be used to critically appraise reviews, as it goes through what it is necessary to report. Fig. 1 shows an example of the first page of the checklist (Page 2021). Most people are aware of PRISMA guidelines, but more for their use in PRISMA flowcharts (Fig. 2). A PRISMA flowchart is recommended for use in systematic reviews, documenting how many records were retrieved and each stage of the inclusion/exclusion process.

Relevant RCTs from across the world might have been overlooked as a result.

Assessment of publication/reporting bias was demonstrated through funnel plots, although this could only be calculated for SSRIs, as the calculation was dependent on having >10 trials. Risk of bias was assessed using the Cochrane risk of bias tool (Higgins 2011). Quality of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework (Schünemann 2013).

What did the results show?

In total, 66 RCTs were eligible for inclusion, with 54 included in the meta-analysis, involving 7442 individuals aged 18–82 years with PTSD. The review explained that six RCTs not included were small and of poor quality, with not enough information for the meta-analysis. The omission of these RCTs was documented to be unlikely to have had an impact on the results, although there does not seem to be any evidence that this was tested. It is not clear why a further six trials were excluded.

All articles were in English, perhaps suggesting that studies in other languages could not be found.

SSRIs had a statistically significant beneficial effect compared with placebo (RR = 0.66, 95% CI 0.59–0.74), from 8 studies with moderate-certainty evidence. The review found that 58% of the SSRI group responded, compared with 35% on placebo. Sertraline (RR = 0.68, 95% CI 0.56–0.81) and

PRISMA 2020 expanded checklist

Selection and topic	Item	Elements recommended for reporting
Title	1	- Identify the report as a systematic review in the title. - Report an informative title that provides key information about the main objective or question the review addresses (e.g. the population(s) and intervention(s) the review addresses). - Consider providing additional information in the title, such as the method of analysis used, the designs of included studies, or an indication that the review is an update of an existing review, or a continually updated ("living") systematic review.
Abstract	2	- Report an abstract addressing each item in the PRISMA 2020 for Abstracts checklist.
Introduction – Rationale	3	- Describe the current state of knowledge and its uncertainties. - Articulate why it is important to do the review. - If other systematic reviews addressing the same (or a largely similar) question are available, explain why the current review was considered necessary. If the review is an update or replication of a particular systematic review, indicate this and cite the previous review. - If the review examines the effects of interventions, also briefly describe how the intervention(s) examined might work. - If there is complexity in the intervention or context of its delivery (or both) (e.g. multi-component interventions, equity considerations), consider presenting a logic model to visually display the hypothesised relationship between intervention components and outcomes.
Introduction – Objectives	4	- Provide an explicit statement of all objective(s) or question(s) the review addresses, expressed in terms of a relevant question formulation framework. - If the purpose is to evaluate the effects of interventions, use the Population, Intervention, Comparator, Outcome (PICO) framework or one of its variants, to state the comparisons that will be made.
Methods – Eligibility criteria	5	- Specify all study characteristics used to decide whether a study was eligible for inclusion in the review, that is, components described in the PICO framework or one of its variants, and other characteristics, such as eligible study design(s) and setting(s), and minimum duration of follow-up. - Specify eligibility criteria with regard to report characteristics, such as year of dissemination, language, and report status (e.g. whether reports, such as unpublished manuscripts and conference abstracts, were eligible for inclusion). - Clearly indicate if studies were ineligible because the outcomes of interest were not measured, or ineligible because the results for the outcome of interest were not reported. - Specify any groups used in the synthesis (e.g. intervention, outcome and population groups) and link these to the comparisons specified in the objectives (item #4). - Consider providing rationales for any notable restrictions to study eligibility.

FIG 1 Example of a section of the PRISMA checklist (adapted from Page et al, 2021, licensed under CC BY 4.0).

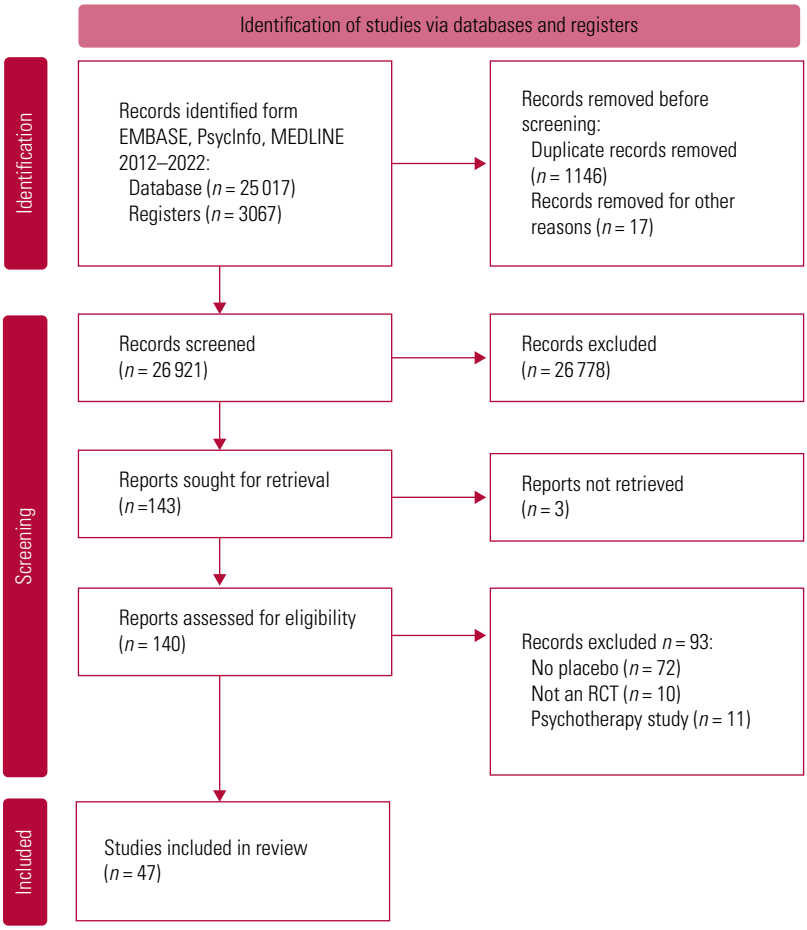

FIG 2 A mock PRISMA flowchart (created using the template in Page et al, 2021).

paroxetine (RR = 0.64, 95% CI 0.55–0.74) showed benefit, but not fluoxetine (RR = 0.73, 95% CI 0.19–2.82), possibly owing to the small sample size (65 participants).

Positive results were also found for mirtazapine (RR = 0.45, 95% CI 0.22–0.94, 1 study), with 65% response versus 22% for placebo (low-certainty evidence), and for amitriptyline (RR = 0.60, 95% CI 0.38–0.96, 1 study), with 50% response versus 17% for placebo (low-certainty evidence).

No benefit was found for antipsychotics (RR = 0.51, 95% CI 0.16–1.67, 2 studies), anticonvulsants, GR205171, GSK561679 and brofaromine. No studies could be found that used the CGI-I as an outcome measure for venlafaxine or other included medications. The review also looked at the total effect of medications compared with placebo across all medication classes, showing a benefit (RR = 0.74, 95% CI 0.64–0.85).

In total, 17 comparisons with placebo were performed between medication classes, ranging from those currently recommended, such as SSRIs (NICE 2018a), to lesser-known drugs, such as NK-1 receptor antagonists. Results suggested there was no evidence that most of the listed medications improved treatment efficacy. The strength of these conclusions was limited by the low quality of available evidence.

Sixteen studies were measured as being at high risk for at least one type of bias (Box 3); most studies had an unclear risk of bias. High/unclear risk of bias was related to studies that did not describe satisfactory randomisation (44 trials), allocation concealment (53 trials), participant masking (57 studies) and assessor masking (53 trials) – the most crucial domains in RCTs. Other sources of bias included industry involvement, which left a significant number of studies ranked as unclear.

A high level of heterogeneity was also seen between RCTs (Box 4).

GRADE ratings suggested that most of the certainty of evidence was very low or low (Schünemann 2013).

Subgroup analysis showed evidence of better treatment response in trials including participants with major depressive disorder (22 trials clearly included such participants, seven did not and the rest were unclear). The review authors queried

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BOX 3 Risk of bias

Risk of bias can be assessed using the Cochrane risk of bias tool. This has guidelines that support the author in the assessment of each study, looking at different areas where bias could be introduced (Sterne 2019). In the current version (RoB 2) the areas evaluated are:

- randomisation (selection bias)
- allocation concealment (selection bias)
- masking ('blinding') of participants and staff (performance bias)
- masking ('blinding') of outcome assessment (detection bias)
- missing data (attrition bias)
- selective reporting (reporting bias)
- other bias.

Each area is given a ranking – low, unclear or high risk of bias – and the reasoning for the ranking is given.

Risk of bias assessments can be displayed in a chart for easier reading, as shown in Fig. 3.

whether this response was related to treating PTSD or depressive symptoms. There was also a non-significant between-group benefit on the CGI-I for trials that did not include war veterans compared with trials that did, perhaps because there was more treatment-resistance in the latter subgroup.

Thoughts on the results and review

This Cochrane Review showed a beneficial effect of SSRIs, mirtazapine and amitriptyline in treating PTSD. The review attempted to find high-quality evidence from RCTs, but it was difficult to assess the clinical significance of the results found, given the mostly unclear risk of bias for the included studies (due to lack of information within trials) and the certainty of evidence being 'very low' to 'moderate'.

Bias

Of the 66 trials, 16 were assessed as being at high risk of bias. However, one trial (Li 2017) showed that it was feasible to conduct a trial with a relatively low level of bias, with only one domain scoring as unclear (publication bias). Although SSRIs had the most studies, the majority were assessed as being at unclear risk of bias for randomisation, which has an impact on their internal validity.

It is unclear why the review authors used an archived version of the Cochrane Handbook and risk of bias tool (Higgins 2011), as the most recent version of the handbook is from February 2022 (Higgins 2022) and the RoB 2 was published in 2019 (Sterne 2019).

Heterogeneity

There was significant methodological and clinical heterogeneity between studies. No clear definition

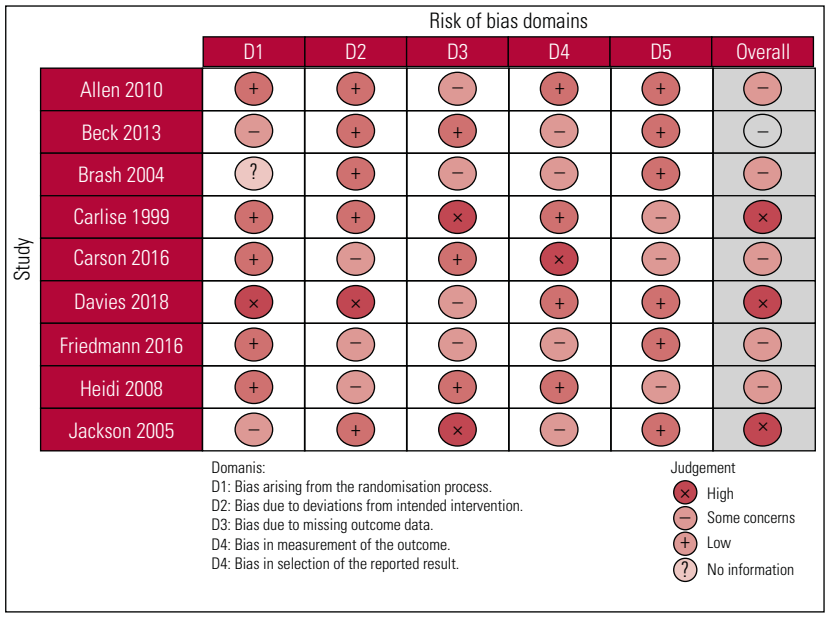

FIG 3 A mock risk of bias chart created using the Risk-of-bias VISualization (robvis) tool (robvis is described in McGuinness & Higgins, 2020).

BOX 4 Heterogeneity

It is impossible to complete clinical studies that are the same in their methods, population demographics and statistics. There will always be some level of variability between studies. The measure of heterogeneity is the difference between studies not thought to be due to chance.

Heterogeneity is also demonstrated within the methods and statistical tests used. It is more difficult to compare two randomised controlled trials if one is double-blind and the other is not. In this review it seems that there was a lack of information on the level of masking ('blinding') and randomisation in the studies (Williams 2022).

Heterogeneity can be measured as a statistic. Confidence intervals are calculated for each study, and generally, if these do not cross, then there is evidence of heterogeneity. This can be seen visually on a forest plot and can be commented on using a χ^2-test and I^2-statistic. If the *P*-value of the χ^2-test is <0.1, then there is statistically significant heterogeneity between the studies. A high *P*-value is related to the low power of the χ^2-test when there are few studies or small sample size; heterogeneity can be missed when $P < 0.05$. When the number of studies is low, it is better to look at the I^2, a percentage giving an estimate of the level of variability due to heterogeneity rather than chance.

For example, a statistically significant χ^2-test *P*-value of 0.007 and an I^2 of 54% indicate that there may be substantial heterogeneity present.

was provided for a PTSD diagnosis, only that it was 'as determined by the study author'. The review authors may have done this to capture the widest number of studies. In individual studies, the diagnostic criteria used included the CAPS, MINI, DSM-III, DSM-III-R, DSM-IV and DSM-IV-TR. It would have been helpful to have a definitive guideline regarding a diagnosis of PTSD in this review, even if it was that participants met the relevant DSM diagnostic criteria at the time of the study. The phrase 'as determined by the study author' leaves a lot of questions. The non-specific definition gives rise to possible problems with the review's findings: participants in the various studies might have varied significantly in symptom severity, dose and treatment resistance, thus affecting treatment efficacy. The review authors mentioned they did 'tabulate' the differences in clinical features between participants, but they did not include an analysis looking into whether these clinical characteristics had any effect on response.

To highlight some of the variety in clinical factors: treatment length varied between 13 days and 28 weeks; the mean age ranged from 27.9 to 59.8 years; sample sizes ranged from 12 to 551 participants; and follow-up ranged from 2 weeks to 6 months. There were no comparisons made for duration of illness, and no subgroup analysis looking at the possible heterogeneity between these clinical factors. It is unclear whether this would have made a difference to the findings.

Subgroup analysis was conducted to examine the effect of heterogeneity between single versus multicentre trials – results indicating low or no heterogeneity. The analysis also assessed the differences between trials including and excluding participants with depression, showing an I^2 of 61.1%. This indicates possible substantial heterogeneity, although this statistic needs to be interpreted with caution because only one small trial was available in this subgroup, responsible for all of the heterogeneity.

Eligibility criteria

Many of the RCTs excluded participants with substance misuse or physical health problems, common comorbidities in PTSD, thus reducing the generalisability of the results. The review authors could have explored this in a subgroup analysis – the impact of comorbid physical health conditions on response.

There was further variability among study inclusion and exclusion criteria, some including participants with sleep disorders, some excluding women of childbearing potential if they did not use contraception, and whether participants could be on other medication. Some studies included participants having ongoing psychotherapy, which was in contradiction to the exclusion criteria for the review, which specified that those receiving psychological therapy should be excluded.

Lack of studies

The review authors intended to investigate a large range of medications, but most medications had only one or no trials to draw data from, leaving the results for these non-significant, biased or absent.

Surprisingly, no studies were found on the efficacy of venlafaxine as determined by the CGI-I (primary outcome), despite it being recommended by NICE (NICE 2018a). Two venlafaxine studies were found that used the CAPS to measure the secondary outcome of PTSD symptom reduction. This shows that perhaps the secondary outcome of change in symptom severity may have been more suitable as the primary outcome, as there seemed to be more data.

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The SSRI group had the most studies, but for the primary outcome, this only included eight studies. Despite SSRIs being reported to be superior, some studies showed no difference in reduction of PTSD symptoms.

Mirtazapine and amitriptyline each had only one study, but the review authors were transparent about the paucity of evidence, making it clear in the abstract.

Funding of the trials

A relevant aspect is that 35 of the 66 identified RCTS (53%) were industry-funded, potentially increasing the risk of sponsorship bias – a common problem with pharmacotherapy trials. A larger reduction in PTSD symptom scores in industry-funded studies was observed, with potential implications for the reliability of these results. However, when you look at the CGI-I, although there was an improvement in symptoms in both groups, the differences between the groups were not statistically significant, perhaps indicating that again symptom severity scores would have been more valid.

What conclusions can we make?

This review concluded that SSRIs have the most evidence of benefit in the treatment of PTSD, in line with previous reviews and guidelines (Albucher 2002; Asnis 2004; Ipser 2012; Hoskins 2015, 2021; American Psychological Association 2017; NICE 2018a; Coventry 2020). These guidelines also mention several other helpful medications, including venlafaxine and antipsychotics, that were found in the secondary outcomes of this review. The review also found positive evidence for mirtazapine and amitriptyline.

The high level of heterogeneity between studies and low quality of data, with mostly low certainty and generally unclear risk of bias, makes it difficult to reach any definitive conclusions. Further RCTs with lower risk of bias, improved study design and involving a more generalisable population are therefore needed.

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Declaration of interest

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References

Ahmadpanah M, Sabzeiee P, Hosseini SM, et al (2014) Comparing the effect of prazosin and hydroxyzine on sleep quality in patients suffering from posttraumatic stress disorder. *Neuropsychobiology*, **69**: 235–42.

Albucher R, Liberzon I (2002) Psychopharmacological treatment in PTSD: a critical review. *Journal of Psychiatric Research*, **36**(6): 355–67.

American Psychological Association (2017) *Clinical Practice Guideline for the Treatment of Posttraumatic Stress Disorder*. APA.

Asnaani A, Reddy M, Shea M (2014) The impact of PTSD symptoms on physical and mental health functioning in returning veterans. *Journal of Anxiety Disorders*, **28**: 310–7.

Asnis G, Kohn S, Henderson M, et al (2004) SSRIs versus non-SSRIs in post-traumatic stress disorder – an update with recommendations. *Drugs*, **64**: 383–404.

Brady K, Killeen T, Brewerton T, et al (2000) Comorbidity of psychiatric disorders and posttraumatic stress disorder. *Journal of Clinical Psychiatry*, **61**(suppl 7): 22–32.

Buckley T, Mozley SL, Bedard MA, et al (2004) Preventive health behaviors, health-risk behaviors, physical morbidity, and health-related role functioning impairment in veterans with post-traumatic stress disorder. *Military Medicine*, **169**: 536–40.

Charlson F, van Ommeren M, Flaxman A, et al (2019) New WHO prevalence estimates of mental disorders in conflict settings: a systematic review and meta-analysis. *Lancet*, **394**: 240–8.

Coventry P, Meader N, Melton H, et al (2020) Psychological and pharmacological interventions for posttraumatic stress disorder and comorbid mental health problems following complex traumatic events: Systematic review and component network meta-analysis. *PLoS Medicine*, **17**(8): e1003262.

Davidson J, Kudler H, Smith R, et al (1990) Treatment of posttraumatic stress disorder with amitriptyline and placebo. *Archives of General Psychiatry*, **47**: 259–66.

Davidson J (1997) Biological therapies for posttraumatic stress disorder: an overview. *Journal of Clinical Psychiatry*, **58**(suppl 9): 29–32.

Davis LL, Schein J, Cloutier M, et al (2022) The economic burden of posttraumatic stress disorder in the United States from a societal perspective. *Journal of Clinical Psychiatry*, **83**(3): e1–10.

Debell F, Fear NT, Head M, et al (2014) A systematic review of the comorbidity between PTSD and alcohol misuse. *Social Psychiatry and Psychiatric Epidemiology*, **49**: 1401–25.

Facer-Irwin E, Blackwood NJ, Bird A, et al (2019) PTSD in prison settings: a systematic review and meta-analysis of comorbid mental disorders and problematic behaviours. *PLoS One*, **14**(9): e0222407.

Head M, Goodwin L, Debell F, et al (2016) Post-traumatic stress disorder and alcohol misuse: comorbidity in UK military personnel. *Social Psychiatry and Psychiatric Epidemiology*, **51**: 1171–80.

Higgins JPT, Altman DG, Sterne JAC (2011) Assessing risk of bias in included studies. In *Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0* (eds JPT Higgins, S Green): Ch. 8. Cochrane Collaboration (https://handbook-5-1.cochrane.org/).

Higgins J, Thomas J (eds) (2022) *Cochrane Handbook for Systematic Reviews of Interventions, Version 6.3*. Cochrane Collaboration.

Hoskins M, Pearce J, Bethell A, et al (2015) Pharmacotherapy for post-traumatic stress disorder: Systematic review and meta-analysis. *British Journal of Psychiatry*, **206**: 93–100.

Hoskins M, Bridges J, Sinnerton R, et al (2021) Pharmacological therapy for post-traumatic stress disorder: a systematic review and meta-analysis of monotherapy, augmentation and head-to-head approaches. *European Journal of Psychotraumatology*, **12**(1): 1802920.

Ipser J, Stein D (2012) Evidence-based pharmacotherapy of post-traumatic stress disorder (PTSD). *International Journal of Neuropsychopharmacology*, **15**: 825–40.

Kessler R (2000) Posttraumatic stress disorder: the burden to the individual and to society. *Journal of Clinical Psychiatry*, **61**(suppl 5): 4–12.

Koenen KC, Ratanatharathorn A, Ng L, et al (2017a) Posttraumatic stress disorder in the World Mental Health Surveys. *Psychological Medicine*, **47**: 2260–74.

Koenen KC, Sumner JA, Gilsanz P, et al (2017b) PTSD and cardiometabolic disease: improving causal inference to inform practice. *Psychological Medicine*, **47**: 209–25.

Kosten TR, Frank JB, Dan E, et al (1991) Pharmacotherapy for post-traumatic stress disorder using phenelzine or imipramine. *Journal of Nervous and Mental Disease*, **79**: 366–70.

Kubzansky LD, Koenen KC, Spiro A 3rd, et al (2007) Prospective study of posttraumatic stress disorder symptoms and coronary heart disease in the normative aging study. *Archives of General Psychiatry*, **64**: 109–16.

Li W, Ma YB, Yang Q, et al (2017) Effect and safety of sertraline for treat posttraumatic stress disorder: a multicenter randomised controlled study. *International Journal of Psychiatry in Clinical Practice*, **21**: 151–5.

McGuinness L, Higgins J (2020) Risk-of-bias VISualization (robvis): an R package and Shiny web app for visualizing risk-of-bias assessments. *Research Synthesis Methods*, **12**: 55–61.

National Institute for Health and Care Excellence (2018a) *Post-Traumatic Stress Disorder NICE Guideline NG116*. NICE.

National Institute for Health and Care Excellence (2018b) *Post-Traumatic Stress Disorder: Evidence Reviews for Pharmacological Interventions for the Prevention and Treatment of PTSD in Adults*. NICE.

Page MJ, McKenzie JE, Bossuyt PM, et al (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*, **372**: n71 (https://www.bmj.com/content/372/bmj.n71).

Pollack M, Hoge E, Wothington J, et al (2011) Eszopiclone for the treatment of posttraumatic stress disorder and associated insomnia: a randomized, double-blind, placebo-controlled trial. *Journal of Clinical Psychiatry*, **72**: 892–7.

Possemato K, Wade M, Andersen J, et al (2010) The impact of PTSD, depression, and substance use disorders on disease burden and health care utilization among OEF/OIF veterans. *Psychological Trauma Theory Research Practice and Policy*, **2**: 218–23.

Raskind MA, Peskind ER, Hoff DJ, et al (2007) A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. *Biological Psychiatry*, **61**: 928–34.

Schünemann H, Brożek J, Guyatt G, et al (2013) *GRADE Handbook*. Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.

Stein DJ, Zungu-Dirwayi N, van der Linden G, et al (2000) Pharmacotherapy for post traumatic stress disorder (PTSD). *Cochrane Database of Systematic Reviews* **4**: CD002795 (https://doi.org/10.1002/14651858.CD002795).

Stein DJ, Ipser JC, Seedat S (2006) Pharmacotherapy for post traumatic stress disorder (PTSD). *Cochrane Database of Systematic Reviews*, **1**: CD002795 (https://doi.org/10.1002/14651858.CD002795.pub2).

Sterne JAC, Savović J, Page MJ, et al (2019) RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*, **366**: l4898.

Williams T, Phillips N, Stein D, et al (2022) Pharmacotherapy for post traumatic stress disorder (PTSD). *Cochrane Database of Systematic Reviews* **3**: CD002795 (https://doi.org/10.1002/14651858.CD002795.pub3).