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Medication versus trauma-focused psychotherapy for adults with posttraumatic stress disorder: A systematic review and meta-analysis

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ABSTRACT

The goal of this study was to summarize evidence from head-to-head randomized trials for treatment of posttraumatic stress disorder (PTSD) in adults comparing trauma-focused psychotherapies and selective serotonin reuptake inhibitors (SSRIs) or serotonin/norepinephrine reuptake inhibitors (SNRIs) in a systematic review and meta-analysis. We conducted a search of multiple databases to identify trials comparing a trauma-focused psychotherapy (cognitive behavioral therapy, prolonged exposure, cognitive therapy, cognitive processing therapy or eye movement desensitization and reprocessing) to an SSRI or SNRI. Cochrane Risk of Bias 2.0 was used to assess risk of bias; high risk of bias trials were included only in sensitivity analyses. PTSD symptom reduction was the primary outcome. Four trials met inclusion criteria. Random effects meta-analysis of the two trials that were not high risk of bias showed no difference in PTSD symptom reduction, but a wide confidence interval, including effects favoring psychotherapy and effects favoring medication. Heterogeneity was high. Inclusion of the two high risk of bias trials did not change substantive conclusions. There is insufficient evidence to determine whether SSRIs or trauma-focused psychotherapies are more effective for PTSD symptom reduction among adults with PTSD.

1. Introduction

1.1. Rationale

Systematic reviews have shown that some selective serotonin reuptake inhibitors (SSRIs; paroxetine, sertraline and fluoxetine) and one serotonin norepinephrine reuptake inhibitor (SNRI), venlafaxine, are effective for the treatment of posttraumatic stress disorders (PTSD) among adults (Hoffman et al., 2018). Psychotherapies that are classified as trauma-focused have received the strongest evidence of effectiveness for treatment of PTSD (Hoffman et al., 2018) including cognitive-behavioral therapy, prolonged exposure therapy (Foa et al., 2019), cognitive therapy (Ehlers and Clark, 2000), cognitive processing therapy (Resick et al., 2016) and eye movement desensitization and reprocessing (EMDR; Shapiro, 2001). However, a key clinical question remains unanswered: which treatment class is more effective for adults with PTSD, psychotherapy or medication?

Most systematic reviews of PTSD treatments have focused exclusively on psychological treatments compared to controls, or pharmacological treatments compared to placebo, and have not included any trials comparing those two treatment modalities (Bisson et al., 2013; Cusack et al., 2016; Hoskins et al., 2015). Lee et al. (2016) explained that the goal of their systematic review was to compare the effectiveness of medications and psychotherapies for PTSD, but conclusions about comparative effectiveness were based solely on the relative magnitude of effect sizes in separate trials, and not on head-to-head trials comparing medication to psychotherapy.

A recently published meta-analysis assessed short-term (end-of-treatment) and long-term outcomes, comparing psychotherapy to medications for treatment of PTSD (Merz et al., 2019). However, in the primary analyses, that meta-analysis included a trial (Mithoefer et al., 2011) that used a non-standard medication (3,4-methylenedioxymethamphetamine, MDMA), for which there is insufficient evidence of efficacy compared to placebo, in the estimation of the group-effect of medications. It also estimated the long-term effect of medications based on three trials, two of which (comprising 75% of the participants) have been rated high risk of bias by a previous comprehensive systematic review of PTSD treatments (Hoffman et al., 2018). In addition, none of the medication trials included in the comparison of long-term effects of treatments required that participants continue taking medication over the long-term follow-up period. Thus, the long-term analyses compare a non-standard medication course of uncertain duration to a standard

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(typically 12-week) course of psychotherapy (Sonis and Cook, 2019). That is not a clinically relevant comparison because it is already known that, among patients with PTSD who respond to a short course of an SSRI, those who discontinue the SSRI are more likely to have symptom recurrence than those who maintain treatment long term (Batelaan et al., 2017).

Several guidelines for treatment of PTSD in adults (Department of Veterans Affairs and Department of Defense, 2017; National Institute for Health and Clinical Practice, 2018; Phoenix Australia-Centre for Posttraumatic Mental Health, 2013), though not all (American Psychological Association, 2017), have recommended that trauma-focused psychotherapies be used as first-line treatments, over any medication, for PTSD. This is based primarily on the fact that, in meta-analyses of PTSD treatments, the effect sizes for those psychotherapies compared to inactive treatments were substantially larger than the effect sizes for medications compared to placebos.

However, judgments about comparative effectiveness of psychotherapy and medications for PTSD treatment based on indirect comparisons of effect sizes from separate clinical trials can lead to faulty conclusions. This is due, in part, to differences in methodologic characteristics between psychotherapy trials and medication trials. One difference that can have a substantial impact on effect sizes is blinding. In psychotherapy trials, participants and clinicians administering the interventions cannot be blinded to the treatment condition, whereas in randomized trials of medications, they can be and usually are. In two meta-epidemiological studies (of 134 randomized trials with 31,321 research participants), the trials that had no or unclear blinding had, on average, standardized mean differences (SMDs) that were 0.37 greater than trials that had double-blinding of participants and clinicians for subjective outcomes (Page et al., 2016).

A second difference is that psychotherapy trials have often used wait-list controls, while medication trials have routinely used concurrent controls. A meta-epidemiological study of meta-analyses of adult psychiatric disorders found that psychotherapy trials that used wait-list controls reported effect sizes that were approximately twice as large as effect sizes from trials that used concurrent controls (Huhn et al., 2014). We calculated that, in a recent systematic review of treatments for PTSD, wait-list controls were used by 4 of 7 trials of cognitive processing therapy, 3 of 5 trials of cognitive therapy, 11 of 25 trials of prolonged exposure therapy, 16 of 31 trials of cognitive behavior therapy, and 6 of 10 trials of eye movement desensitization and reprocessing (Hoffman et al., 2018).

A third difference is average sample size. In a meta-epidemiological study including 13 meta-analyses, encompassing 153 randomized trials, studies with sample sizes less than 100 had effect sizes that were substantially larger (SMD 0.21, 95% CI, 0.08 to 0.34) than trials with sample sizes greater than 100 (Nuesch et al., 2010). We calculated that, in a recent meta-analysis of treatments for PTSD among adults, the median sample size for the 80 trauma-focused psychotherapy trials ($n = = 74$) was about half the median sample size ($n = = 169$) of the 19 trials of SSRI and SNRI medications (Hoffman et al., 2018).

Most importantly, in a systematic review of meta-analyses of psychotherapy and pharmacotherapy for adult mental disorders, Huhn (2014) showed that, for major depressive disorder, indirect comparison of effect sizes not only could, but actually would, lead to incorrect conclusions. The SMD for trials comparing psychotherapy to placebo or no treatment was 0.67, and the SMD for trials comparing antidepressants to placebo was 0.31, suggesting that psychotherapy had much stronger beneficial treatment effects than medications. However, head-to-head trials comparing psychotherapy to medications indicated no difference in effectiveness (SMD 0.05, 95% CI, −0.13 to 0.24; Huhn et al., 2014).

1.2. Objectives

To overcome the limitations of indirect comparison of effect sizes, we conducted a systematic review of head-to-head randomized trials comparing trauma-focused psychotherapies (i.e., those psychotherapies with the highest strength of evidence) to medications in the two classes (i.e., SSRI or SNRI antidepressants) with the best evidence of effectiveness for treatment of PTSD among adults. We sought to answer one question: Among adults with PTSD, what is the comparative effectiveness of trauma-focused psychotherapies and medications of either the SSRI or SNRI category, based only on head-to-head randomized trials?

2. Methods

2.1. Reporting

We followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines (Liberati et al., 2009) for reporting.

2.2. Eligibility

Inclusion and exclusion criteria for studies were developed using the PICOTS (**P**opulations, **I**ntervention, **C**omparator, **O**utcomes, **T**iming, **S**etting, **S**tudy design) framework, shown in online supplementary Table 1. We included randomized trials, published between 1/1/1980 and 12/31/2018, that compared one SSRI or SNRI medication to one trauma-focused psychotherapy (i.e., cognitive behavior therapy, prolonged exposure therapy, cognitive therapy, cognitive processing therapy, or eye movement desensitization and reprocessing) for treatment of adults with PTSD of any duration resulting from any type of trauma. We excluded trials that compared: (1) medication to placebo or psychotherapy to controls; (2) combinations of medications and psychotherapies to either treatment alone; (3) combinations of medications and psychotherapies. Studies that included a randomized comparison of an eligible medication and a trauma-focused psychotherapy, but did not report data for the randomized comparison separately from non-randomized comparison of medication and psychotherapy, were excluded. If a trial included more than two arms, but one treatment arm was an SSRI or SNRI, and a second arm was one of the eligible psychotherapies, that trial was included for inclusion of data from the medication / psychotherapy comparison.

2.3. Identification and selection of studies

We used two methods for identifying studies eligible for inclusion. First, we searched PubMed, PsycINFO, Cumulative Index of Nursing and Allied Health Literature (CINAHL) and PTSDpubs (the database sponsored by the U.S. Department of Veterans Affairs' National Center for PTSD), using a minor modification of the search strategy used by a recent comprehensive systematic review of PTSD treatments (Hoffman et al., 2018), with dates 1/1/1980 to 12/31/2018. Title, abstracts and, if necessary, full-text articles were reviewed to determine eligibility. The search strategy and hits identified at each stage are shown in the supplementary online Table 2. Second, we searched the bibliographies of studies that were eligible for inclusion, and the bibliographies of a systematic reviews of PTSD treatments that included trials of medications and psychotherapies (Hoffman et al., 2018), to identify any additional studies.

2.4. Outcomes

The primary outcome was reduction in PTSD symptoms, measured immediately post-treatment. Secondary outcomes were reduction in PTSD symptoms measured at long-term follow-up, PTSD remission, loss of PTSD diagnosis, change in depression symptoms, and change in quality of life, measured post-treatment or on follow-up. We did not assess side effects, harms, costs, or burdens of treatments.

2.5. Data collection and abstraction

The following data elements were abstracted by one reviewer (JS) and assessed for accuracy by a second reviewer (JMC): Study characteristics (e.g., sample size per intervention group); sample baseline characteristics (e.g., percent female); psychotherapy characteristics (e.g., number and duration of sessions); medication characteristics (e.g., starting and mean or median dose); methodological characteristics necessary for risk of bias assessment (see below); results (for continuous outcomes: pre-treatment, post-treatment and long-term follow-up mean) and variability measure (standard deviation or standard error or 95% confidence interval); for categorical outcomes: number and percent in each group).

2.6. Risk of bias assessment

Two experienced researchers independently rated risk of bias using the Cochrane Risk of Bias (ROB) 2.0 criteria (Higgins et al., 2016). Disagreements were resolved by discussion and consensus. Each of the following domains were rated: (1) Randomization process; (2) Deviations from intended interventions; (3) Missing outcome data; (4) Measurement of the outcome; and (5) Selective reporting of results.

Each domain was rated low risk of bias, some concerns, or high risk of bias. Items within domains were rated as "no information" if there was no information in the publication, and the corresponding trial author did not respond to our email inquiry. Studies were rated high risk of bias overall if any of the five domains were rated high risk of bias, or if multiple domains were rated "some concerns," and those concerns threatened the validity of the findings. Subgroup analyses and meta-regression to identify predictors of outcomes were not done because of the small number of studies that met inclusion criteria.

2.7. Data analysis

Meta-analyses were performed using random effects models with Comprehensive Meta-Analysis software (Borenstein et al., 2013) to account for statistical heterogeneity introduced into summary estimates as a result of differences in patient characteristics and methods used across trials (DerSimonian and Kacker, 2007). We used raw (unadjusted) results from trials as inputs for calculating summary estimates, if available; adjusted results were utilized if unadjusted results were not reported or available. For continuous outcomes, results are reported as SMDs based on intention to treat analyses. The I^2 statistic, representing the percentage of variation in summary effect estimates that is due to study heterogeneity, rather than chance, is reported as a measure of heterogeneity (Higgins and Thompson, 2002).

Narrative reviews, rather than meta-analyses, were performed for categorical outcomes for which definitions differed substantially across included trials.

Studies that were rated high risk of bias were not included in primary quantitative meta-analyses (Boutron et al., 2018). We conducted sensitivity analyses to determine whether the substantive conclusions would be different if all eligible trials, including those rated high risk of bias, were included in the meta-analyses.

Due to the small number of studies that met inclusion criteria for this systematic review (see below), the difficulty in interpreting a funnel plot with a small number of studies and the low power of statistical tests for publication bias (Lin et al., 2018), we did not assess for publication bias.

3. Results

3.1. Selection of studies

As shown in Fig. 1, we identified 1466 unique citations through database searches and 4 randomized trials that met inclusion criteria for this systematic review (Frommberger et al., 2004; Popiel et al., 2015; Rauch et al., 2018; van der Kolk et al., 2007). Although we included terms for SNRIs and venlafaxine in our searches, we did not identify any trials comparing venlafaxine to a trauma-focused psychotherapy. No additional studies were identified by searching the reference lists of included trials or the lists of trials included or excluded from a recent comprehensive systematic review of treatments for PTSD among adults (Hoffman et al., 2018).

Trials that included only combinations of medications and psychotherapies as interventions were excluded (i.e., Buhmann et al., 2016; Otto et al., 2003; Rothbaum et al., 2006; Schneier et al., 2012; Simon et al., 2008). A doubly randomized preference trial comparing PE to sertraline did not meet criteria for inclusion. In that trial, patients were initially randomized to choice of treatment or no choice of treatment. Patients in the choice group were permitted to choose their treatment (PE or sertraline) and patients in the no choice group were randomly assigned to either PE or sertraline. In the analyses reported in the publication, outcomes for persons who received PE (both those who chose PE and those randomly assigned to PE) were compared to persons who received sertraline (both those who chose sertraline and those randomly assigned to PE). The reported findings are therefore a combination of results from a randomized comparison of PE and sertraline, and a non-randomized comparison of PE and sertraline.

Characteristics of the trials included in the systematic review are shown in Table 1. Baseline PTSD severity was high for all studies. The modal number of psychotherapy sessions was 12. Only one of the trials (Rauch et al., 2018) achieved a mean medication dose greater than 60% of the maximum allowable dosage for that medication. Two trials included participants with a single type of traumatic exposure, motor vehicle collisions (Popiel et al., 2015) and combat (Rauch et al., 2018), and two trials (Frommberger et al., 2004; van der Kolk et al., 2007) included participants who had experienced a range of different types of trauma. None of the included trials compared an SNRI medication to a trauma-focused psychotherapy.

3.2. Risk of bias ratings

Two of the studies (Frommberger et al., 2004; Popiel et al., 2015) were rated high risk of bias, and two (Rauch et al., 2018; van der Kolk et al., 2007) were rated "some concerns" (Table 3). Both of the studies that were rated high overall risk of bias were rated high risk of bias in multiple categories. In Popiel's study (2015), none of the participants randomly allocated to PE, but 47% of the 57 participants allocated to paroxetine, refused to participate after treatment was assigned, but prior to treatment initiation. In addition, there was a large amount of missing outcome data that may have been related to the true (but unknown) value of the outcome variable, and it was unclear if assessment of the outcome was blinded. In the Frommberger study, there were imbalances in baseline prognostic factors, a large amount of missing outcome data (27% to 50% for various outcome measures) with use of completer-only analysis and non-blinded outcome assessment.

3.3. Meta-analyses

Random effects meta-analysis for PTSD symptom reduction of the two trials that were rated some risk of bias showed a point estimate weakly favoring medication, near the null value of 0, with a wide 95% confidence interval including values consistent with a moderate effect favoring psychotherapy (values less than 0) to a moderate effect favoring medications (values greater than 0; SMD 0.08, −0.48 to 0.64, $p = 0.99$; Fig. 2). Heterogeneity was high, as indicated by $I^2 = 81\%$, $p = 0 = .02$ and by SMDs for the van der Kolk trial (−0.24) and Rauch trial (0.34) that were approximately similar in magnitude but opposite in direction. The small number of trials precluded investigation of possible causes of heterogeneity.

Although both of the trials that were rated some risk of bias

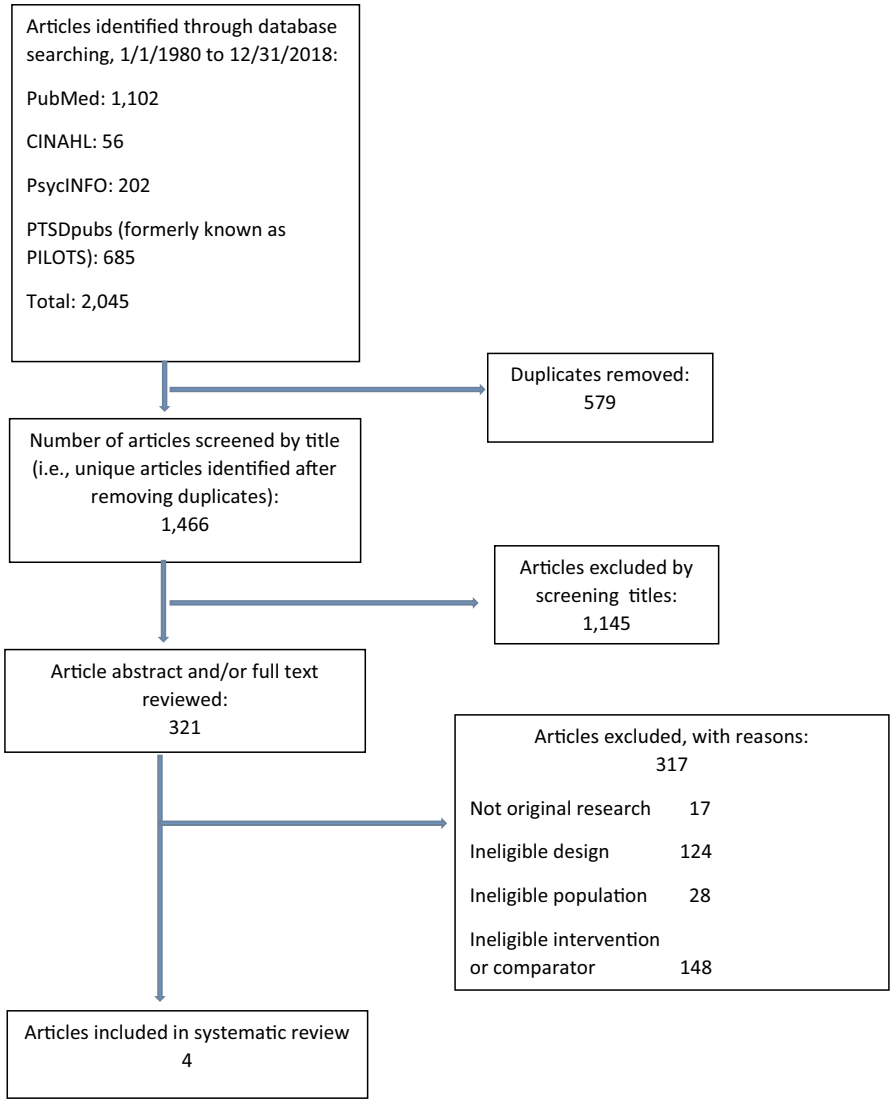

Fig. 1. Disposition of articles.

included categorical PTSD outcomes, we did not attempt meta-analysis of those outcomes because the definitions used by the two trials were substantively different. Narrative review of those findings are described below.

Although both of the trials that were some risk of bias included depression symptoms as secondary outcomes, we were not able to conduct meta-analyses on that outcome because Rauch et al. (2018) did not report data on depression symptoms in the findings published to date from that trial. We also did not perform meta-analyses of any outcomes six months post-treatment because those findings have not yet been reported by Rauch et al. (2018). Neither of the two trials rated some risk of bias reported data on quality of life.

3.4. Sensitivity analysis

Sensitivity analysis (i.e., meta-analysis of all four eligible trials, including the two trials that were rated some risk of bias and the two trials that were rated high risk of bias) for PTSD symptom reduction (Fig. 3) showed a small effect size favoring psychotherapy with a wide confidence interval including the null value (SMD −0.16, 95% CI, −0.62 to 0.30). The difference in point estimates between the meta-analysis of the two trials that were not high risk of bias and the meta-analysis of all four trials was due primarily to the high risk of bias Popiel trial; the effect size for the Popiel trial (SMD −0.96, 95% CI −1.38 to −0.54), favoring psychotherapy, was at least three times as large as the effect size of any other trial.

3.5. Narrative review of categorical outcomes

As noted above, different definitions of categorical PTSD outcomes, by the two included trials that were rated some risk of bias, precluded summary estimates. Van der Kolk et al. (2007) defined asymptomatic as a score on the Clinician Administered PTSD Scale (CAPS) as less than 20. Based on that definition, van der Kolk et al. (2007) reported that 58% in the EMDR group were asymptomatic at the post-treatment follow-up compared to 0% in the fluoxetine group. Loss of PTSD diagnosis was achieved by 88% of those in the EMDR group and 73% in the fluoxetine group.

In the trial of Rauch et al. (2018), a clinical response, defined as a 50% decrease in baseline CAPS, was achieved by 41% in the sertraline group, and 27% in the PE group, risk ratio (RR) 1.57, 95% CI, 0.96 to 2.54, based on unadjusted data. Remission, defined as a CAPS score less than 35, was achieved by 39% in the sertraline group, and 21% in the PE group, RR 1.89, 95% CI, 1.09 to 3.26, also based on unadjusted data.

Table 1
Characteristics of included randomized controlled trials

Study	Arm (*n*)	Country	Trauma type	Baseline PTSD severity, mean	Psychotherapy sessions, number	Mean Medication dose, mg (% of maximum)	Percent female	Percent non-white
Frommberger (2004)	CBT (10) Paroxetine (11)	Germany	Mixed	CAPS 67.6	12	28 (56)	57	NR
Van der Kolk (2007)	EMDR (29) Fluoxetine (30) Placebo (29)[a]	United States	Mixed	CAPS 73.8	6	30 (38)	81	66
Popiel (2015)	PE (114) Paroxetine (57) PE+Paroxetine (57)[a]	Poland	MVC	SCID-I 11.8	10–12	20 (40)	22	NR
Rauch (2018)	PE (74) Sertraline (74) PE + Sertraline (75)[a]	United States	Combat	CAPS 78.1	13	171 (86)	9	43

Notes. CAPS = Clinician Administered PTSD Scale, CBT = Cognitive behavior therapy, EMDR = =Eye Movement Desensitization and Reprocessing, MVC = =Motor vehicle collision, NR = Not reported, PE = =Prolonged Exposure Therapy, SCID-I = =Structured Clinical Interview for DSM-IV Axis I Disorders.
[a] Intervention groups that received placeboes or combination of treatments that were included in included trials are shown but were not included in meta-analyses or narrative review.

4. Discussion

4.1. Summary of findings

In head-to-head trials between SSRI medications and trauma-focused psychotherapy, this meta-analysis found a point estimate near null, but a very wide confidence interval consistent with large effects in both directions. There was also a high I^2 value indicating a large amount of heterogeneity. In short, evidence is insufficient to determine whether SSRI medications or trauma-focused psychotherapy are more effective for PTSD symptom reduction among adults who have been diagnosed with PTSD. The substantive conclusion from the meta-analysis was essentially unchanged by a sensitivity analysis conducted with addition of two high risk of bias trials.

The narrative review of the categorical outcomes mirrors the heterogeneity observed in the PTSD symptom reduction data: van der Kolk et al. (2007) report greater improvements in the group randomized to a trauma-focused psychotherapy than SSRI, and Rauch et al. (2018) report greater improvements in those randomized to SSRI than a trauma-focused psychotherapy.

Although there were more trials (four total, including two that were not high risk of bias) included in this systematic review than in an updated PTSD systematic review published in 2018 (two total, including one that was not high risk of bias; Hoffman et al., 2018), we came to an equivalent conclusion: there is insufficient evidence to determine whether SSRI or medications are more effective than psychotherapy for treatment of PTSD in adults.

In the sensitivity analysis including all four eligible trials, the SMD was −0.16, 95% CI, −0.62 to 0.30. In results reported in the supplementary appendix of the meta-analysis conducted by Merz et al. (2019), based on the same four trials, the SMD was −0.05, 95% CI, −0.31 to 0.21. The most likely explanation for the minor difference in results is that, for the Popiel trial, we calculated the SMD based on results from the Structured Clinical Interview for DSM-IV and Merz et al. (2019) appeared to base the SMD on results from the self-report Posttraumatic Diagnostic Scale. Despite that difference, results from our sensitivity analysis were broadly similar to the findings from the meta-analysis of the same four trials of Merz et al. (2019), i.e., a small to null point estimate with a wide confidence interval.

4.2. Limitations of the primary trials

Of the two trials that were not high risk of bias, one included only participants with combat-related PTSD (Rauch et al., 2018). Although there is insufficient evidence to determine whether the effectiveness of any PTSD treatment differs by patient characteristics or exposure type (Hoffman et al., 2018), generalizability to civilian populations may be uncertain. In addition, participants randomized to the medication arm in that trial received an additional 15 min, during each medication management visit, devoted “psychoeducation and / or active listening” (Rauch et al., 2018). Generalizability to typical outpatient settings that do not include those additional features of “enhanced medication management” is also uncertain.

4.3. Limitation of this systematic review

The main limitation of this systematic review is that there were few published head-to-head comparisons of a trauma-focused psychotherapy and an SSRI. In addition, although four trials met inclusion criteria, two were not included in substantive analyses because of high risk of bias. Furthermore, we were not able to include data from a recently published moderate-sized comparison of sertraline and prolonged exposure because data from the non-randomized comparison of sertraline and prolonged exposure ($n = = 97$) were combined with the data from the randomized comparison ($n = = 103$) in the published report (Zoellner et al., 2018).

Table 2
Risk of bias ratings.

Study	Randomization process[a]	Deviations from intended interventions[b]	Missing outcome data[c]	Measurement of outcome[d]	Selection of reported result[e]	Overall risk of bias
Frommberger 2004	B	C	C	C	B	C
van der Kolk, 2007	B	A	B	A	B	B
Popiel 2015	B	C	C	C	A	C
Rauch 2018	A	B	A	A	B	B

Notes: A: Low risk of bias. B: Some risk of bias. C: High risk of bias.
[a] Random sequence generation and allocation concealment.
[b] Blinding of participants, blinding of persons who delivered intervention, withdrawal due to experimental context and analysis that includes all randomized participants (i.e., intention-to-treat).
[c] Amount of missing outcome data, differences in proportion of missing data across intervention groups, likelihood that missingness depended on true value of missing data.
[d] Differences in outcome assessment across groups, blinding of outcome assessors, likelihood that outcome assessment dependent on knowledge of allocation assignment.
[e] Reported results differ from pre-specified plan or are a non-random selection from among multiple outcome measurements.

A second limitation is that the pooled effect estimate for PTSD symptom reduction comparing SSRI medication to trauma-focused psychotherapy might underestimate the benefit of SSRI medication. Sertraline was the SSRI medication used by one of the two trials included in this meta-analysis that were not high risk of bias (Rauch et al., 2018). However, a previous meta-analysis (Hoskins et al., 2015) and a network meta-analysis (Hoffman et al., 2018) suggest that sertraline has smaller effect sizes, compared to placebo, than do fluoxetine or paroxetine compared to placebo, for treatment of PTSD.

4.4. Implications for policy and clinical practice

Among major guidelines for treatment of PTSD in adults, two of them recommend psychotherapy over medications as first-line treatment for PTSD, based primarily on larger effect sizes in psychotherapy trials than in medication trials (Phoenix Australia-Centre for Posttraumatic Mental Health, 2013; National Institute for Health and Clinical Practice, 2018). The VA/DOD (2017) guideline recommended psychotherapy over medication but based that decision not only on larger effect sizes in psychotherapy trials than medication trials but also on the belief that adverse effects of medications were more frequent than for psychotherapy and that beneficial effects after cessation of treatment lasted longer in psychotherapies than medications.

Due to the impact of methodological differences between psychotherapy trials and SSRI or SNRI medication trials on effect size estimates, we believe that only results from systematic reviews of head-to-head trials, and not indirect comparisons, should be used to draw conclusions about the comparative effectiveness of psychotherapy and medications for treatment of PTSD. We conclude from the current systematic review based exclusively on head-to-head trials that there is insufficient evidence to determine whether SSRI or SNRI medication or trauma-focused psychotherapy are more effective for treatment of PTSD among adults. Others have come to similar conclusions, based on narrative review of available evidence for treatment of PTSD.

Until there is more definitive evidence about the relative effectiveness of medications and psychotherapy for treatment of PTSD from direct comparison, we recommend that treatment guidelines should not favor trauma-focused psychotherapies over medications (or vice versa) if effect size is the primary determinant of which treatment modality to favor. For the important decision about whether someone with PTSD should be treated initially with one of the trauma-focused psychotherapies or medications that have proven effectiveness compared to inactive controls, guideline panels should consider emphasizing shared decision-making incorporating patient preferences (Harik et al., 2016). The PTSD Treatment Decision Aid, developed by the U.S. Department of Veteran Affairs' National Center for PTSD, is a good example of how patient preferences for all of the following treatment characteristics can be incorporated into shared decision-making about treatment: (1) putative mechanism of action; (2) what the patient will need to do; (3) whether the patient will need to talk about the trauma; (4) frequency of visits required; (5) time between initiation of treatment and onset of benefit; (6) duration of benefit after cessation of treatment; and (7) risks and adverse effects (U.S. Department of Veterans Affairs National Center for PTSD, n.d.).

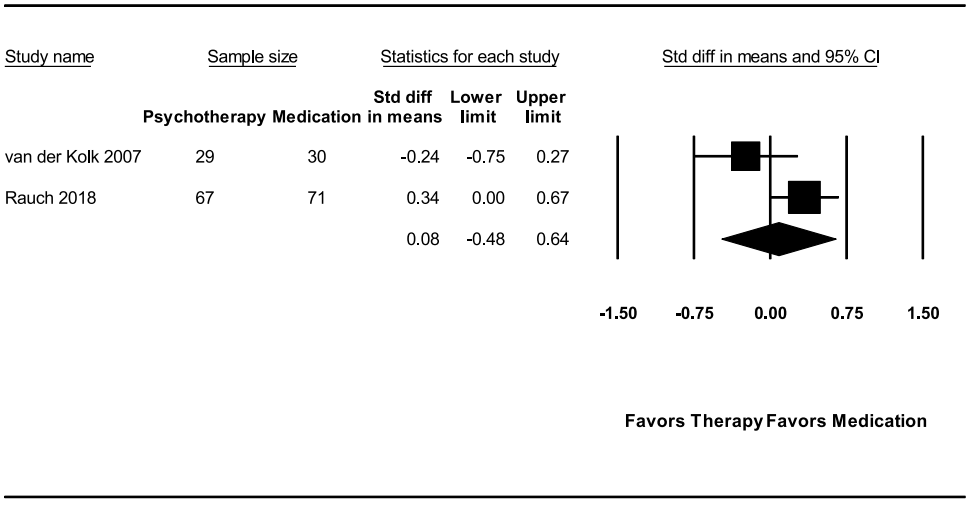

Fig. 2. Effectiveness of psychotherapy versus medication for PTSD symptom reduction.

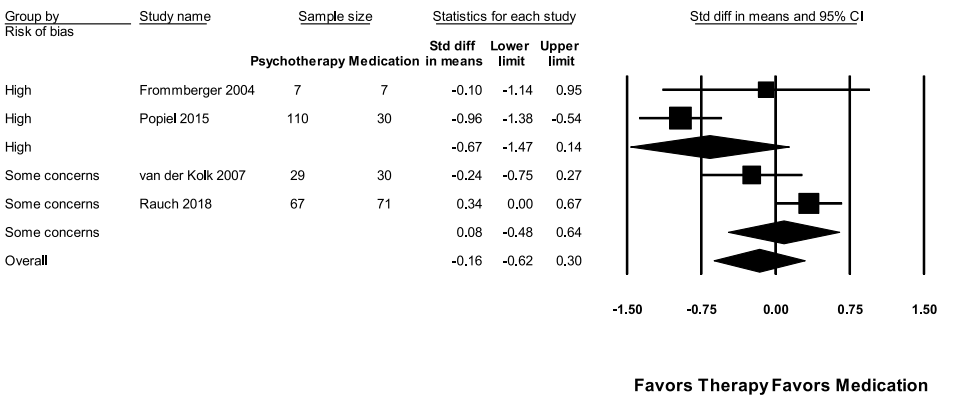

Fig. 3. Sensitivity analysis: meta-analysis with high risk of bias trials included.

Although a systematic review found that, across multiple treatment settings, substantially more persons with PTSD prefer to be treated with psychotherapy than medications (Simiola et al., 2015) a substantial minority may prefer medications for treatment of PTSD. Accordingly, clinicians should be guided by the preferences of each individual patient.

4.5. Conclusion

In summary, we found insufficient evidence to determine whether trauma-focused psychotherapies or SSRI or SNRI medication are more effective for treatment of PTSD. Large trials addressing this fundamental question are needed. We are hopeful that a significant amount of the $15 million pledged by the Patient-Centered Outcomes Research Institute to fund comparative effectiveness research on treatment of PTSD in adults will be devoted to trials comparing trauma-focused psychotherapy and SSRI or SNRI medication (Patient Centered Outcomes Research Institute, 2019).

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None. This was an unfunded study.

Declaration of Competing Interest

None

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None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.112637.

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