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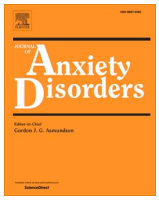

A systematic review and meta-analysis of PTSD symptoms at mid-treatment during trauma-focused treatment for PTSD

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ABSTRACT

There is concern that trauma memory processing in psychological therapies leads to PTSD symptom exacerbation. We compared PTSD symptoms at mid-treatment in trauma-focused psychological therapy to control groups. We systematically searched multiple databases and searched grey literature. We included randomised controlled trials involving adults comparing trauma-focused psychological interventions with active non-trauma-focused interventions or waitlist conditions. Twenty-three studies met our inclusion criteria. We found no evidence of PTSD symptom exacerbation at mid-treatment in trauma-focused interventions compared to control groups (g=−.16, [95 % confidence interval, CI, −.34,.03]). Sensitivity analyses with high quality studies (risk of bias assessment ≥ 7; g=−.25; [95 % CI −.48, −.03], k = 12) and studies with passive controls (g=−.32; [95 % CI −.59, −.05], k = 8) yielded small effect sizes favouring trauma-focused interventions. At post-treatment, trauma-focused interventions yielded a medium effect on PTSD symptoms compared to all controls (g=−.57; [CI −.79, −.35], k = 23). Regarding depression, trauma-focused interventions yielded a small effect size compared to controls at mid-treatment (g=−.23; [95 % CI −.39, −.08], k = 12) and post-treatment (g=−.45; [CI −.66, −.25], k = 12). This meta-analysis found no evidence that trauma-focused psychotherapies elicit symptom exacerbation at mid-treatment in terms of PTSD or depression symptoms. Instead, this meta-analysis suggests that the benefits of trauma-focused interventions can be experienced through improved depression and possibly PTSD before the conclusion of therapy. However, it is possible that symptom exacerbation occurred before mid-treatment and/or that people who experience symptom exacerbation drop out of studies and so are not included in the analysis.

1. Introduction

Posttraumatic stress disorder (PTSD) is common, with a lifetime prevalence of around eight per cent (Kilpatrick et al., 2013). It is diagnosed by the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition; DSM-5-TR) after exposure to a traumatic event when symptoms develop, including re-experiencing, avoidance of associated stimuli, negative alterations in cognition and mood, and hyperarousal (American Psychiatric Association, 2022). Clinical practice guidelines from professional associations and national organisations recommend trauma-focused psychological therapy for adult PTSD (Hamblen et al., 2019). Trauma-focused psychological therapies use cognitive and/or behavioural techniques (e.g., imagery rescripting, cognitive restructuring, exposure) to target trauma memories and the meanings associated with these (Watkins et al., 2018). Trauma memory processing is a central component in trauma-focused psychological interventions and begins early in treatment, e.g. in Cognitive Therapy for PTSD (CT-PTSD), imaginal reliving (a form of trauma memory processing) usually begins

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in session two of treatment (Murray et al., 2022).

Numerous meta-analyses of randomised controlled trials (RCTs) have examined changes in PTSD symptoms from pre- to post-treatment in trauma-focused interventions and reported large effect sizes (e.g. Lewis et al., 2020; Mavranezouli et al., 2020). However, despite this accruing evidence for trauma-focused interventions, relatively recent research suggests trauma-focused interventions are not widely implemented in practice (e.g. research from the UK National Health Service found that trauma-focused CBT (TF-CBT) was self-reported to be implemented by less than 60 % of clinicians [Finch et al., 2020b]; research from the US Department of Veterans Affairs found that 13 % of a sample within the clinic initiated trauma-focused interventions [Lu et al., 2016]). Therefore, there is a need to understand the barriers to providing trauma-focused interventions.

Clinician concerns about trauma memory processing leading to symptom exacerbation have long been raised in the literature. For example, Kilpatrick and Best (1984) suggested that exposure during therapy could increase levels of anxiety in victims of sexual assault. From focus group discussions, Frueh et al. (2006) found that clinicians reported a fear of directly addressing trauma memories, fearing this would exacerbate symptoms. A more recent publication on misconceptions of TF-CBT notes that clinicians often fear that when patients with PTSD think or talk about trauma memories, it will increase PTSD symptoms (Murray et al., 2022). Similarly, a fear of increasing patient distress, or potentially "retraumatising" patients, through therapy was a theme in a systematic review of clinicians' perceived barriers to using trauma-focused interventions (Finch et al., 2020a). However, this clinician fear does not appear to be currently supported by research. Although there is a lack of research on PTSD symptom exacerbation during trauma-focused treatments, available literature appears to suggest that temporary symptom exacerbation during treatment is not indicative of poorer outcomes (e.g. Foa et al., 2002; Larsen et al., 2016; Resick et al., 2015) and so might not necessarily be detrimental in the context of trauma-focused treatment.

Although a recent meta-analysis on the incidences of harm during RCTs of psychological treatments for PTSD reported that TF-CBT was at least as safe as other psychological interventions for PTSD, the meta-analysis notes that 64 % of the potentially eligible RCTs did not report on harm and therefore could not be included (Hoppen et al., 2022). The limitation demonstrates the need to undertake research to ascertain the impact of trauma-focused psychological treatment using different indices and methodologies to summarise the literature. Drop-out rates could be examined as a potentially important outcome; however, there could be a plethora of reasons for dropout (even including PTSD symptom alleviation). Furthermore, although one meta-regression found evidence that trauma-focused interventions were significantly associated with greater dropout (rate of 18 %) compared to those without a trauma focus (rate of 14 %), this was a small difference (Lewis et al., 2020) and another meta-analysis found that trauma-focus did not predict dropout (Imel et al., 2013). We, therefore, decided to examine symptom severity at mid-treatment as a methodology to address clinicians' concerns about exacerbating patients' symptoms by commencing memory processing in therapy.

Depression commonly co-occurs with PTSD; one meta-analysis suggested that more than half of people with PTSD also meet diagnostic criteria for major depressive disorder (Rytwinski et al., 2013). Trauma-focused psychological treatments for PTSD have been suggested to have important impacts on other aspects of mental health, for example, by reducing symptoms of depression (Jayawickreme et al., 2014; Resick et al., 2002) and suicidal ideation (Gradus et al., 2013). Previous research has operationalised an increased severity of a co-morbid mental health disorder as an occurrence of an adverse event (Hoppen et al., 2022). Therefore, it is interesting to consider symptom exacerbation during therapy in terms of depression, especially as it is pertinent to clinicians' fear of increasing patient distress through therapy as a common symptom of depression concerns suicidal ideation and/or attempts (APA, 2022).

We aimed to research the clinician concern of symptom exacerbation during trauma-focused interventions for PTSD. Due to the previously found lack of reporting on harm during psychological interventions for PTSD (Hoppen et al., 2022), we investigated this by examining mid-treatment PTSD symptoms in RCTs on the efficacy of trauma-focused psychological treatments for adult PTSD compared to control groups (non-trauma-focused psychological treatments or passive controls). We examined PTSD symptoms during therapy, specifically at mid-treatment, to evaluate change after trauma memory processing has begun. As secondary outcomes, we aimed to examine depression symptoms at mid- and post-treatment and PTSD symptoms at post-treatment in trauma-focused treatments compared to controls. In addition, we conducted moderator analyses by quality (score of ≥ 7 on risk of bias assessment), military sample, concurrent substance misuse treatment, outlier-adjust and post-hoc moderator analysis by mid-treatment measure type (clinician v self-report).

2. Method

2.1. Preregistration

We adhered to the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Page et al., 2021) throughout this review (reported in Supplementary Material A). We registered the review with PROSPERO (CRD42023377077; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=377077). Ethical approval was not required as no new data were collected.

2.2. Search strategy

We developed optimal search terminology through scoping searches and based search terms for trauma-focused treatments on those from a previous review (Morina et al., 2021). We combined search terms for PTSD, interventions and RCTs (full search terms [with database adaptations] are provided in Supplementary Material B). The first author ran the searches on PsycINFO, MEDLINE, CINAHL and PTSDpubs between 31st March and 4th April 2023. The search was re-run on 9th February 2024 to update the review to include any publications since the initial search was run.

As an additional search process, the first author searched the included studies' reference lists, the 2018 International Society for Traumatic Stress Studies guidelines (Bisson et al., 2019), National Institute for Health and Clinical Excellence (NICE) guidelines for PTSD regarding trauma-focused interventions (National Institute for Health and Clinical Excellence, 2018), recent meta-analyses of RCTs for adult trauma-focussed treatment for PTSD published since 2020 (see Supplementary Material C) and papers reporting the original data for any studies that were excluded at the full-text screen due to reporting secondary analyses.

2.3. Eligibility criteria

We screened articles against the following inclusion criteria:

2.3.1. Population

Studies used a sample of adults (mean age >18 years) with PTSD. PTSD was defined through a diagnosis according to the International Classification of Diseases (ICD) and/or DSM criteria (through clinician diagnosis or an established diagnostic interview), being above the threshold on a self-report measure, or reporting subsyndromal PTSD symptoms. There were no restrictions on symptom severity or trauma type.

2.3.2. Intervention

We defined "trauma-focused psychological treatments" as

interventions, including exposure therapy, CT-PTSD, TF-CBT, EMDR, PE, CPT, and any other psychological intervention that describes the theoretical underpinning and targets trauma and/or PTSD symptoms (Furuta et al., 2018). By "targets trauma," we refer to interventions that use "techniques to facilitate processing a traumatic experience and in which the trauma focus is a central component of the therapeutic process" (Schnurr, 2017).

We included interventions of any length, in a one-to-one/couple/group format, and where treatment was offered in a standard format. We did not include interventions delivered in an intensive format as outcome measures would not be sensitive to change over short treatment courses (e.g. within the five days of intensive CT-PTSD; Ehlers et al., 2010). There was no limit on whether the intervention was delivered face-to-face or online.

2.3.3. Outcome measures

The main outcome measure was a mid-treatment measure of PTSD (self- or clinician-rated; where both were available, we used the clinician-rated measure).

2.3.4. Exclusion criteria

Studies were excluded if: a) more than 50 % of participants had a traumatic brain injury, b) they conducted secondary analyses of data, c) were published before 1980 (when PTSD was introduced into the DSM), d) were written in a language other than English, e) mid-treatment PTSD data was reported to be collected but could not be obtained (after a minimum of two email attempts at least one month apart) or f) augmented therapy with medication.

2.4. Screening process

The screening process is outlined in a PRISMA diagram (Fig. 1). After removing duplicates, we screened articles by title, abstract, and full text for eligibility. For the abstract screen, the first and second authors screened the first five papers together, and then both screened the next 100 papers independently. We had high inter-rater reliability for the first 100 abstract screens ($\kappa = .91$). The first author then screened the remaining abstracts. For the full-text screen, both authors independently screened all the texts with high inter-rater reliability ($\kappa = .92$). Throughout the screening process, conflicts were resolved through discussion with the last author.

2.5. Data extraction

The first author extracted data into pre-defined tables from all included studies: first author, publication year and country; sample details (size, age, percentage female, ethnicity, index trauma type, military/civilian sample); intervention and control arms (type, number and length of sessions); the format (individual/couples/group; online/in person; any concurrent substance misuse treatment) and PTSD and available depression symptom data at mid- and post-treatment (mean, standard deviation, number of participants at measurement point). Missing data was marked as "not reported." The data extracted was checked by author AG.

If a study had more than one eligible control group (e.g., emotion focused therapy and waitlist), we selected the more active group (i.e., emotion focused therapy). If a study had more than one type of trauma-

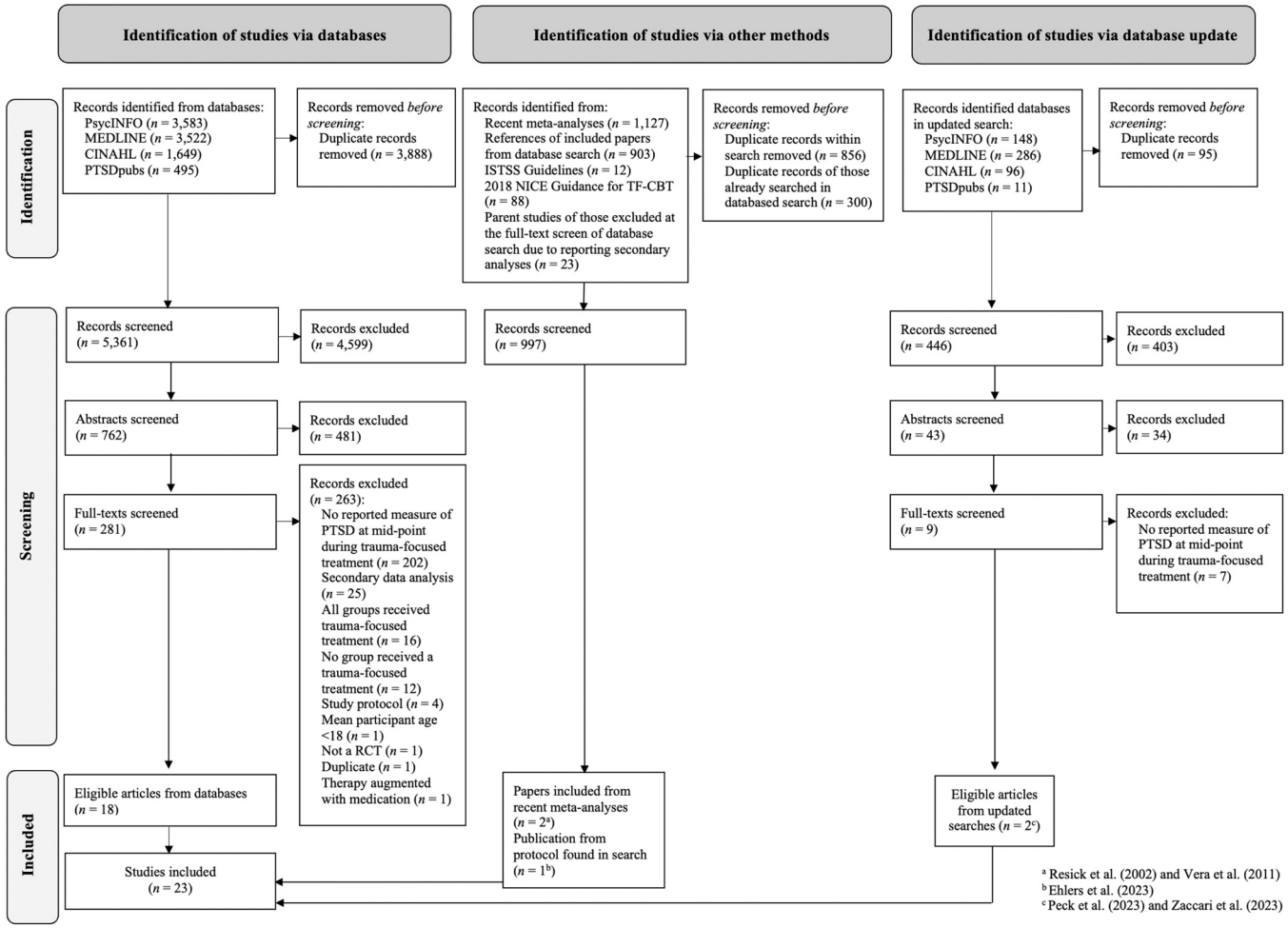

Fig. 1. PRISMA flowchart.

focused psychological therapy (e.g., prolonged exposure and cognitive processing therapy), we extracted data for both types.

2.6. Quality assessment

We used a method of assessing study quality based on criteria for defining empirically supported therapies (Chambless & Hollon, 1998) and the Cochrane Collaboration criteria for assessing the methodological validity of studies (Higgins & Green, 2008), which has been used by several similar meta-analyses (e.g. Cuijpers et al., 2010; Hoppen et al., 2022; Hoppen et al., 2023; Morina et al., 2021). We based our categorisation of "high quality" studies on these meta-analyses, and so a risk of bias score of ≥ 7 was categorised as high quality.

We assessed each study on the following criteria: 1) all participants met diagnostic criteria for PTSD at baseline; 2) use of treatment manual; 3) clinicians were trained in specific treatment; 4) treatment integrity was formally checked; 5) data were analysed using intention-to-treat; 6) the study had a minimal level of statistical power to find significant effects, and included ⩾50 participants; 7) independent randomisation; 8) blinded assessors of PTSD outcome (self-report assessment also received a positive score). We coded each criterion with '1′ if the criterion was fulfilled or '0′ if it was not met or reported, meaning each study scored between zero and eight, with a higher score indicating a higher quality. LP and AG independently assessed quality. We resolved discrepancies with at least two authors.

2.7. Data analysis

We used the metafor package in R (Viechtbauer, 2010) for all analyses. Hedges' *g* was calculated, and we used Cohen's convention for the interpretation of small (.2), medium (.5), and large (.8) effects (Cohen, 1988). The heterogeneity of studies was assessed with Cochran's Q test (Cochran, 1954), including its statistical significance and the I^2 statistic (i.e. the proportion of heterogeneity that can be attributed to between-study heterogeneity rather than error; Deeks et al., 2023). We calculated both 95 % confidence intervals (CI) of effect sizes as well as 95 % prediction intervals (PI; an interval within which the true estimate is to be expected as trials accumulate; IntHout et al., 2016) to provide better estimates of effect size based on study heterogeneity. We assessed publication bias through inspection of funnel plots and Egger's test (Egger et al., 1997). When Egger's test statistic was statistically significant, we used the trim-and-fill method Field (Duval & Tweedie, 2000) to correct detected asymmetry.

We re-ran the analysis for the studies that included more than one trauma-focused psychological therapy group with the less commonly occurring trauma-focused group (and the same control groups). We defined outliers as studies where the 95 % CI of the effect size did not overlap with the pooled effect size (Cuijpers, 2016) and ran outlier-adjusted analyses. We ran four sensitivity analyses to examine the effect of 1) control group type (active vs passive), 2) military sample (civilian vs military sample), 3) concurrent substance misuse treatment (concurrent substance misuse treatment vs no concurrent treatment) and 4) study quality (high vs not high). We ran a post hoc moderator analysis to determine whether there was an effect of the mid-treatment measure type (clinician vs - self-report).

3. Results

3.1. Study selection

The study selection process for the identification of studies via databases, other methods and the updated database search is presented in Fig. 1 in accordance with the PRISMA 2020 guidelines (Page et al., 2021). For the identification of studies via databases in the original search, after the deletion of duplicates, 5361 records remained. We removed 4600 at the title screen and 481 at the abstract screen, leaving 280 at the full-text review (see Supplementary Material D for reasons for exclusion at the full-text screen). After the full-text review, 18 eligible articles remained. An additional three records were included from other methods of searching, and two records were included from updating the database searches. Therefore, twenty-three studies are included in this review.

3.2. Study characteristics

Study characteristics are summarised in Table 1. Studies were conducted in the United States ($k = 17$; including two from Puerto Rico), Europe ($k = 5$) and Australia ($k = 1$) and published between 2002 and 2023. In the main intervention group, the mean age of participants was 39.8 (SD = 3.5; range = 18.2 – 54.9), and under half (47.9 %) were female. Of the studies that reported on ethnicity ($k = 18$), over half (61.9 %) of participants were White. Nine studies used a military sample, and five delivered concurrent treatment for alcohol and/or substance misuse.

Five different types of therapy were included in the trauma-focused psychological therapy groups (PE = 12; CPT = 5; TF-CBT = 3; CT-PTSD = 2; structured writing therapy for PTSD = 1). See Supplementary Material E for details on the timing and type of trauma memory processing within different trauma-focused interventions. There were eight studies with a passive control group (all waitlist) and 15 with an active control group (see Table 1 for details). Three studies had more than one trauma-focused group (Reger et al., 2016; Resick et al., 2002; Wells et al., 2015).

Study sample sizes at randomisation ranged from 14 to 212 (M = 88.6; SD = 56.5). Across all studies, 1986 participants were randomised, and 1543 (77.7 % of those randomised) completed mid-treatment measures. Trauma-focused psychological interventions were delivered to groups ($k = 4$), couples ($k = 1$), and individuals ($k = 18$). The mean number of sessions in the trauma-focused psychological therapy interventions was 13 (SD = 5.6), with an average session length of 82 min (SD = 22.38).

Approximately half of the studies ($k = 12$; 52.2 %) used a version of the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1990) at mid-treatment, and a significant majority of the remainder ($k = 6$) used a version of the PTSD Checklist (PCL; e.g. PCL-5, Weathers et al., 2013). Further details on study PTSD eligibility criteria, trauma type, PTSD/depression measure(s) at mid-treatment and timing of the mid-treatment measure(s) can be found in Supplementary Material F.

3.3. Study quality

The quality of trials was high for 12 studies (sum score ≥ 7 out of 8), and the mean quality score across trials of 6.2 (out of 8; SD = 1.6). Total quality ratings are reported in Table 1, and quality ratings for each item per study are reported in Supplementary Material G.

3.4. Mid-treatment PTSD symptoms

See Table 2 for results at mid-treatment for PTSD symptoms. Across the 23 included trials, 1454 participants completed the mid-treatment assessment of PTSD symptoms. The effect size at mid-treatment for trauma-focused psychological interventions compared to control conditions was non-significant as the 95 % CI crossed zero ($g = -.16$ 95 % CI [−.34,.03]). Heterogeneity was substantial, Q = 55.51, df = 22, $p < .001$, $I^2 = 63$ %. The prediction interval was wide and crossed zero (−.87,.54). When the outlier (Zaccari et al., 2022) was removed, the effect size was significant ($g = -.19$ 95 % CI [−.36, −.03]; $k = 22$); however, the prediction interval remained quite wide (−.75,.37). A forest plot of all effect sizes and CIs from each study is shown in Fig. 2, split by studies with an active and passive control group. From inspection of the funnel plot (Fig. 3), there was asymmetry. Egger's test was significant (intercept: −.012; 95 % CI [−.54,.56]; $p = .52$, $z = -.64$).

Table 1
Study characteristics.

Author (year) Country	N[a] ran.	N[a] mid	Study groups	Intervention frequency	Treatment format	Age, mean (SD)	% female	Total sample ethnicity	Military sample?	SM intervention?	Total quality score
Allen et al. (2022)	25	16	iCBT	6 sessions over 10 weeks	Ind Online	41.9 (14.5)	90.5	NR	N	N	5
Australia	24	19	WL (P)	11 weeks		41.3 (13.5)	89.5				
Back et al. (2019)	54	41	COPE	12 weekly sessions (90 mins)	Ind In person	39.7 (11.0)	7.4	49.0 % W; 30.0 % AA/B; 3.0 % H/L; 2.0 % O	Y	Y	7
US	27	15	Relapse prevention (A)			41.9 (10.3)	9.9				
Ehlers et al. (2014)[b]	31	31	CT-PTSD	12 weekly sessions (90 mins for initial sessions, 60 mins thereafter)	Ind In person	41.5 (11.7)	58.1	70.0 % W; 30.0 % NW	N	N	8
UK	30	30	Emotion focused supportive therapy (A)			37.8 (9.9)	56.7				
Ehlers et al. (2023)	107	98	iCT-PTSD	12 weeks of SMS and short weekly phone calls (designed to last on average 20 min)	Ind Online	36.3 (12.2)	74.0	87.0 % W; 5.0 % B; 5.0 % O; 3.0 % A	N	N	8
UK	105	96	iStress-PTSD[c] (A)			35.8 (11.5)	73.0				
Ghafoori et al. (2017)	47	25	PE	12 weekly sessions (60 - 90 mins)	Ind In person	35.1 (12.8)	83.0	28.2 % W; 43.7 % H/L; 19.7 % AA; 8.4 % O	N	N	7
US	24	18	Person centred therapy (A)			35.3 (10.4)	83.3				
Kline et al. (2021)	63	35	COPE	12 sessions (90 mins) once/twice per week	Ind In person	43.2 (13.5)	8.9	65.1 % W; 13.8 % B; 5.5 % A; 15.6 % O	Y	Y	4
US	56	38	Seeking Safety[d] (A)			39.7 (11.3)	11.1				
Markowitz et al. (2015)[b]	38	29	PE	10 sessions over 14 weeks (90 mins)	Ind In person	41.8 (12.0)	55.0	65.0 % W; 17.0 % AA; 8.0 % A/PI; 9.0 % O	N	N	7
US	40	37	Interpersonal psychotherapy (A)	14 weekly sessions (50 mins)		38.1 (11.2)	70.0				
Monson et al. (2006) US	30	24	CPT	12 sessions twice weekly, over 2 weeks when possible (session length NR)	Ind In person	54.9 (6.5)	6.7	93.3 % W; 1.7 % A; 5 % O	Y	N	8
	30	28	WL[e] (P)	6 weeks		53.1 (6.1)	13.3				
Monson et al. (2012) US	20	16	Conjoint CBT for PTSD	15 sessions (twice weekly/weekly; session length NR)	Couple In person	40.4 (11.3)	65.0	72.5 % W; 27.5 % NW	N	N	7
	20	18	WL (P)	12 weeks		33.8 (10.5)	85.0				
Peck et al. (2023)	10	8	PE	12 weekly sessions (60 mins)	Ind	33.8 (4.6)	60.0	96.7 % W; NR	N	Y	6
US	10	10	TAU (P)	12 weeks	In person	44.7 (8.9)	70.0				
Rauch et al. (2015)	18	11	PE	10–12 sessions (80 mins; period over which sessions occurred NR)	Ind In person	30.0 (18.4)	18.2	83.3 % W; 13.9 % B; 2.8 % O	Y	N	2
US	18	15	Present-centered therapy (A)			53.6 (28.7)	0				
Reger et al. (2016) US	54	39	PE	10 sessions (90 –120 mins; weekly/twice weekly, with flexibility)	Ind In person	30.9 (7.1)	5.6	72.2 % W; 13.0 % H/L; 7.4 % A/PI; 3.7 % B; 3.7 % O	Y	N	8
	54	52	Waitlist (P)	5 weeks		30.4 (6.5)	1.9				
	54	36	Virtual reality exposure (O)	10 sessions (90 –120 mins; weekly or twice weekly, with flexibility)		29.5 (6.5)	3.7				
Resick et al. (2002) US	62	41	PE (O)	12 sessions over 6 weeks (90 mins; except 1st session which was 30 mins)	Ind In person	31.9 (10.4)	100	71.0 % W; 25.0 % AA; 4.0 % O	N	N	7
	47	28	Waitlist (P)	6 weeks		33.9 (9.6)	100				
	62	44	CPT (O)	12 sessions over 6 weeks (90 mins)		30.6 (9.7)	100				
Resick et al. (2015)	56	42	Group CPT (cognitive version only)	12 sessions over 6 weeks (90 mins)	Group In person	31.8 (7.3)	7.0	63.0 % W; 20.0 % B; 9.0 % H/L; 9.0 % O	Y	N	5
US	52	43	Group present-centered therapy (A)			32.4 (7.9)	8.0				

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Table 1 (*continued*)

Author (year) Country	N[a] ran.	N[a] mid	Study groups	Intervention frequency	Treatment format	Age, mean (SD)	% female	Total sample ethnicity	Military sample?	SM intervention?	Total quality score
Rosner et al. (2019) Germany	44	36	Developmentally adapted CPT	30 sessions over 16 to 20 weeks (50 mins; with 6 optional sessions)	Ind In person	18.2 (2.2)	89.0	NR	N	N	5
	44	41	Waitlist with treatment advice[f] (P)	At least 28 weeks		18.1 (2.2)	82.0				
Ruglass et al. (2017)[b]	39	18	COPE	12 sessions over 6 weeks (90 mins)	Ind In person	43.1 (10.0)	28.2	59.1 % N/AA; 20 %	N	Y	6
US	43	27	Relapse prevention (A)			44.2 (9.1)	37.2	H/L; 18.2 % W; 2.7 % O			
Sloan et al. (2018)	98	87	Group CBT	14 sessions over 16 weeks (120 mins)	Group In person	54.4 (11.4)	0	74.2 % W; 16.7 % AA;	Y	N	8
US	100	94	Group present-centered therapy (A)			57.22 (12.5)	0	9.1 % O			
van Dam et al. (2013) Netherlands	19	16	Structured Writing Therapy for PTSD + group intensive SUD CBT	10 weekly sessions (45–60 mins) + 20 sessions over 14 weeks (120 mins)	Ind In person	42.6 (8.4)	31.6	73.5 % W; 14.7 % O; 11.8 % B	N	N	3
	17	11	Group intensive SUD CBT (A)	20 sessions over 14 weeks (120 mins)		41.9 (10.0)	33.3				
Vera et al. (2011)	7	5	PE (culturally adapted)	15 weekly sessions (90–120 mins)	Ind In person	45.8 (NR)	0	NR	N	N	6
Puerto Rico	7	7	UC[7] (A)	15 weeks			0				
Vera et al. (2021)	49	37	PE (culturally adapted)	12 –15 weekly sessions (90 mins)	Ind In person	44.1 (11.5)	73.5	100 % H/L	N	N	7
Puerto Rico	49	37	Applied relaxation (A)	12 –15 weekly sessions (60–90 mins)		43.2 (12.7)	89.3				
Wells et al. (2015)	11	10	PE	8 weekly sessions (60 mins)	Ind In person	40.5 (10.9)	40.0	NR	N	N	6
UK	10	10	WL (P)	8 weeks		42.7 (18.5)	60.0				
	11	9	Metacognitive therapy (O)	8 weekly sessions (60 mins)		40.6 (11.9)	36.4				
Zaccari et al. (2022)	17	10	CPT	12 weekly sessions (90 mins)	Group In person	44.2 (7.9)	100	80.5 % AA; 12.2 % W;	Y	N	6
US	24	12	Trauma-sensitive yoga[g] (A)	10 weekly sessions (60 mins)		46.1 (12.4)	100	7.3 % O			
Zaccari et al. (2023)	58	34	CPT	12 weekly sessions (90 mins)	Group In person	48.3 (11.6)	100	72.6 % AA; 19.1 % W;	Y	N	7
US	71	59	Trauma-sensitive yoga[g] (A)	10 weekly sessions (60 mins)		48.2 (11.0)	100	0.8 % A; 6.9 % O			

Note. Ind= individual; NR = not reported; SM = substance misuse. **Ethnicity:** A = Asian; AA = African American; B = Black; H/L = Hispanic/Latino; NW = Non-white; O = Other/unknown; PI = Pacific Islander; W = White. **Other:** CBT = Cognitive Behavioural Therapy; COPE = Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure; NR = not reported; SM = substance misuse. **Intervention types**: CBT = cognitive behavioural therapy; CPT = cognitive processing therapy; iCT-PTSD = cognitive therapy for PTSD; PE = prolonged exposure; UC = usual care; WL = waiting list. **Study groups**: A = active control; O = other trauma-focused Tx; P = passive control.

[a] N at ran. = N randomised; N at mid = N at mid-treatment assessment.

[b] This study also included an intensive Cognitive Therapy group which has been excluded from this systematic review.

[c] iStress-PTSD was a stress management programme (Asplund Persson et al., 2018) that was adapted for people with PTSD by Andersson and colleagues for this trial.

[d] Seeking Safety is a present-focused therapy focused on coping skills and establishing safety (e.g., reducing substance use, terminating harmful relationships) for people with comorbid PTSD and substance use disorder (Najavits, 2002).

[e] Participants in WL were allowed to continue interventions not focused on PTSD.

[f] Four participants received pharmacological treatment, one participant received psychotherapy, and two participants received both pharmacological and psychological treatment.

[g] Protocol "integrates themes related to establishing safety, individual choice, interoception, being in the present moment, and taking effective action" (Zaccari et al., 2022).

Applying the trim and fill method inputted four missing studies (see Fig. 4).

Although control condition type (i.e. active vs passive control group) did not moderate the overall effect ($p = .11$), the studies with a passive control group had a small and statistically significant effect ($g = -.32$), unlike studies with an active control group where the effect was trivial and not significantly different from zero ($g = -.07$). Estimates of heterogeneity suggested there was considerable variance between the studies with an active control (Q = 39.35, I^2 = 71 %), but non-significant variance in studies with a passive control (Q = 12.04, I^2 = 40 %).

There was no significant difference in the effect size between high quality studies ($k = 12$) and those that were not ($k = 11$; $p = .12$); however, the high quality studies had a statistically significant effect size ($g = -.25$), while the non-high quality studies did not ($g = -.01$). There was also no significant difference in the effect size between studies with military or civilian samples ($p = .13$), studies that concurrently treated substance misuse versus those that did not ($p = .13$) or studies that used a self-rated versus clinician rated measure at mid-treatment ($p = .11$).

When we re-ran the analysis using the other intervention groups of trauma-focused interventions from the three studies that had more than one trauma-focused intervention, trauma-focused psychological interventions yielded non-significant negative effect compared to control

Table 2
Mid-treatment PTSD symptoms.

Analysis	*k*	N	*g*	95 % CI	95 % PI	Q	I^2	*p* of moderation test
All	23	1454	−.16	−.34,.03	−.87,.54	55.51***	63 %	
By control group type								.11
Active	15	1058	−.07	−.32,.17	−.86,.72	39.35***	71 %	
Passive	8	396	−.32	−.59, −.05	−.86,.22	12.04	40 %	
By study quality								.12
High	12	1014	−.25	−.48, −.03	−.92,.41	30.41**	66 %	
Not high	11	440	−.01	−.34,.32	−.91,.89	23.44**	62 %	
By military								.13
Civilian	14	775	−.20	−.42,.02	−.79,.40	25.12**	50 %	
Military	9	679	−.09	−.47,.28	−1.14,.96	29.75***	81 %	
By substance misuse treatment								.13
No concurrent substance misuse treatment	18	1235	−.18	−.38,.02	−.85,.49	43.71***	63 %	
Concurrent substance misuse treatment	5	219	−.04	−.54,.45	−1.06,.98	11.62**	66 %	
Outlier-adjusted								.07
All, excluding outlier	22	1432	−.19	−.36, −.03	−.75,.37	43.25**	53 %	
All active control groups, excluding outlier	14	1036	−.13	−.33,.08	−.71,.46	27.97**	57 %	
Mid-treatment measure								.11
Self-rated	11	726	−.09	−.28,.10	−.48,.30	17.23	33 %	
Clinician-rated	12	728	−.20	−.54,.13	−1.22,.81	37.73***	76 %	

* $p < .05$;
** $p < .01$;
*** $p < .001$

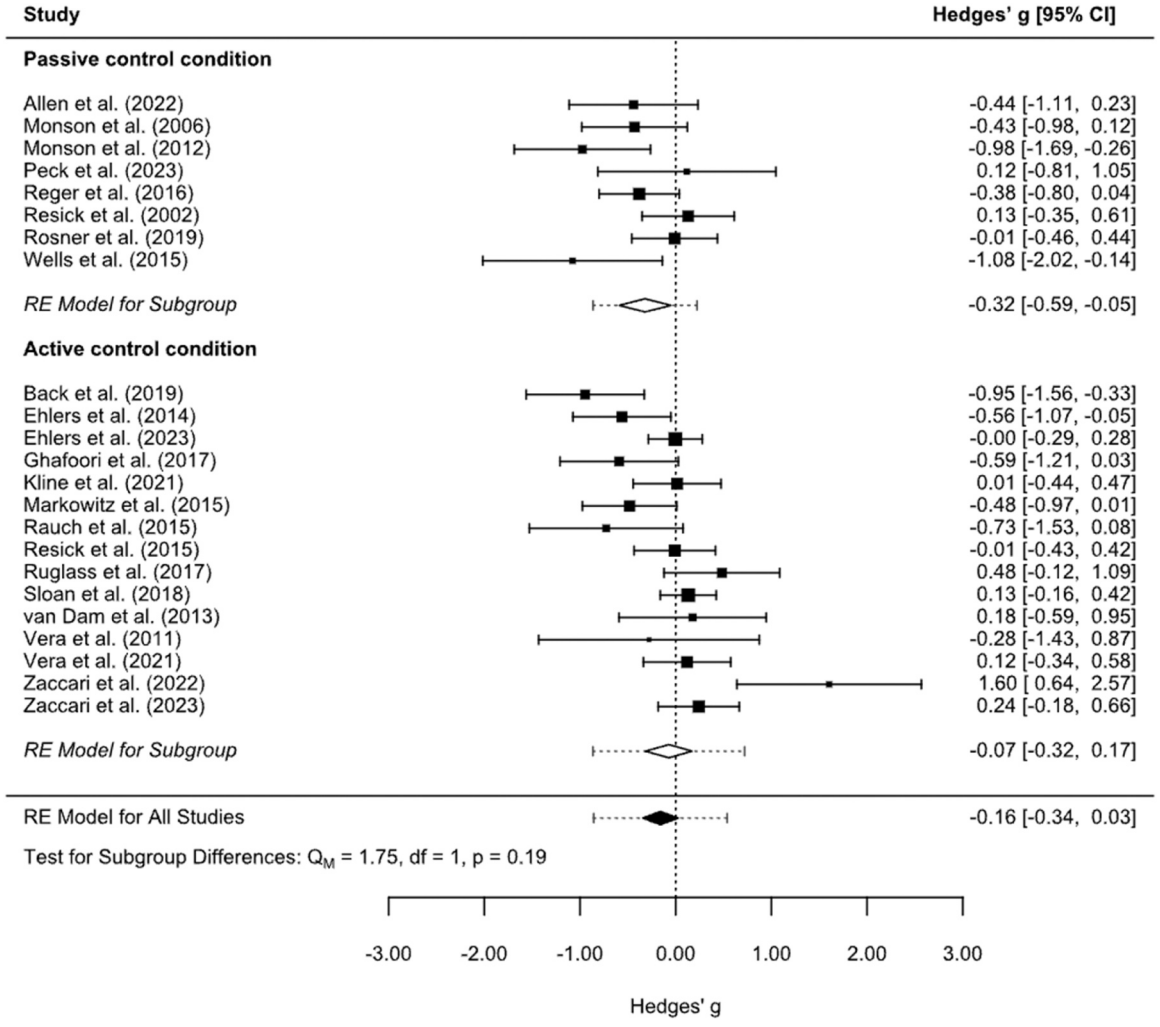

Fig. 2. Forest plot of mid-treatment PTSD symptoms by active and passive control conditions.

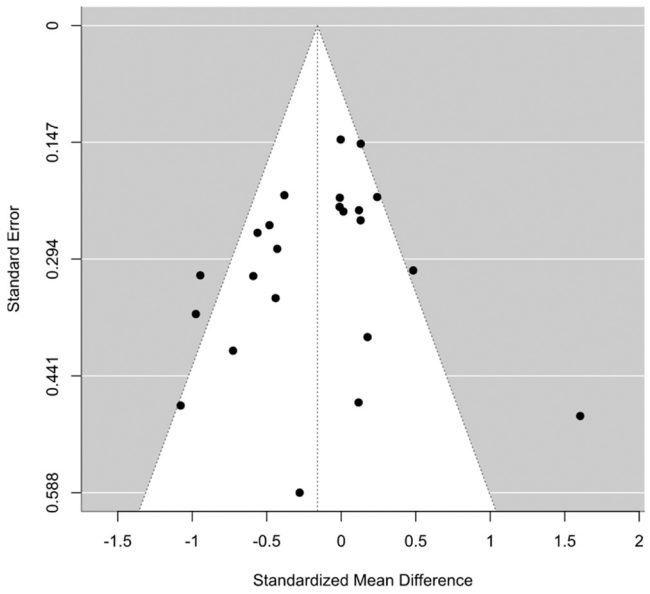

Fig. 3. Funnel plot of mid-treatment PTSD Symptoms Note. Data point on the far right is outlier (Zaccari et al., 2022) The dashed lines creating a triangular area indicate the 95 % confidence limits and the vertical dashed line represents the overall effect size.

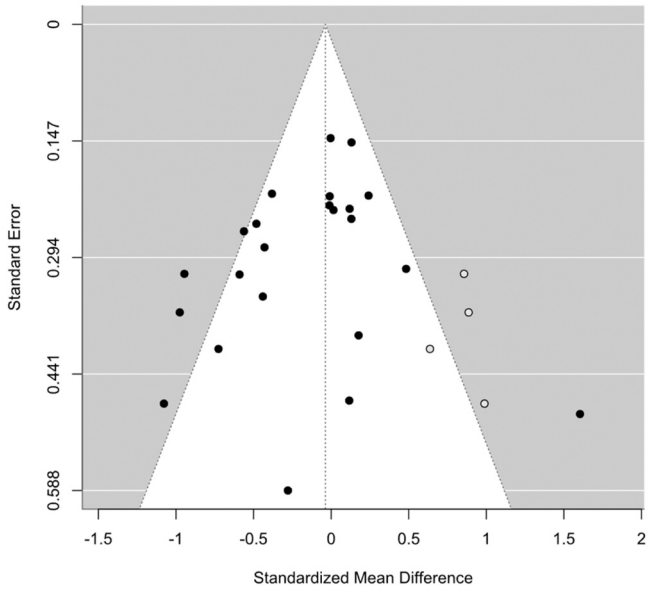

Fig. 4. Funnel plot of mid-treatment PTSD Symptoms after applying the trim-and-fill method.

groups ($g = -.18$ [95 % CI −.39,.03]; $k = 23$).

3.5. Mid-treatment depression symptoms

Twelve of the included trials reported mid-treatment assessment measures of depression (N = 957). Trauma-focused psychological

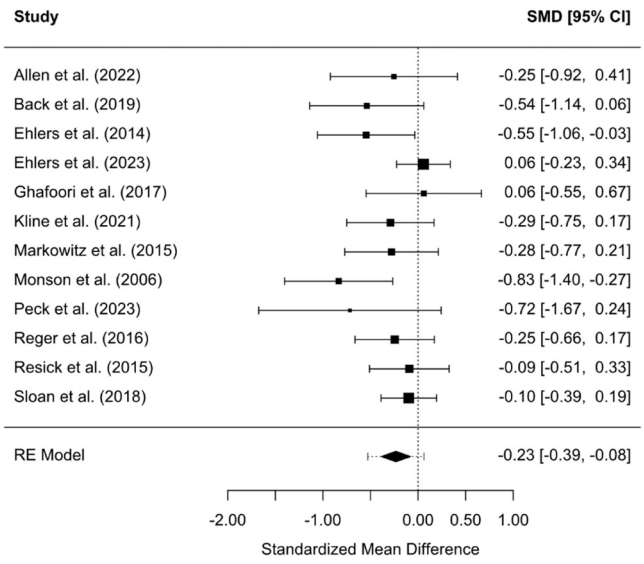

Fig. 5. Forest plot of mid-treatment depression symptoms.

interventions yielded a small and statistically significant effect size compared to controls in terms of depression at mid-treatment ($g = -.23$ [95 % CI −.39, −.08]; $k = 12$). Estimates of heterogeneity suggested little variance between the studies, Q = 18.81, df = 11, p = .24, I^2 = 24 %. See Table 3 for results at mid-treatment for depression symptoms and a forest plot of all effect sizes and CIs from each of the studies in Fig. 5.

Of the studies that reported mid-treatment for depression symptoms, eight studies had an active control group (N = 761), and four had a passive control group (N = 196). The studies with a passive control produced a small statistically significant effect size ($g = -.46$). Studies with an active control yielded an effect size of $g = -.15$, with the 95 % confidence interval including 0 (−.30,.00). Moderation analysis did not reveal a significant difference between these groups.

When re-ran the analysis using the other intervention groups of trauma-focused interventions from the three studies that had more than one trauma-focused group, we similarly found that trauma-focused psychological interventions yielded a small effect size compared to control conditions for depression at mid-treatment (g −.21 [95 % CI −.38, −.07]; $k = 12$).

3.6. End of treatment PTSD and depression symptoms

Trauma-focused psychological interventions yielded a medium effect on PTSD symptoms ($g = -.57$ [95 % CI −.79, −.35]; $k = 23$) and a small effect on depression symptoms (g −.45 [95 % CI −.66, −.25]; $k = 12$) at post-treatment compared to control conditions. There was a substantial degree of heterogeneity between the studies in terms of post-treatment PTSD symptoms (I^2 = 70 %) and a moderate degree of heterogeneity between the studies in terms of post-treatment depression symptoms (I^2 = 47 %). Table 4 reports the post-treatment PTSD and depression symptom results for trauma-focused psychological interventions compared to control conditions, and a forest plot for post-treatment PTSD symptoms can be found in Fig. 6 and for depression symptoms

Table 3
Mid-treatment depression symptoms.

	k	N	*g*	95 % CI	95 % PI	Q	I^2	*p* of moderation test
All	12	957	−.23	−.39, −.08	−.53,.06	13.81	24 %	
By control group type								.09
Active	8	761	−.15	−.30,.00	−.34,.04	7.25	7 %	
Passive	4	196	−.46	−.79, −.12	−.91,.00	3.30	21 %	

Table 4
Post-treatment PTSD and depression symptoms.

	k	N	*g*	95 % CI	95 % PI	Q	I^2	*p* of moderation test
PTSD								
All trials	23	1298	−.57	−.79, −.35	−1.45,.30	67.38***	70 %	
By control condition type								< .001
Active	15	935	−.33	−.57, −.09	−1.07,.40	35.92**	64 %	
Passive	8	363	−1.00	−1.22, −.78	−1.22, −.78	4.00	0 %	
Depression								
All trials	12	854	−.45	−.66, −.25	−.96,.06	13.81	47 %	
By control group type								.01
Active	8	680	−.32	−.47, −.17	−.47, −.17	9.48	.02 %	
Passive	4	174	−.82	−1.36, −.29	−1.79,.14	7.18	59 %	

* $p < .05$;
** $p < .01$;
*** $p < .001$

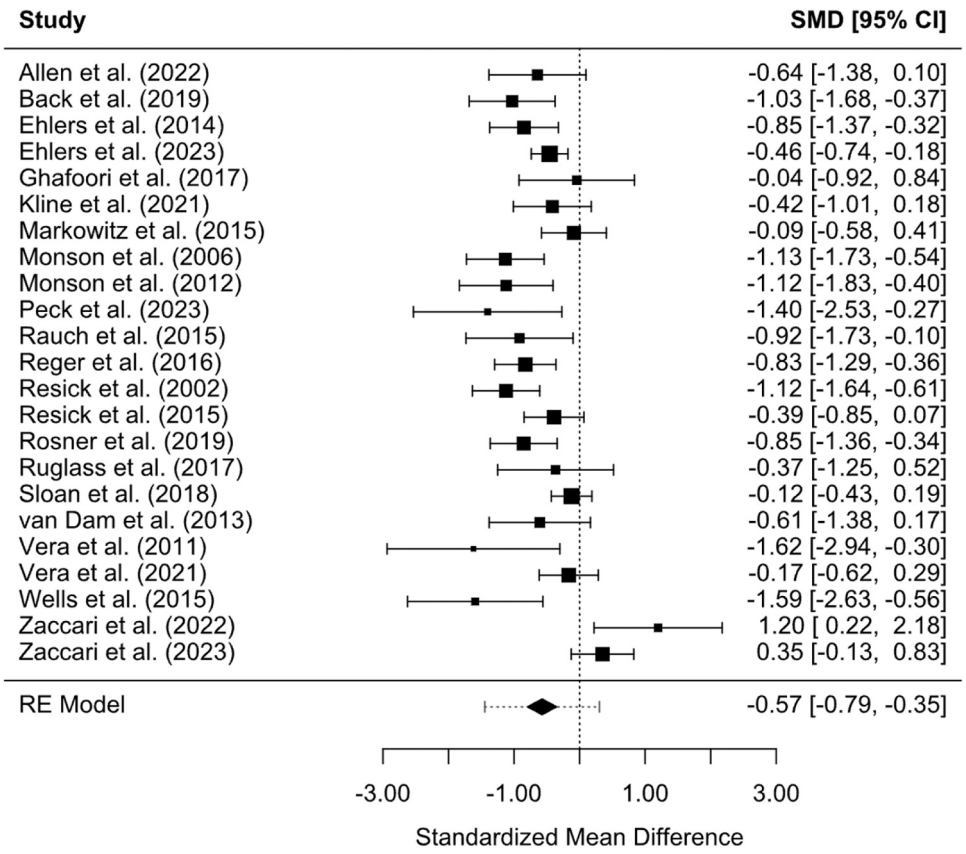

Fig. 6. Forest plot of post-treatment PTSD symptoms.

in Fig. 7. The effect sizes for both outcomes were moderated by control type, with passive control conditions yielding larger effects than active control condition trials.

4. Discussion

This systematic review and meta-analysis examined mid-treatment PTSD symptoms in RCTs comparing trauma-focused psychological treatments for adult PTSD to controls. As secondary aims, this review examined depression symptoms at mid- and post-treatment and PTSD symptoms at post-treatment in trauma-focused treatments compared to controls.

Since we found no evidence of PTSD symptom exacerbation at mid-treatment in trauma-focused psychological interventions compared to control groups (i.e., effect sizes produced from all analyses had a negative magnitude), this meta-analysis suggests that if there is any symptom exacerbation during trauma-focused interventions, it appears to be limited in that it has reduced by mid-treatment assessment or occurs between mid- and post-treatment. Our analysis of mid-treatment data suggests that not only is there no evidence for PTSD symptom exacerbation at mid-treatment, there is some evidence of PTSD symptom relief in trauma-focused psychological therapies compared to control groups at mid-treatment (e.g. in high quality studies). It is important to note that in all analyses of mid-treatment PTSD symptoms, the prediction interval was non-significant, meaning that in future studies, there is a chance that the effect sizes observed may not be replicated. Furthermore, although we did not find evidence of symptom exacerbation in trauma-focused compared to non-trauma-focused psychological treatments, it is important to note that this is a comparison of mean scores, so it is possible that some patients receiving trauma-focused treatment for PTSD may experience symptom exacerbation. However, Jayawickreme and colleagues (2014) argue that trauma-focused treatments

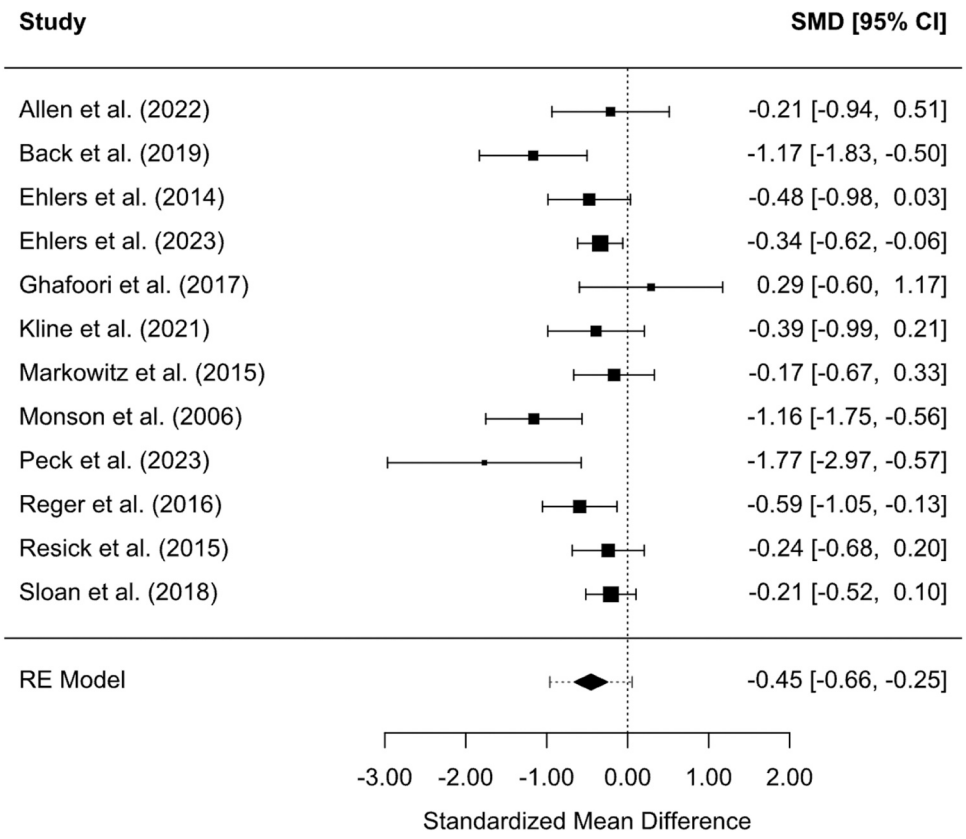

Fig. 7. Forest plot of post-treatment depression symptoms.

reduce the risk of symptom exacerbation compared to not receiving treatment from their study pooling data from four RCTs which found that no participants in the trauma-focused conditions experienced PTSD symptom exacerbation from pre- to post-treatment, compared to 8.1 % of participants in the waitlist.

This meta-analysis reports a large effect size when only compared to studies with a passive control group ($g = -1.00$; [CI −1.22, −.78]), similar to that reported at post-treatment in previous meta-analyses, e.g. Mavranezouli and colleagues (2020) found that TF-CBT compared to waitlist at post-treatment produced a standardised mean difference of −1.46 (95 % CI −1.87, −1.05). In the main analysis at post-treatment trauma-focused interventions yielded a medium effect on PTSD symptoms when compared to all control conditions ($g = -.57$; [CI −.79, −.35]). Crucially, these findings suggest that trauma-focused therapies included in this review yielded significant improvements compared to control conditions (regardless of which type of control) with respect to PTSD at post-treatment, even if they had not by the mid-treatment assessment.

Trauma-focused psychological interventions yielded a significant reduction in depression symptoms at mid- and post-treatment in trauma-focused interventions compared to control conditions. These results support the suggestion that trauma-focused treatments for PTSD can have impacts beyond the focus of the trauma work (e.g. Resick et al., 2002). This is important as research has found a reliable worsening of symptoms of depression in around 12 % of patients during waitlist conditions (compared to 2 % of patients during trauma-focused interventions) therefore suggesting the rate of harm (in terms of depressive symptoms) to be lower during trauma-focused interventions compared to not receiving treatment (Jayawickreme et al., 2014). Since trauma-focused interventions can potentially alleviate symptoms of depression as well as PTSD, this strengthens the argument for their use. However, in all analyses of depression symptoms, the prediction interval crossed the line of no effect suggesting that an effect in this direction might not be observed in future studies.

4.1. Strengths and limitations

We strengthened this review by following best practice: we pre-registered it with PROSPERO and adhered to PRISMA guidance. The reliability of the review process was confirmed by an independent rater for screening, data extraction and quality assessment. The search process was extensive since we used deliberately broad search criteria, conducted our search on four databases, searched included studies' reference lists and searched papers from other relevant publications and recent meta-analyses of RCTs.

Using different therapy modalities within one analysis has limitations as different modalities introduce trauma-focused components at different times, meaning that potential symptom exacerbation could occur at different time points in treatment depending on the modality being used. For example, CT-PTSD begins trauma processing via imaginal reliving in session two (Murray et al., 2022), while PE begins trauma processing via in vivo exposures in session 3 (Fina et al., 2021). However, there were only a small number of studies of each intervention type, meaning comparisons between different types of trauma-focused interventions were not possible. This meta-analysis only includes a small proportion of the overall literature reporting data on mid-treatment PTSD symptoms and therefore the studies reporting this may not be representative of all studies on trauma-focused interventions for PTSD.

Of all the participants randomised to the included studies, 77.7 % completed mid-treatment measures. While non-competition of mid-treatment measures could be due to a variety of factors (e.g., participant's incomplete response to measures, drop-out due to symptom alleviation, drop-out for practical reasons such as moving away from study site), it is possible that there were participants in the included studies who had dropped out from treatment before mid-treatment due

to symptom exacerbation. Therefore, a limitation of this study is that, by examining mid-treatment measures, drop-out due to symptom exacerbation is not examined meaning that results of this meta-analysis might not be generalisable to participants who discontinue treatment before mid-treatment. However, a study by Foa and colleagues (2002) reported that participants who dropped out of treatment of PE were not more likely to show symptom exacerbation than those who did not drop out.

It could be argued that symptom exacerbation might be more likely earlier in treatment than mid-treatment, potentially when active trauma memory processing begins, as this is when the trauma is initially approached (as opposed to avoiding trauma-related stimuli, which is a key PTSD criterion). Therefore, the included mid-treatment study data might not capture all experiences of symptom exacerbation during treatment.

4.2. Future research

Incidences of harm can be defined through PTSD symptom exacerbation pre- to post-treatment, as well as the occurrence of adverse events, i.e. aversive but non-lethal states (e.g. increased severity of comorbidity) or more "serious" potentially lethal events (e.g. acute suicidality; Hoppen et al., 2022). This review only considered symptom exacerbation during therapy through PTSD and depressive symptoms, while other possible incidences of harm were not evaluated, so it is important that other incidences of harm throughout treatment are researched to further examine the clinician concern of "retraumatising" patients during trauma-focused interventions for PTSD. Further, future meta-analytic research could examine PTSD symptoms at the point of treatment in which trauma memory processing is introduced in each intervention type in order to examine potential symptom exacerbation due to the initiation of trauma memory processing.

We encourage future RCTs on trauma-focused interventions for PTSD to collect and report (even in a repository) on PTSD symptoms throughout treatment, or at least at mid-treatment. This will allow future research to draw more reliable conclusions on PTSD symptom exacerbation during trauma-focused therapy. It would be clinically relevant to research symptom exacerbation during trauma-focused interventions when these treatments are delivered by less experienced clinicians.

4.3. Clinical implications

The results of this meta-analysis suggest that trauma-focused psychological therapies are not associated with PTSD symptom exacerbation at mid-treatment, and therefore any potential symptom exacerbation before this is short-lived. This meta-analysis, along with research suggesting that symptom exacerbation occurs more frequently in waitlist conditions than conditions receiving trauma-focused therapy (Jayawickonreme et al., 2014) suggests that trauma-focused interventions should not be withheld from patients based on clinician fear of PTSD symptom exacerbation. Indeed, clinicians might provide reassurance to patients concerned that talking about their trauma will make them worse, given that across studies, by mid-treatment, patients receiving trauma-focused interventions do not exhibit symptom exacerbation and, in fact, are likely doing better in terms of PTSD and depression symptoms than if they had received a non-trauma-focused intervention or no treatment at all. However, since the size of the effect increased from mid-treatment to post-treatment, a full course of treatment is necessary for the full benefits of trauma-focused psychological therapies for PTSD to be detected.

Since Finch and colleagues (2020a) reported fear of increasing patient distress through therapy as a theme in a systematic review of clinicians' perceived barriers to using trauma-focused interventions, there is a need to address this concern. For example, training could be useful necessary to share information with clinicians on symptom change during trauma-focused interventions. This meta-analysis suggests that trauma-focused interventions might show gains relative to non-trauma-focused interventions and waitlist conditions in terms of symptoms of depression and PTSD, even at mid-treatment.

Clinicians should discuss with patients the potential for symptom exacerbation during trauma-focused treatment for PTSD and explain that this is not indicative of treatment failure based on research. For example, Resick and colleagues' (2015) RCT reported PTSD symptom exacerbation (measured by an increase of 15 of more on the PCL-5 [Weathers et al., 2013] compared to baseline) in only a small minority of patients during treatment (5.7 % in the CPT group), and that only one patient experienced symptom exacerbation by follow-up. Similarly, Foa and colleagues (2002) found that patients who reported symptom exacerbation (in terms of PTSD, anxiety or depression) during PE benefited from treatment as much as those who did not report symptom exacerbation. Further, although Larsen and colleagues (2016) found a difference between patients who reported symptom exacerbation during PE or CPT and those who did not, all post-treatment means fell within norms for non-clinical populations (rather than norms for a PTSD population), and the difference was less than the reliable change index. Therefore, it could be argued that temporary symptom exacerbation might not necessarily be detrimental in the context of trauma-focused treatment. Since avoidance of trauma-related reminders is a key symptom of PTSD, it follows that some patients may experience a temporary increase in symptoms when exposed to trauma memories.

4.4. Conclusion

We found no evidence of PTSD symptom exacerbation at mid-treatment in trauma-focused psychological interventions compared to controls. Further, sensitivity analyses with high quality studies and with studies with passive controls yielded statistically significant small effect sizes favouring trauma-focused psychological interventions. At post-treatment, trauma-focused psychological interventions yielded a medium effect on PTSD symptoms ($g = -.57$) when compared to all control conditions and a large effect when only compared to studies with a passive control ($g = -1.0$), therefore suggesting that a full-course of treatment is necessary to continue to reduce PTSD symptoms from mid-treatment. We found evidence to suggest that trauma-focused psychological interventions can impact symptoms of depression, finding a statistically significant effect size compared to control conditions in terms of depression symptoms at mid-treatment and post-treatment. In sum, we found no evidence for PTSD or depression symptom exacerbation at mid- or post-treatment in trauma-focused interventions compared to controls, suggesting that trauma-focused interventions should not be withheld based on fear of symptom exacerbation.

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CRediT authorship contribution statement

Richard Meiser-Stedman: Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **David Trickey:** Writing – review & editing. **Kenny Chiu:** Writing – review & editing, Supervision, Project administration. **Alicia Graham:** Methodology. **Lucy Purnell:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests. RMS & DT train mental health professionals in the use of trauma-focused

cognitive-behavioural therapies for the treatment of PTSD.

All other authors declare they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.janxdis.2024.102925.

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