Pharmacotherapy for post-traumatic stress disorder: systematic review and meta-analysis

Mathew Hoskins, Jennifer Pearce, Andrew Bethell, Liliya Dankova, Corrado Barbui, Wietse A. Tol, Mark van Ommeren, Joop de Jong, Soraya Seedat, Hanhui Chen and Jonathan I. Bisson

Post-traumatic stress disorder (PTSD) is a common mental disorder with an estimated prevalence of 15.4% in the most robust epidemiological studies (those using diagnostic interviews and random samples) of conflict-affected populations, and a 12-month prevalence across the world of 3–4%. The disorder may occur in people of any age who have been exposed to one or more exceptionally threatening or horrifying events. Characteristic symptoms include re-experiencing, avoidance and hyperarousal. The disorder is associated with substantial comorbidity, such as depression, anxiety and substance misuse, and significant economic burden. Previous meta-analyses of pharmacological treatment of PTSD have been inconsistent. The UK’s National Institute for Health and Care Excellence (NICE) guidelines found that only paroxetine, mirtazapine, amitriptyline and phenelzine may be considered as potential treatments for the disorder. For most drugs there is inadequate evidence regarding efficacy for PTSD, pointing to the need for more research in this area.

Method
A systematic review and meta-analysis of randomised controlled trials was undertaken; 51 studies were included.

Results
Selective serotonin reuptake inhibitors were found to be statistically superior to placebo in reduction of PTSD symptoms but the effect size was small (standardised mean difference $-0.23$, 95% CI $-0.33$ to $-0.12$). For individual pharmacological agents compared with placebo in two or more trials, we found small statistically significant evidence of efficacy for fluoxetine, paroxetine and venlafaxine.

Conclusions
Some drugs have a small positive impact on PTSD symptoms and are acceptable. Fluoxetine, paroxetine and venlafaxine may be considered as potential treatments for the disorder. For most drugs there is inadequate evidence regarding efficacy for PTSD, pointing to the need for more research in this area.

Declaration of interest
None.

Aims
To determine the efficacy of all types of pharmacotherapy, as monotherapy, in reducing symptoms of PTSD, and to assess acceptability.

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Conclusions
Some drugs have a small positive impact on PTSD symptoms and are acceptable. Fluoxetine, paroxetine and venlafaxine may be considered as potential treatments for the disorder. For most drugs there is inadequate evidence regarding efficacy for PTSD, pointing to the need for more research in this area.

Declaration of interest
None.

Participants
All studies of participants with PTSD according to ICD or DSM criteria were eligible. There was no restriction on the basis of onset, duration or severity of PTSD symptoms, or on the presence of comorbid disorders, trauma type, age or gender of participants.
Interventions
Pharmacological treatments for adults with PTSD, in which the comparator was a placebo or other medication, were eligible for inclusion.

Outcome measures
The primary outcomes of interest were clinician-administered continuous measures of symptom severity such as the Clinician Administered PTSD Scale. Self-rated PTSD symptom scales were considered separately. The total number of participants who left the trial early for any reason was used as a proxy measure of treatment acceptability.

Search strategy
We conducted a primary bibliographic database search of Medline, Medline In Process, EMBASE, the Health Management Information Consortium (HMIC) database, PsychINFO, ASSIA and CINAHL using the Ovid interface on 22 February 2013. In order to avoid language bias, we separately searched (using the same search strategy, and in consultation with regional experts) the Japanese, Chinese and WHO regional databases (Spanish, Russian and Portuguese languages). This initial broad search was intended to identify not only the RCTs of interest but also reviews of pharmacotherapy for PTSD. The comprehensive search term used (see online Appendix DS1) was created by amalgamating the previous search strategies from the NICE, Cochrane and ACPMH guideline reviews with an updated list of medications. Additional searches for published and unpublished studies were made in the National Center for PTSD PILOTS database, the Cochrane Library, the Controlled Trials Register, Web of Knowledge, OpenSIGLE and Google Scholar. Reference lists of all selected studies and reviews were further scrutinised for any additional RCTs. An expert group was consulted to identify any additional studies they were aware of. Authors of identified studies were contacted to request data if outcome information was missing.

Study selection
One reviewer transferred the initial search hits and studies included in the earlier systematic reviews into EndNoteX4 software for Windows. Duplicates were removed. Two reviewers then independently screened the titles and abstracts. Studies that were clearly irrelevant were excluded; potentially relevant ones were assessed for inclusion as full texts. Any discrepancies between reviewers’ decisions were resolved by discussion with a third reviewer.

Data extraction and risk of bias assessment
All data from newly identified studies were double-extracted by two independent reviewers into a standardised table and any discrepancies were discussed with a third reviewer. Data for change from baseline to end-point were extracted when available, otherwise end-point data were used. 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. Dichotomous data were extracted for number of people withdrawing from the trial using total number of participants in the group as the denominator. One reviewer entered the outcome data into Review Manager 5 software for Windows, which was then checked by another reviewer. Data from studies included in previous systematic reviews were double-extracted by two independent reviewers, cross-checked for accuracy and any discrepancies were discussed with a third reviewer.

Risk of bias
Two reviewers, using the domain-based evaluation method recommended by the Cochrane Collaboration, independently assessed risk of bias in individual studies for each trial. This method considers the following domains: random sequence generation; allocation concealment; masking of participants and personnel; masking of outcome assessment; incomplete outcome data; selective reporting; and other sources of bias. Any discrepancies between reviewers’ decisions were resolved by discussion with a third reviewer. Risk of bias across studies was assessed by considering publication bias through the visual examination of funnel plots.

Statistical analysis
Review Manager 5 software was used to synthesise data using meta-analysis and to provide forest plots for dichotomous and continuous data. Confidence intervals of 95% were used for all analyses. Categorical outcome measures such as leaving the study early were analysed using relative risk (RR) calculations. For continuous data, standardised mean differences (SMD) were used. The degree of heterogeneity between studies was calculated using the I² statistic. Where this was less than 30%, indicating a mild degree of heterogeneity, a fixed effects model was used; a random effects model was used when I² was greater than 30%. Data were analysed from the intention to treat (ITT) sample in the ‘once randomised always analysed’ fashion where possible, to avoid effects of bias from completers-only analyses. Analyses were performed for individual drugs and, in order to maximise the information available from data synthesis, whenever possible for classes of drugs (e.g. tricyclic antidepressants, SSRIs) and trauma type (e.g. combat trauma, sexual trauma, interpersonal violence trauma, all non-combat trauma).

Results
The database search yielded 13 634 records and an additional 74 were identified from other sources. From these, 4613 duplicates were removed leaving 9095 records. These were screened and 8064 irrelevant studies were removed. This left 1031 abstracts from which 896 were removed as ineligible. This left 135 full-text articles which were reviewed to find 84 not meeting the inclusion criteria. A total of 51 studies were included in this systematic review (Fig. 1). Sixteen new studies were found from our database search.17–32 The remaining 35 were found in previous reviews. An additional 28 studies were identified from the NICE guidelines, of which five did not meet our inclusion criteria.33–37 This left 23 studies included from the NICE guidelines (references 38–54 plus six unpublished studies A–F in Appendix 1). Thirty-five studies were identified in the Cochrane review, of which 19 were already included in the NICE review and removed as duplicates. A further four used completer-only data and were not included;55–58 another allowed concomitant psychotropic medications and was excluded.59 This left an additional 11 studies from the Cochrane review,60–70 which were included. There were 12 additional pharmacotherapy studies identified from the ACPMH guidelines, of which seven were already present in the above reviews and were removed as duplicates. A further four did not meet our inclusion criteria,71–74 leaving one additional study which was included.75

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Efficacy of pharmacotherapy

Data from 21 studies (n = 3932) were available for inclusion in a meta-analysis of reduction in severity of PTSD symptoms for any SSRI vs. placebo (Fig. 2). This found a small positive effect for SSRIs when grouped together. The results of meta-analyses for individual drugs, which had been tested against placebo in at least two RCTs, are shown in Table 1. Three drugs were significantly superior to placebo on either clinician- and self-rated PTSD symptom severity combined (paroxetine) or clinician-rated PTSD symptom severity alone (fluoxetine and venlafaxine). We found insufficient evidence to support the preferential use of individual agents in either combat-related or non-combat-related trauma (Table 2).

Discussion

This systematic review found statistically significant evidence on meta-analysis for three pharmacological agents vs. placebo in the treatment of PTSD (fluoxetine, paroxetine and venlafaxine) but no evidence for brofaromine, olanzapine, sertraline or topiramate. Four drugs – amitriptyline, GR205171 (a neuropeptide-1 antagonist), mirtazapine and phenelzine – showed superiority over placebo in single RCTs, whereas eleven did not: alprazolam, citalopram, desipramine, escitalopram, imipramine, lamotrigine, nefazodone, risperidone, tiagabine and valproate semisodium. When meta-analyses were undertaken by class of drug rather than individual drug, SSRIs were found to perform better than placebo. The absence of sufficient data precluded meta-analyses of other drug classes. The absence of difference in numbers of individuals leaving the study early for any reason suggests that the drugs included were well tolerated overall.

The effect sizes for pharmacological treatments for PTSD compared with placebo are low and inferior to those reported for psychological treatments with a trauma focus over waiting-list or treatment as usual controls. They are, however, similar to those found for antidepressants for depression compared with placebo. Unfortunately, the absence of a common control condition and head-to-head pharmacological v. psychological treatment trials makes comparison of the relative efficacies of these treatment approaches difficult. This is compounded by the fact that a significant number of participants in psychological treatment trials were continuing pre-existing pharmacological treatment at the same time.

It is well accepted that a well-masked, placebo-controlled trial is a tougher test for an experimental intervention than a trial with a waiting-list control. The UK’s NICE guidelines development group attempted to address this by determining a higher effect size threshold for psychological treatments than pharmacological ones (0.8 v. 0.5), but it is unclear whether such arbitrary cut-offs may have introduced bias against either form of treatment. What is clear is the marked effect of the placebo in several of the trials reported in this review. For example, in the two venlafaxine studies the mean reduction in PTSD symptoms of those on placebo was greater than 40%. There is a need for RCTs of specific psychological interventions compared with an adequate non-specific psychological intervention. It is only through such trials and direct head-to-head comparisons that the relative effectiveness of differing treatment approaches could be established. The current meta-analyses are a later iteration of the sufficiently information to judge the masking of participants, personnel and outcome assessors as being of low risk. Incomplete outcome data were addressed adequately in 15 studies. Thirty-eight of the studies were deemed to be free from selective reporting.

Risk of bias assessments

Risk of bias assessments are included in online Table DS1. Seventeen of the studies included enough information on adequate random sequence generation to be judged as having a low risk of bias; the remainder were unclear. Only eight studies included an adequate description of allocation concealment. All 51 studies described themselves as ‘double blind’ but only eight provided
evidence used to determine what to recommend for recent WHO guidelines. A WHO guidelines development group examined this evidence and recommended antidepressants as a second line of treatment of PTSD when psychological interventions with known efficacy did not work or were not available. The recently updated Australian guidelines also concluded that pharmacological interventions should not be preferentially used as a routine first treatment of PTSD over trauma-focused psychological treatments. There are various other reasons for considering the prescription of antidepressants, including

### Table 1: Efficacy and tolerability of individual agents v. placebo

<table>
<thead>
<tr>
<th>Active drug</th>
<th>PTSD symptoms (clinician-rated)</th>
<th>PTSD symptoms (self-reported)</th>
<th>Leaning study early</th>
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</thead>
<tbody>
<tr>
<td><strong>SSRIs</strong></td>
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<tr>
<td>Paroxetine</td>
<td>Four studies, 30, 33, 34, 41 n = 1134</td>
<td>SMD = 0.43 (95% CI: 0.53 to -0.29)</td>
<td><strong>F</strong> = 0%</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Nine studies, 27, 38, 42, 43, 44, 45, 46, 47, 48 n = 1411</td>
<td>SMD = 0.13 (95% CI: 0.27 to 0.0)</td>
<td><strong>F</strong> = 37%</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Three studies, 23, 32, 34 n = 771</td>
<td>SMD = 0.24 (95% CI: 0.41 to -0.08)</td>
<td><strong>F</strong> = 0%</td>
</tr>
<tr>
<td><strong>MAOIs</strong></td>
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<tr>
<td>Brofaromine</td>
<td>Two studies, 43, 44 n = 159</td>
<td>SMD = -0.24 (95% CI: 0.81 to 0.33)</td>
<td><strong>F</strong> = 63%</td>
</tr>
<tr>
<td><strong>Other antidepressants</strong></td>
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<tr>
<td>Venlafaxine</td>
<td>Two studies, 14, a n = 68</td>
<td>SMD = 0.19 (95% CI: 0.4 to 0.01)</td>
<td><strong>F</strong> = 0%</td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
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<tr>
<td>Olanzapine</td>
<td>Two studies, 21, 32, 33, 34, 35, 36, 37, 38, 39 n = 67</td>
<td>SMD = 0.61 (95% CI: 1.27 to 0.05)</td>
<td><strong>F</strong> = 53%</td>
</tr>
<tr>
<td><strong>Other drugs</strong></td>
<td></td>
<td></td>
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<tr>
<td>Topiramate</td>
<td>Two studies, 27, 30, 31, 32, 33 n = 69</td>
<td>SMD = 0.56 (95% CI: 0.94 to 0.02)</td>
<td><strong>F</strong> = 0%</td>
</tr>
</tbody>
</table>

**MOA, monoamine oxidase inhibitor; NA, not applicable; PTSD, post-traumatic stress disorder; RR, relative risk; SMD, standardised mean difference; SSRI, selective serotonin reuptake inhibitor.**

*P < 0.05.
Pharmacotherapy for PTSD

concurrent depression, lack of availability of psychological treatments, failure to respond to or tolerate psychological treatments and the personal preference of the individual with PTSD.

The variation in efficacy between different agents is striking and could be explained by a number of factors. First, there may be real differences between drugs, even those in the same family. For example, paroxetine’s superior efficacy over sertraline may possibly be explained by its increased dopamine receptor activity. Differences in the pharmacology of phenelzine and brofaromine are also marked, and grouping all drugs in one class together seems less desirable than considering each one individually. This confirms previous observation that class membership does not confer the same level of efficacy in the treatment of PTSD.11 This meta-analysis supports this assertion, with the SSRIs paroxetine and sertraline, which suggests that power was not the issue. The same cannot be said for the majority of drugs reviewed, the evaluation of which was based on single RCTs with fewer than 100 participants. This review added 15 new RCTs to the evidence previously reported in systematic reviews but added no new trials for three of the four drugs recommended in the NICE guidelines (mirtazapine, amitriptyline and phenelzine). Of particular note is that new evidence resulted in drugs not recommended by NICE (fluoxetine and venlafaxine) now meeting the requirements laid down by NICE for recommendation as a second-line treatment. This review used particular rigour in assessing studies. Most of the other reviews that have concluded more favourably about pharmacotherapy grouped drugs from the same class together,10,11 which did not include unpublished studies,79,80 and adopted different inclusion criteria.8,10,79,80 This probably accounts for differences having the same raw data available. For example, sertraline performed significantly better than placebo in two recent meta-analyses,79,80 which did not include the two unpublished studies included in our review.10,11

Table 2 Trauma type subanalysis of individual agents v. placebo

<table>
<thead>
<tr>
<th>Active drug</th>
<th>Combat</th>
<th>Sexual</th>
<th>Interpersonal violence</th>
<th>Natural disaster/accident</th>
<th>All non-combat trauma combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRIs</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Paroxetine</td>
<td>NA</td>
<td>NA</td>
<td>One study,56 n = 52</td>
<td>One study,64 n = 52</td>
<td>One study,64 n = 52</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Four studies,71,72,73,74,75 n = 447</td>
<td>One study,76 n = 183</td>
<td>(95% CI -0.73 to 0.36)</td>
<td>(95% CI -0.73 to 0.36)</td>
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</tr>
<tr>
<td>Fluoxetine</td>
<td>Two studies,77,78 n = 313</td>
<td>Two studies,79,80 n = 458</td>
<td>(95% CI -0.10)</td>
<td>(95% CI -0.61 to 0.41)</td>
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<tr>
<td>MAOIs</td>
<td></td>
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<tr>
<td>Brofaromine</td>
<td>One study,81 n = 114</td>
<td>NA</td>
<td>One study,82 n = 55</td>
<td>One study,82 n = 55</td>
<td>NA</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>NA</td>
<td>NA</td>
<td>Two studies,83,84 n = 687</td>
<td>Two studies,83,84 n = 687</td>
<td>NA</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td></td>
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<tr>
<td>Olanzapine</td>
<td>One study,85 n = 11</td>
<td>One study,86 n = 28</td>
<td>One study,87 n = 39</td>
<td>One study,87 n = 39</td>
<td></td>
</tr>
<tr>
<td>Other drugs</td>
<td>Topiramate</td>
<td>One study,88 n = 38</td>
<td>One study,89 n = 32</td>
<td>One study,89 n = 32</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(95% CI -1.07 to 1.39)</td>
<td>(95% CI -1.71 to -0.14)*</td>
<td>(95% CI -0.94 to 0.02)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>0.16</td>
<td>0.93</td>
<td>0.61</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(95% CI -0.35 to -0.05)*</td>
<td>(95% CI -1.27 to 0.05)</td>
<td></td>
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<tr>
<td>Other non-</td>
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<td></td>
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</table>
| MAOIs, monoamine oxidase inhibitor; NA, not applicable; SMD, standardised mean difference; SSRIs, selective serotonin reuptake inhibitor. 

*P<0.05.

Study limitations

There were, however, some important methodological flaws in the studies identified in this review as illustrated by the risk of bias assessment undertaken. Clinical and statistical heterogeneity was apparent in the meta-analyses; this makes interpretation and generalisation across different trauma populations difficult. A major issue was that, despite having systematically tried to access unpublished data on the studies without ITT efficacy data, sufficient data for analysis were only available from only 41 of the 51 studies included. This raises the risk of outcome reporting bias.83 Incorrect definition of the ITT sample population was a
problem. This is an important principle where data from every person who is randomised should be included in the analysis of efficacy. Participants might leave a study because of adverse effects, failed efficacy or greater symptom severity at baseline; not including their data in the analysis leads to bias, as a treatment might appear to be more effective than it is. Another important issue to consider is that this review considers drug monotherapy as opposed to drug or placebo in combination with psychological treatment. This evidence cannot, therefore, be used to consider whether or not pharmacotherapy augments psychological treatment for PTSD; many people with the disorder do receive both.

Several of the new studies identified by our search defined their ITT population as participants who received at least one dose of the study medication and received at least one post-baseline assessment. This could exclude some participants from analysis who had received treatment but not been assessed after the baseline. The most extreme case was a study of fluoxetine that defined ITT in this way,23 but measured PTSD symptom severity only at baseline and end-point, so was actually a completers sample. We decided to include these studies in our analysis but acknowledge that this affects the reliability of the results.

Implications
Pharmacological interventions for PTSD can be effective but the magnitude of effect unfortunately is small, and the clinical relevance of this small effect is unclear. This review supports the use of paroxetine, venlafaxine and fluoxetine as pharmacological interventions for PTSD. For most drugs, there remains inadequate evidence regarding efficacy for PTSD, pointing to the need for more research in this area to confirm the utility of pharmacological treatments for this disorder.

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

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Appendix 1
Unpublished studies
Further details of the studies listed below are available from the authors.


