Systematic Review

Comparing treatments for post-traumatic stress disorder – a systematic review

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ABSTRACT

INTRODUCTION. The recommended treatments for post-traumatic stress disorder (PTSD) are psychological therapies and medication, but the best approach is still discussed. Exposure to traumatic events in psychotherapy tends to cause high drop-out rates. Likewise, little effect or adverse events of medications may lead to attrition. The aim of this study was to compare the outcomes of treatment by psychotherapy and medications. An additional aim was to explore the combinations of treatment modalities in adults with PTSD and to investigate differences in drop-out rates.

METHODS. A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. PubMed and Embase were searched for relevant randomised clinical trials. The Cochrane risk-of-bias tool was used to assess the quality of the retrieved trials.

RESULTS. Seven eligible studies were identified. Three studies showed that psychotherapy was superior to selective serotonin reuptake inhibitors. Two studies showed an augmenting effect with prolonged exposure. Two studies showed no differences across the treatment groups. In four of the included studies, patients treated with psychotherapy were more likely to drop out.

CONCLUSIONS. Extant evidence is insufficient to assess whether combined therapy is superior to monotherapy. Both medication and psychotherapy have an effect on PTSD, but psychotherapy tends to provide greater and more long-lasting outcome improvements. Trauma type, PTSD severity and other variables affect drop-out rates and treatment outcomes.

KEY POINTS

- Medication and psychotherapy have both shown a documented effect on post-traumatic stress disorder (PTSD).
- Psychotherapy seems to provide greater and more long-lasting improvements than medication.
- Treatment outcomes are affected by trauma type, PTSD severity and other variables.

Post-traumatic stress disorder (PTSD) is a debilitating mental disorder, which is triggered by an extremely traumatic or stressful event [1, 2]. The estimated lifetime prevalence of PTSD varies according to social background, country of residence and diagnostic system [1]. In adults, the prevalence is approximately 8% in the U.S. [2, 3] and 2% in European countries [4].

Early diagnosis and appropriate treatment are essential to reduce complications. The disorder has shown risk of chronicity, functional impairment and comorbidity [2, 5]. Several beneficial treatments are available, including a

range of psychotherapeutic and pharmacological treatments. However, recommendations are inconsistent. Most treatment guidelines recommend trauma-focused psychotherapy as first-line treatment of adults with PTSD [6-9], but it remains unclear whether antidepressants such as selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors should be used together with psychotherapy.

Two systematic reviews found insufficient evidence to determine whether trauma-focused psychotherapy is more effective than SSRI in reducing PTSD symptoms [5, 10]. Another systematic review suggested that psychotherapy may be superior to pharmacotherapy [2]. Thus, the evidence seems inconsistent.

The aim of this study was to investigate the effect of psychotherapy treatment alone and combined with medications, as proposed in the current guidelines, to reduce PTSD symptoms. Furthermore, we aimed to describe dropout differences between these two treatment regimens.

METHODS

Reporting guidelines

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines [11].

Identification of studies

An initial search was made to identify the current guidelines for treating adults with PTSD [6-9]. A systematic database search was performed in PubMed, Embase and ClinicalTrials between 15 February 2020 and 15 April 2020 with no restriction on publication year.

The search strategy in PubMed was divided into three steps. First "*PTSD*" and *post-traumatic stress disorder [MeSH Terms]* were combined with OR. Second, the first-line treatments *("fluoxetine", "paroxetine", "sertraline", "venlafaxine", "trauma-focused cognitive behavioral therapy", "cognitive processing therapy", "EMDR", "prolonged exposure", "stress management"* and *"narrative exposure therapy"*) recommended in the current guidelines [6-9] were combined with OR. Third, the terms (psychotherapy [MeSH Terms], drug therapy [MeSH Terms], "psychological treatment", "pharmacological treatment", therapeutics [MeSH Terms], practice guidelines as topic [MeSH Terms], patient dropouts [MeSH Terms], evidence-based medicine [MeSH Terms], treatment outcome [MeSH Terms], "first-line" and "clinical practice guidelines") specifying the aim of this review were combined with OR. Finally, all three steps were combined with AND. The search identified 1,243 records.

The search in Embase produced 980 records. Subsequently, the following filters were applied: Randomized Controlled Trial, Adult: 19-44 years, Middle Aged: 45-64 years and Aged: 65+ years. These filers were combined with the following language restrictions: English, Danish, Swedish and Norwegian. A total of 355 records were identified. After an initial screening of the title and abstract of studies with comparative outcomes, 26 records were considered relevant. The full text of 26 records was screened for eligibility and seven records were included in this review.

No records identified in ClinicalTrials met the eligibility criteria. The references of the included studies were screened for potentially relevant studies.

Eligibility criteria

We included randomised clinical trials evaluating the outcome of a trauma-focused psychotherapy, cognitive behavioural therapy (CBT), prolonged exposure therapy (PE), cognitive processing therapy, eye movement desensitisation and reprocessing (EMDR), or narrative exposure therapy or stress management compared with

treatment by sertraline, paroxetine, fluoxetine or venlafaxine, or combinations of these, to reduce PTSD symptoms in adults.

We included participants exposed to a traumatic event as specified in the PTSD diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM) versions DSM-3, DSM-4 and DSM-5 and the International Classification of Diseases (ICD) versions ICD-10 or ICD-11. We excluded participants with active psychosis, bipolar disorder or current alcohol/substance dependence, pharmacotherapy-refractory PTSD or participants who were undergoing preventive treatment for PTSD, as it was difficult to determine the potential impact of these factors on the treatment.

Outcome and data collection

The primary outcome was PTSD, and symptom severity was validated by interviews and questionnaires, i.e. the Clinician-Administered PTSD Scale (CAPS), the PTSD Symptom Scale (PSS-I), the Harvard Trauma Questionnaire (HTQ) and the Structured Interview for PTSD. Outcome was measured immediately after treatment termination and at long-term follow-up. The secondary outcome was the acceptability of the treatment, which was assessed by comparing the number of dropouts before end of treatment.

The following data elements were collected: intervention, number of patients allocated, trauma type, treatment duration, follow-up, number of sessions, PTSD severity measure, baseline PTSD severity score, post-treatment PTSD severity and number of dropouts.

Effect sizes (Cohen's d) were calculated (see **Table 1**) by the following equations [12] (M_x = mean of group x, SD = standard deviation):

Cohen's d = $(M_2 - M_1) / SD_{pooled}$

where:

$SD_{pooled} = \sqrt{((SD_1{}^2 + SD_2{}^2) / 2)}$

TABLE 1 The effect of intervention on symptoms of post-traumatic stress disorder.

Reference	PTSD severity measure	Intervention	Baseline PTSD severity score, mean (± SD)	Post-treatment PTSD severity, mean (± SD)	Effect size, Cohen's d	Key findings	Dropouts, n (rate %)
Zoellner et al., 2019 [14]	PSS-I	PE	29.4	10.5	_[b]	PE superior to sertraline both after the acute treatment, at wk 10 and at follow-up	39 (34)
		Sertraline	29.8	13.3	_[b]		27 (32)
Rauch et al., 2019 [15]	CAPS	PE + sertraline	76.0 (± 14.2)	43.3 (± 27.2)	1.65	PE + placebo was no better than PE + sertraline or sertraline + enhanced medication management	28 (40.6)
		PE + placebo	80.9 (± 13.2)	51.5 (± 25.3)	1.46		32 (47.8)
		Sertraline	75.5 (± 15.0)	41.7 (± 25.7)	1.86		19 (26.8)
Buhmann et al., 2016 [16]	HTQ	Medicine and CBT	3.2 (± 0.6)	3.2 (± 0.6)	0.00	No effect of CBT and medication but a small effect on depression in the combination group	10 (23)
		Medicine	3.3 (± 0.5)	3.2 (± 0.6)	0.18		7 (13)
		CBT	3.3 (± 0.5)	3.3 (± 0.5)	0.00		10 (26)
		Waiting list	3.3 (± 0.5)	3.3 (± 0.5)	0.00		16 (29)
Schneier et al., 2012 [17]	CAPS	PE + paroxetine	72.6 (± 12.9)	21.5[a] (± 19.9)	3.05	PE + paroxetine superior to PE + placebo after 10 wks but not at follow-up	6 (31.6)
		PE + pill placebo	65.4 (± 12.8)	35.6[a] (± 31.3)	1.25		5 (27.8)
van der Kolk et al., 2007 [18]	CAPS	EMDR	69.4 (± 12.7)	28.37[a] (± 19.66)		EMDR superior to fluoxetine and pill placebo both after 8 wks and at follow-up	5 (17)
		Fluoxetine	73.7 (± 13.4)	38.69[a] (± 20.30)			4 (13)
		Placebo	70.3 (± 13.0)	39.81[a] (± 18.76)			3 (10)
Rothbaum et al., 2006 [19]	SIP	Sertraline	Wk 10: 14.5 (± 11.65)	Wk 15: 14.9 (± 15.27)		Sertraline + PE better than sertraline alone	1 (3)
		PE + sertraline	Wk 10: 16.1 (± 10.64)	Wk 15: 10.2 (± 8.83)			6 (11)
Frommberger et al., 2004 [20]	CAPS	Paroxetine	65 (± 13.4)	36.1 (± 12.1)	2.32	CBT superior to paroxetine both after 12 wks and continued reduction at follow-up	3 (27.3)
		CBT	70.5 (± 7.2)	34.8 (± 15.0)	3.03		2 (20)

CAPS = Clinician-Administered PTSD Scale; CBT = cognitive behavioural therapy; EMDR = eye movement desensitisation and reprocessing; HTQ = Harvard Trauma Questionnaire; PE = prolonged exposure; PSS-I = The PTSD Symptom Scale – interview; PTSD = post-traumatic stress disorder; SD = standard deviation; SIP = structured interview for PTSD.
a) Completers only.
b) Standard deviation was unavailable in the study.
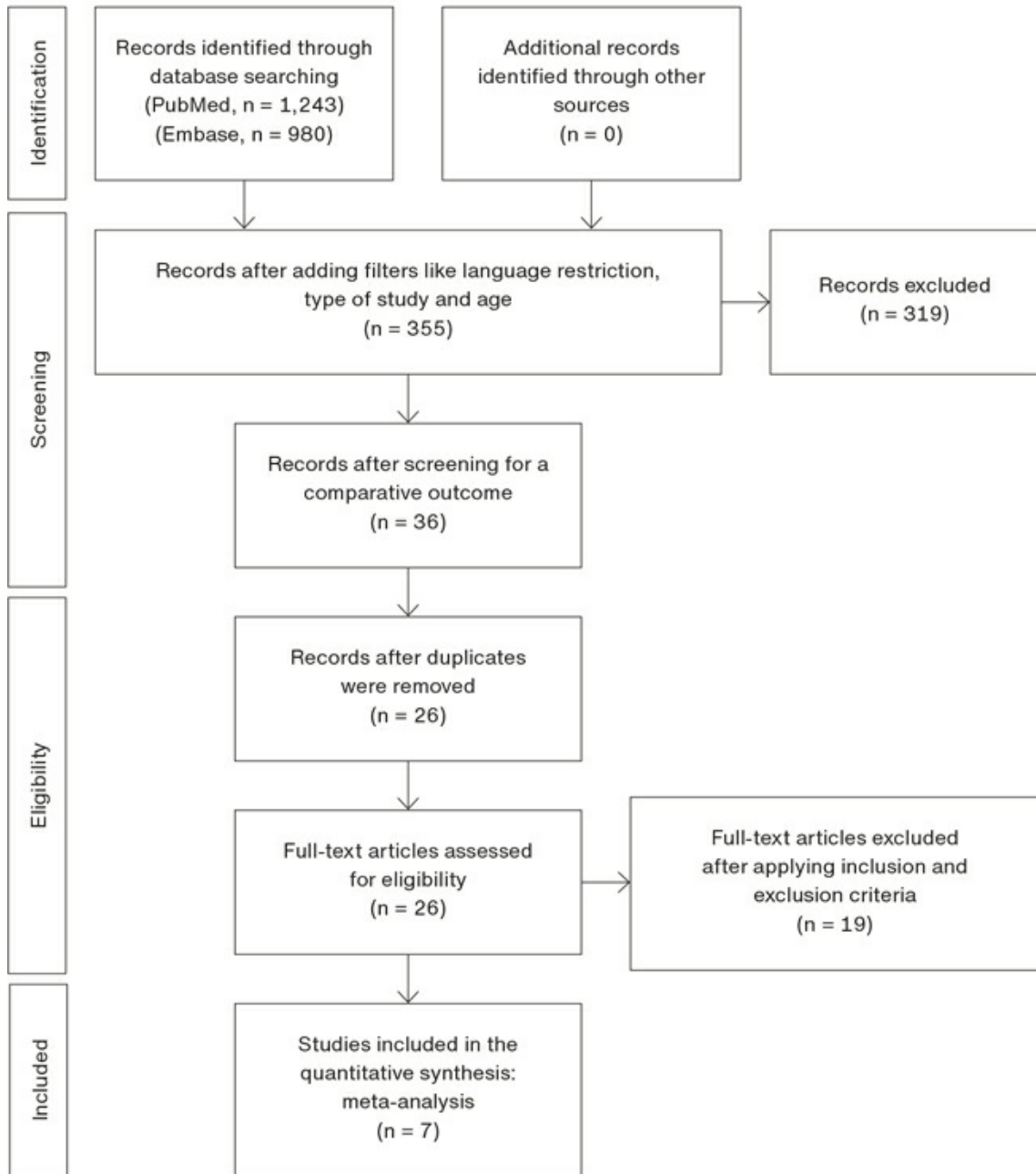
Quality assessment of the included studies

The Cochrane risk-of-bias tool for randomised trials was used to assess the risk of bias [13]. Each of the following domains were rated and categorised into *low, unclear or high* risk of bias: random-sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. The overall risk was rated as low if at least four of the above-mentioned domains were rated as having a low risk.

RESULTS

Selection of studies

The systematic database search identified 26 studies. After full-text screening, the eligibility of each study was assessed and 19 studies were excluded. Twelve studies were excluded because they compared only psychotherapies against each other, five studies were excluded because the aim was not to reduce PTSD symptoms, one study was excluded because the included participants had other psychotic comorbidities, and one was excluded because it consisted of a study protocol only. Hence, seven studies were eligible for inclusion. An overview of the selection process is presented in the PRISMA flow diagram in **Figure 1.** No study comparing venlafaxine to a trauma-focused psychotherapy was identified.

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 flow diagram.

Risk of bias

Risk of bias assessments for the included studies are presented in **Table 2**. Six studies were rated to have a low risk of bias [14-19], and one study, Frommberger et al. [20], was rated to have a high risk of bias. Most of the studies were rated to have a low risk of selection bias, and random sequence generation and allocation concealment were described in detail. All of the included studies were rated to have a low risk of performance and detection bias, excluding the study by Frommberger et al. [20]. The risk of attrition bias differed among the included studies, and one study, Buhmann et al. [16], had a high percentage of dropouts, whereas other studies did not address this type of bias. A study protocol was available only in few of the included studies. Therefore, it

was difficult to determine whether the studies reported on pre-specified outcome measures. However, most studies were rated as having a low risk of reporting bias.

TABLE 2 Risk of bias.

Reference	Selection bias		Blinding of participants and personnel: performance bias	Blinding of outcome assessment: detection bias	Incomplete outcome data: attrition bias	Selective reporting: reporting bias	Other sources of bias	Summary assessment at outcome level
	random-sequence generation	allocation concealment						
Zoellner et al., 2019 [14]	Unclear risk A computer-generated urn was used for randomisation sequence The randomisation was stratified by PTSD severity according to the PSS-I and current antidepressant status	Low risk Sealed envelopes were used	Low risk Clinicians were blinded to assignment No blinding of participants but this was unlikely to introduce bias	Low risk All assessors of outcome were blinded to randomisation status	Low risk Analyses were intent-to-treat Missing data did not have a clinical impact on the observed effect	Unclear risk Not described	Low risk Funders had no influence on the study design	Low risk
Rauch et al., 2019 [15]	Low risk A secure centralised interactive web-based application was used for randomisation	Unclear risk Only masked allocation without any details provided	Low risk Participants and clinicians were blinded	Low risk All evaluators were blinded to treatment assignments	Unclear risk Not described	Low risk Study protocol is available	Low risk Funders had no influence on the study design besides type of participants	Low risk
Buhmann et al., 2016 [16]	Low risk Random sequence generation was done by a computer	Low risk Sealed envelopes were used	Low risk Participants and clinicians were not blinded, but the outcome assessment was blinded	Low risk Outcome assessment was blinded by self-rated outcome measures	High risk Only 78% of the participants completed treatment	Unclear risk No study protocol is available	Low risk Only government funding	Low risk
Schneier et al., 2012 [17]	Low risk Randomisation was done by a data manger with no patient contact	Low risk Allocation was concealed, tablets were packed in bottles	Low risk Participants and personnel were blinded	Low risk Assessors were blinded to treatment assignment	Unclear risk Study did not address this outcome	Low risk Outcome described in the Method section were reported in the Results section	High risk Funding by a pharmaceutical company	Low risk
van der Kolk et al., 2007 [18]	Unclear risk Randomisation was not described	Unclear risk Allocation concealment was not described	Low risk Participants and personnel were blinded	Low risk All raters were blinded to treatment condition and never assigned the same participant	Low risk Missing data had been imputed by an early termination assessment or a last-observation-carried forward	Low risk Outcome described in the Methods section were reported in the Results section	Unclear risk Funding source was not mentioned	Low risk
Rothbaum et al., 2006 [19]	Unclear risk Randomisation was not described in detail	Unclear risk Allocation concealment was not described	Low risk Blind independent raters	Low risk Only self-rated outcome measures were used	Low risk Participants were analysed as they were randomised	Low risk All expected outcomes were reported	High risk Funding by a pharmaceutical corporation	Low risk
Frommberger et al., 2004 [20]	Unclear risk No description of random-sequence generation	Unclear risk	Low risk Even though participants were not blinded, this would not influence the outcome	High risk Treatment was provided by the author of the study	High risk Data from the discontinued patients were excluded	High risk Not all outcomes were reported	Unclear risk Funding source was not mentioned	High risk

PSS-I = The PTSD Symptom Scale – interview; PTSD = post-traumatic stress disorder.

Study characteristics

A summary of characteristics and effect is presented in Table 1 and **Table 3**. Three studies compared the efficacy of PE and sertraline; Zoellner et al. [14], Rauch et al. [15] and Rothbaum et al. [19].

TABLE 3 Characteristics of the included studies.

Reference	Intervention treatment	patients allocated, n	Trauma type	Treatment duration, wks	Follow-up	Sessions, n	Recruitment
Zoellner et al., 2019 [14]	PE	116	Mixed trauma	10	24 mos.	10-wk 90- to 120-min. individual sessions	From 2 outpatient clinics in Seattle and Cleveland Referrals from community agencies and treatment providers Fliers, brochures, newspapers, bus and magazine advertisements
	Sertraline	84					
Rauch et al., 2019 [15]	PE + sertraline	69	Combat related	24	52 wks	PE participants had 13-, 90-min. therapy, individual sessions by wk 12 and were allowed to complete all sessions at wk 24	From 4 Veteran Affairs
	PE + placebo	67					
	Sertraline	71					
Buhmann et al., 2016 [16]	Medicine and CBT	71	Traumatised refugees	24	-	CBT participants had 12 individual sessions[a] Those who received medication had 9 individual sessions[a]	Refugees in Denmark
	Medicine	71					
	CBT	70					
	Waiting list	68					
Schneier et al., 2012 [17]	PE + paroxetine	19	Survivors from WTC, 11 Sep 2001	10	6 mos.	10-wk 90-min. individual sessions	Referred by clinicians Responding to advertisements Responding to direct mail
	PE + pill placebo	18					
van der Kolk et al., 2007 [18]	EMDR	29	Mixed trauma	8	6 mos.	8-wk 90-min. individual sessions	Via newspaper advertisements, Internet, solicitation From medical and mental health professionals
	Fluoxetine	30					
	Placebo	29					
Rothbaum et al., 2006 [19]	Sertraline	31	Mixed trauma	5	-	All participants received two individual sessions after 2 and 5 wks Those who received PE also had 10 individual sessions 2 per wk each of 90-120 min.	Through advertisements and referrals from professionals[b]
	PE + sertraline	34					
Frommberger et al., 2004 [20]	Paroxetine	11	Serious accidents, sexual or non-sexual violence were the most frequent	12	6 mos.	12-wk individual sessions	From a specialised outpatient PTSD treatment centre
	CBT	10					

CBT = cognitive behavioural therapy; EMDR = eye movement desensitisation and reprocessing; PE = prolonged exposure; WTC = World Trade Center.
a) Average values.
b) Received modest compensation for their participation.

Zoellner et al. [14] compared the effect of PE to sertraline. A total of 200 patients with mixed trauma types were randomised to choice of treatment or no choice of treatment. Participants randomised to no choice of treatment (n = 103) were further randomised to PE (n = 55) or sertraline (n = 48).

The treatment duration was ten weeks with 24 months of follow-up. Both treatments showed improvements by interview-rated (PSS-I) and self-reported measures. Participants treated with PE were more likely to achieve loss of PTSD diagnosis than participants treated with sertraline; this was seen both after the acute treatment and at follow-up. A total of 66 dropped out (33%); no difference was observed between the group treated with sertraline and the group treated with PE. In conclusion, ten-week PE was found to be superior to ten-week sertraline treatment.

In the study by Rauch et al. [15], the aim was to determine the relative efficacy of PE plus placebo, PE plus sertraline, and sertraline plus enhanced medication management (defined as time balance, psychoeducation and clinician support) in combat veterans with PTSD. A total of 223 participants with combat-related PTSD were randomised to one of the three groups, but only 207 participants received treatment for 24 weeks with follow-up after 52 weeks. All treatments yielded significantly reduced PTSD severity levels, but no differences were observed across the three study groups (either for clinically assessed measures or for self-reported measures). A total of 79 participants dropped out (35.4%); the greatest dropout number was seen in the group treated with PE plus placebo. In conclusion, 24-week PE plus placebo was found to be no better than PE plus sertraline or than sertraline plus enhanced medication management.

In the study by Rothbaum et al. [19], the aim was to determine whether augmenting sertraline plus PE would result in greater improvement in adults with mixed trauma types. Sixty-five participants were treated with sertraline for ten weeks and then randomised to five weeks with either sertraline or sertraline plus PE. Sertraline significantly reduced PTSD severity after ten weeks. Only those treated with sertraline plus PE showed a further

reduction after five additional weeks. Seven participants dropped out between weeks 10 and 15 (10.7%); six of these were in the group with PE. In conclusion, sertraline plus PE was found to be better than sertraline alone.

The study by Buhmann et al. [16] estimated the treatment effect of flexible CBT and antidepressants (sertraline and mianserin) in 280 traumatised refugees for six months. The participants were randomised into four groups; combination treatment, medicine, CBT and waiting list. The primary outcome was self-measured by the HTQ. No significant effects of the two treatments were found, although antidepressants combined with psychoeducation showed improvements in observer-rated symptoms of depression. Forty-three participants discontinued the intervention (15.4%). In conclusion, no effect of CBT and medications was seen, except for a small effect on depression in the combination group.

Two studies compared paroxetine treatment to a trauma-focused psychotherapy; Schneier et al. [17] and Frommberger et al. [20]. Schneier et al. [17] compared PE plus paroxetine to PE plus placebo in the treatment of 37 adult survivors of the World Trade Center attacks on 11 September 2001. The participants were randomised to ten weeks of either PE plus paroxetine or PE plus placebo. After ten weeks, 12 additional weeks of continued randomised treatment were offered. The group receiving PE plus paroxetine improved significantly in both quality of life and in response rate. These participants showed greater improvements in PTSD symptoms and in remission status than participants receiving PE plus placebo at week 10. A total 26 participants continued after week 10, but this showed no significant improvement. A total of 11 participants (29.7%) discontinued with no difference between the groups. In conclusion; PE plus paroxetine was found to be superior to PE plus placebo.

Frommberger et al. [20] compared paroxetine to CBT including 21 adults with mixed trauma. The treatment period was 12 weeks with a six-month follow-up. After end of treatment, the improvement was twice as large in the CBT group as in the paroxetine group when measured by the patient-rated PSS-I. At follow up, the CBT participants continued to show reduced PTSD severity, whereas relapse was seen in the paroxetine group. Two patients dropped out from the CBT group due to increased anxiety before the first exposure, and three patients dropped out from the paroxetine group. Thus, a total of 23.8% dropped out. In conclusion, this small-scale study found that 12 weeks of CBT was superior to paroxetine treatment.

The study by van der Kolk et al. [18] compared the efficacy of fluoxetine to EMDR and pill placebo in 88 adults with mixed trauma types. The participants received eight weeks of treatment and were assessed post-treatment and at a six-month follow-up. The participants receiving EMDR had lower CAPS scores than participants treated with fluoxetine and placebo, and higher percentages of the EMDR-treated participants achieved loss of PTSD diagnosis compared with the placebo group. At follow-up, participants receiving EMDR showed lower CAPS scores. This group was also superior to the fluoxetine group in terms of attaining complete remission and a better treatment response. A total of 13.6% dropped out. In conclusion, eight-week treatment with EMDR was found to be superior to treatment with fluoxetine and pill placebo.

DISCUSSION

Treatment effect

The literature regarding treatment of PTSD favours CBT-based approaches, among which PE has been documented to be effective [5]. However, differences in treatment duration, follow-up, trauma types and dropout rates in the included studies make it difficult to conclude anything across studies. We investigated the treatment effect and calculated the effect sizes (Cohen's d). Overall, the calculation showed that both medication and psychotherapy have an effect on PTSD.

Three studies by van der Kolk et al. [18], Frommberger et al. [20] and Zoellner et al. [14] showed that

psychotherapy was superior to SSRI, and continued reduction in PTSD severity was seen at follow-up. Frommberger et al. [20] also showed a large effect size of CBT compared with medication. Similar improvement and effect size emerged in Schneier et al. [17] and Rothbaum et al. [19] when augmenting with PE and combining paroxetine and PE. Still, augmenting with PE only had a slightly larger effect size than sertraline alone. As for EMDR [18], the effect size was not as large as for CBT and PE. Even though EMDR showed lower pre-treatment CAPS scores than fluoxetine and placebo, EMDR had a smaller effect size. This may be the result of all three groups having the same two personalised pre-treatment trauma consultations, which might have played a significant role in the positive outcome. Alternatively, participants in the EMDR group may have been less sick and thus have obtained a smaller effect size [18]. One three-arm study [15] showed that PE plus SSRI was no better than PE plus placebo. This could explain the very similar effect sizes, although with some effect in all groups. Finally, one study found only a small effect on depression in the group of refugees treated with both psychotherapy and SSRI [16].

Risk of bias

The risk of bias was high in the study by Frommberger et al. [20], as only 21 patients were included in the study. Consequently, even small changes had great effect on the outcome. At follow-up, the PTSD severity had increased in two participants in the group treated with medication due to relapse, and this changed the overall outcome. Some data were missing, and the outcome assessment was not blinded. Therefore, even though they showed that CBT was superior to paroxetine, no conclusion may be made from this study. All studies were rated as having a low risk of performance bias because the non-blinding approach was unlikely to introduce bias. The risk of publication bias was partly resolved by screening the reference lists of all included studies.

Recruitment of the participants was handled differently across the included studies. Some participants were recruited from outpatient clinics and others via newspaper ads and the internet. This might have resulted in selection bias due to the broad range of participants. One additional great concern is the heterogeneity of the included studies. Different groups of patients were included and compared even though they may not be clinically comparable.

Trauma types

Buhmann et al. [16] found no effect of flexible CBT and antidepressant on PTSD in their setting with traumatised refugees. The same applied to another study [21] conducted in a similar setting. Although most guidelines recommend psychotherapy and pharmacotherapy, treating patients with severe PTSD, such as traumatised refugees, appears to be more complex. They often suffer from a range of comorbidities and somatic illnesses, which may influence their treatment adherence. These patients have often been exposed to prolonged and repeated traumatic events, which makes it difficult to practice exposure therapy as this is often aimed at the patient's worst experience [22].

Some studies suggest that all these factors and events following migration play a role in the development and maintenance of PTSD in refugees in whom neither medication nor exposure helps [22-24]. The same seems to apply to patients with combat-related PTSD. Rauch et al. [15] found some effect of both sertraline and PE (and combinations), but no difference was seen across the treatment groups.

Patients with pharmacotherapy-refractory PTSD are very affected by fear, anxiety and depression, and they might not respond to the first or second type of treatment used. One study investigated the comparative outcome of combining CBT and sertraline in refugees with pharmacotherapy-refractory PTSD and their findings indicate that combined treatment is more beneficial than pharmacotherapy alone [25].

Dropouts

Different variables have been highlighted to predict treatment discontinuation, including PTSD severity, trauma type and disability status [26]. In the included studies, participants treated with psychotherapy were more likely to drop out than those treated with medication [14-16, 18, 19]. To understand their reasons for dropping out, it should be explored which parts of the treatment fail to work for them. In Rauch et al. [15], treatment adherence differed across the groups in both the unadjusted and adjusted analyses. In Buhmann et al. [16], some patients treated with medication discontinued due to adverse reactions, and those receiving psychotherapy dropped out due to discomfort.

Even though some studies have aimed to investigate why patients discontinue their treatment [27-29], dropout rates remain high. A multifactorial and personalised approach with a professional psychotherapist may be required to reduce dropout [28].

Future perspectives

Psychotherapy and pharmacotherapy have a documented treatment effect in adults with PTSD. Mindfullness-based stress reduction (MBSR) is one way for PTSD patients to obtain greater control of their trauma-related memories and thoughts and to learn how to be less emotionally reactive [30]. Studies investigating the effect of MBSR in veterans have found it useful for treating veterans with mood and emotional dysregulation [31] and have recorded great reductions in PTSD severity [32]. Moreover, MBSR has been found to cause changes in brain function, which have been associated with reduced activation of stress and fear. MBSR is another safe and effective treatment for PTSD [30].

CONCLUSIONS

The treatment of PTSD remains a challenging task. A main limitation is the lack of evidence to assess whether pharmacotherapy and psychotherapy combined is a more effective treatment than monotherapy. This literature review was based on high-quality studies from this field with a low risk of bias. Nevertheless, conflicting results were reported. Both medications and psychotherapy are reported to have an effect on PTSD, but psychotherapy tends to provide greater and more long-lasting improvements

Several factors seem to influence the effectiveness of treatments, the adherence to prescribed treatment regimens and the level of dropout. These factors include trauma type, disability status and PTSD severity. Treating patients with PTSD is a complex and multifaceted issue, and further research is needed to expand our knowledge.

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