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ORIGINAL ARTICLE

Heterogeneity in Treatment Effect in Posttraumatic Stress Syndrome Trials: A Meta-Regression Analysis

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Abstract

Objective: To evaluate the heterogeneity in treatment effect in posttraumatic stress disorder (PTSD) trials.
Patients and Methods: We downloaded data from a publicly available repository that captured PTSD trials published from January 1988 through February 2023. We applied restricted maximum-likelihood random-effect meta-analyses and meta-regression to explore potential moderators of treatment effect including methodologic study features (risk of bias domains and control group response rate), characteristics of the population, and intervention features following the theme, intensity, and platform framework.
Results: We included 199 PTSD trials that reported the outcomes of diagnosis resolution (122 trials, 8437 patients) and clinically meaningful improvement (133 trials, 9895 patients). Multiple treatments demonstrated effectiveness but with significant heterogeneity. Statistically significant moderators included risk of bias domains of randomization sequence and outcome measurement, control group response rate reflecting severity of PTSD in the enrolled population, and whether the psychotherapeutic approach was trauma focused (P values <0.05). There was no statistically significant effect for the frequency of treatments per week, format of the intervention (eg, individual vs group), duration of the intervention, or delivery method (in person vs not), (P values <0.05). Characteristics of the population such as sex, age, and military status did not appear to significantly affect the treatment effect (P values <0.05).
Conclusion: Trauma focused psychotherapies should be considered the first-line intervention to induce remission. Several patient characteristics or treatment context did not modify the treatment effect, which allows tailoring care based on patient values, preferences and logistics.

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Most people experience 1 or more traumatic events in their lifetime, but some develop debilitating symptoms related to their experiences and are diagnosed with posttraumatic stress disorder (PTSD).[1] Posttraumatic stress disorder manifests as intrusive thoughts, nightmares, or flashbacks of past traumatic events; avoidance of reminders of the trauma; emotional arousal or reactivity; and mood or cognitive symptoms such as loss of interest or negative self-appraisals, all leading to significant functional impairment. For some people, PTSD can include dissociation including symptoms of depersonalization or derealization. When PTSD is caused by multiple traumatic events and is associated with psychiatric comorbidities such as a major depressive disorder, it is considered complex and more difficult to treat.[2-4] Overall, the lifetime prevalence of PTSD is 6.8% and is higher in women.[5] In the United States in 2018 alone, the total excess economic burden of PTSD was estimated at $232.2 billion.[6]

Updated clinical practice guidelines have identified multiple treatments that have shown effectiveness over control interventions. These include manualized trauma focused therapies, which explicitly focus on processing the trauma through deliberate focus on memories and reminders of the traumatic experiences. These treatments include various types of

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exposure therapies, eye movement desensitization and restructuring (EMDR), cognitive processing therapy (CPT), and trauma focused cognitive behavioral therapy (CBT). Other psychotherapies that do not directly focus on processing the trauma have also been examined for the treatment of PTSD. In addition to psychotherapy, pharmacologic therapies such as selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) have been studied for the treatment of PTSD and found to be effective in reducing symptoms, yet most studies comparing these treatments with trauma focused psychological treatments suggest they are less effective.[7,8]

Despite the availability of a range of therapies shown to decrease symptoms of PTSD, several meta-analyses[9-11] have identified important heterogeneity in the treatment effect that has not been fully explored. Psychotherapies for PTSD are complex interventions that consist of multiple components, and their outcomes may be affected by various moderators such as age, sex, military status, and PTSD severity. Synthesis of complex interventions extends beyond answering the simple question of whether the intervention is effective and rather focuses on when, in whom, and under which circumstances is the intervention would be most effective.[12,13] Therefore, we conducted this methodologic study to investigate causes of heterogeneity in PTSD trials, leveraging the availability of a large repository of PTSD trials[14] that have been rigorously identified, appraised, and extracted in a manner amenable to meta-analysis and meta-regression.

PATIENTS AND METHODS

Because the focus of this study is on exploring heterogeneity, we followed the reporting guideline for meta-epidemiological methodology research, an adaptation of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[15]

Data Source and Inclusion Criteria

Data were downloaded from the PTSD Trials Standardized Data Repository (PTSD Repository), created by the National Center for PTSD in partnership with the Agency for Healthcare Research and Quality.[14] The repository provides free data download and captures PTSD trials in adults (18 years or older), published in English from January 1988 through February 2023. Study selection in the repository was performed by 2 reviewers, and data extraction was verified by a lead investigator of the repository.[16,17]

Eligible trials for this analysis compared treatments for PTSD with a control group and reported the 2 binary outcomes of diagnosis resolution (not meeting diagnostic criteria) and clinically meaningful improvement. These 2 outcomes were considered most meaningful to patients as opposed to changes on scale data.

Synthesis and Statistical Analyses

We conducted random-effect meta-analysis and meta-regression using a restricted maximum-likelihood estimator for between-study heterogeneity (tau estimator).[18] The random-effect model was chosen a priori owing to anticipated heterogeneity between studies in terms of populations, interventions, and settings.

Subgroup analysis was performed based on 10 intervention types (EMDR, CBT, CPT, dialectical behavior therapy, exposure therapy, other psychological interventions, nonpharmacologic biological interventions, integrative medicine interventions, SSRI/SNRI, and other pharmacologic interventions). In another subgroup analysis, we evaluated the effect of the quartile of control group response to treatment rate on the treatment effect because relative effect measures may not be portable (consistent) across populations with different baseline risks.[19]

We conducted 3 multivariable meta-regression models. The log of the odds ratio (OR) was the dependent variable in these models. Each outcome was analyzed in a separate model. In the first analysis, we explored whether the risk of bias modifies the treatment effect, which has been explored in various studies and can vary based on the context.[20] The 5 risk of bias domains of the Cochrane risk of bias tool were used in this model as predictor variables. Each domain had 3 categories of bias (high, some concern, and low). The second analysis explored characteristics of the population in terms of military status (vs civilian), female sex (as a study level proportion), age (as a study level mean in years)

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and the severity of PTSD (as a standardized measure because severity was assessed at baseline using various instruments). The third analysis evaluated psychological interventions following the theme, intensity, platform (TIP) framework.[21] For the theme domain, we used a predictor variable of trauma focused therapy approach (vs not). For the intensity domain, we used 2 predictor variables: frequency of treatments per week and duration of the intervention in weeks. For the platform domain, we used 2 predictor variables: whether the intervention was individual therapy (vs group or family therapy) and whether the intervention was delivered in person. Risk of bias, which was found to be a statistically significant predictor in the first model, was added post hoc to the second and third models as an overall risk of bias judgment. We conducted a sensitivity analysis that excluded trials that had 3 arms in which the treatment effect could be affected by within-study correlation. The analysis was conducted using R statistical software R (version 4.3.2)[22] applying the "meta" and "metafor" packages.

RESULTS

We downloaded data from 199 eligible PTSD trials that reported 1 of the 2 outcomes of interest. Analysis of the outcome of diagnosis resolution included 122 trials (8437 patients). Analysis of the outcome of clinically meaningful improvement included 133 trials (9895 patients). An alphabetized list of all included trials is provided in Supplemental Table 1 (available online at http://www.mcpiqojournal.org). Description of the patients, interventions, and trials are all freely available from https://www.ptsd.va.gov/ptsdrepository.

The overall effect across trials demonstrated a statistically significant improvement in both outcomes but with substantial heterogeneity: diagnosis resolution (OR, 3.92; 95% CI, 3.11-4.93; I^2=69%, 95% CI, 62%-74%) and clinically meaningful improvement (OR, 2.94; 95% CI, 2.43-3.55; I^2=61%, 95% CI, 53%-67%). The effectiveness of the various intervention types is presented in Table 1 and suggests effectiveness of several psychological interventions on both outcomes, particularly CBT, CPT, EMDR, and exposure therapy. SSRIs, SNRIs, and other pharmacologic interventions improved symptoms but did not significantly affect diagnosis resolution. Several other psychological therapies, nonpharmacologic biologic therapies (eg, transcranial magnetic stimulation and stellate ganglion block) and integrative medicine therapies (eg, yoga) were also effective on at least 1 outcome, but these latter categories included heterogeneous interventions and found heterogeneous effects with high I^2 values.

Heterogeneity due to Methodologic Features of the Studies

Meta-regression of the diagnosis resolution outcome evaluating 5 risk of bias indicators suggested that the domains of randomization methods and outcome measurement significantly modified the treatment effect. Risk of bias domains explained an important part of the heterogeneity of the effect (R^2=19%). The model of symptom improvement did not explain important variability in the treatment effect (R^2<1%). The results are summarized in Supplemental Table 2 (available online at http://www.mcpiqojournal.org).

TABLE 1. Stratification Based on Intervention Type

	Diagnosis resolution				Clinically meaningful symptom improvement			
Intervention	OR	LL	UL	I^2 (%)	OR	LL	UL	I^2 (%)
EMDR	5.38	2.45	11.81	68	3.76	1.23	11.47	64
Exposure therapy	3.86	2.64	5.66	60	2.64	1.71	4.06	66
Nonpharmacologic biological	4.49	1.93	10.48	0	2.59	0.57	11.67	66
CBT	4.34	2.60	7.25	75	5.08	3.01	8.56	64
Other psychotherapy	6.16	3.00	12.64	74	2.47	1.62	3.77	54
DBT	2.85	1.16	7.02	48	5.89	0.63	54.78	77
Integrative medicine approaches	1.84	1.05	3.22	38	2.84	0.38	21.11	83
SSRI/SNRI	1.04	0.56	1.94	51	1.81	1.23	2.66	61
Other pharmacologic therapies	1.72	0.97	3.05	42	3.06	2.13	4.39	13
CPT	13.50	6.54	27.90	0	2.39	1.24	4.58	0

CBT, cognitive behavioral therapy; CPT, cognitive processing therapy; DBT, dialectical behavior therapy; EMDR, eye movement desensitization and restructuring; LL, lower limit; OR, odds ratio; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; UL, upper limit.

TABLE 2. Stratification Based on the Control Group Response Rate

	Diagnosis resolution				Clinically meaningful symptom improvement			
Rate quartile	OR	LL	UL	I^2 (%)	OR	LL	UL	I^2 (%)
1	7.68	4.84	12.19	73	6.96	4.97	9.73	49
2	3.43	2.51	4.70	61	2.73	2.10	3.55	54
3	2.10	1.40	3.16	68	1.26	1.01	1.57	37
4	2.48	1.62	3.80	0	2.33	1.41	3.87	32

LL, lower limit; OR, odds ratio; UL, upper limit.

Subgroup analysis based on quartiles of the control group event rate demonstrated statistically significant interactions for both outcomes. Studies enrolling patients with the lowest quartiles of the proportion of patients who improved in the control group had larger treatment effect (higher OR's of improvement). These results are summarized in Table 2.

Heterogeneity due to Characteristics of the Population

Meta-regression of population characteristics did not exhibit statistically significant modification by patients' military status, proportion of females, and disease severity at baseline using PTSD severity instruments or age. The results are summarized in Supplemental Table 3 (available online at http://www.mcpiqojournal.org). The models for both outcomes did not explain much of the variability in the treatment effect (R^2<1%).

Analysis Based on the TIP Framework

Meta-regression analysis of outcome of diagnosis resolution suggested increased effectiveness when the treatment approach was trauma focused. There was no significant effect for the frequency of treatments per week, duration of the intervention, type of intervention or delivery method, or format. This model explained important part of the variability in the treatment effect (R^2=20%). The same model for the outcome of symptom improvement did not explain the variability in the treatment effect (R^2<1%). The results are summarized in Table 3. Sensitivity analysis that excluded trials with more than 2 arms demonstrated similar conclusions, with the only statistically significant covariate from the TIP framework being the trauma focused treatment approach on the outcome of diagnosis resolution (Supplemental Table 4, available online at http://www.mcpiqojournal.org).

DISCUSSION

Clinical practice guidelines and systematic reviews have acknowledged the availability of several effective treatments for PTSD but

TABLE 3. Meta-Regression Evaluating the Characteristics of the Intervention

	Diagnosis resolution				Clinically meaningful symptom improvement			
	OR	LL	UL	*P*	OR	LL	UL	*P*
Overall risk of bias, low (vs high)	0.65	0.26	1.66	.37	1.44	0.46	4.43	.53
Overall risk of bias, some concern (vs high)	0.47	0.22	1.03	.06	0.65	0.31	1.39	.27
CBT (vs other psychotherapies)	0.59	0.18	1.97	.39	1.02	0.37	2.81	.98
DBT (vs other psychotherapies)	0.43	0.04	4.18	.47	3.27	0.21	50.85	.40
EMDR (vs other psychotherapies)	0.39	0.07	2.08	.27	1.07	0.18	6.46	.94
Exposure therapy (vs other psychotherapies)	0.29	0.07	1.21	.09	0.45	0.13	1.56	.21
Delivery (vs in person)	1.70	0.32	9.15	.54	1.29	0.33	5.06	.71
Delivery (vs individual)	2.02	0.86	4.75	.11	0.95	0.42	2.17	.91
Frequency per week	0.91	0.77	1.07	.26	0.91	0.76	1.09	.31
Duration (wk)	0.98	0.94	1.02	.35	0.97	0.92	1.02	.22
Trauma focused	6.40	2.24	18.29	.00[a]	2.37	0.81	6.94	.11

[a]Indicates value = .0005.

CBT, cognitive behavioral therapy; DBT, dialectical behavior therapy; EMDR, eye movement desensitization and restructuring; LL, lower limit; OR, odds ratio; UL, upper limit.

No. of studies: 62 for the outcome of diagnosis resolution and 64 for the outcome of symptom improvement.

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with residual heterogeneity in the treatment effect. This finding of heterogeneity suggests that factors other than the type of therapy modify the treatment effect.[7,9,10] This analysis aimed to explore causes of heterogeneity with multiple meta-regression analyses based on the TIP framework with a complex intervention perspective.[12,13,21]

The analysis addressed 2 patient-important outcomes—diagnosis resolution and clinically meaningful improvement—and identified potential causes of heterogeneity that have implications for research and clinical practice. These modifiers include baseline severity of PTSD represented by the response to treatment in the control group of the trials, risk of bias in the trials, and whether the psychotherapeutic approach was trauma focused. There was no significant effect for the frequency of treatments per week, format of the intervention (eg, individual vs group), duration of the intervention, type of intervention or delivery method (in person vs not). Characteristics of the population such as sex, age, and military status did not appear to significantly affect the treatment effect. Our analysis of 2 binary outcomes designated in the PTSD repository as being patient-important and clinically meaningful, has shown in general similar results to recent meta-analyses in which the outcome was continuous (ie, various scales standardized to produce Hedge g or Cohen d).[11,23] The consistency in results is reassuring because standardized effect measures are challenging to interpret by patients and clinicians, and hence, we chose the binary outcomes.[24]

Implications

For future PTSD trialists, we point out the importance of bias protection measures particularly in the domains of randomization sequence and outcome measurement. For systematic reviewers addressing PTSD trials, we suggest subgroup analysis based on risk of bias domains and exploring heterogeneity using approaches such as TIP and complex intervention frameworks. We also suggest evaluating the impact of the baseline risk or severity of PTSD on heterogeneity. This study found that trials with a lower response rate in the control group, that is, enrolled population with worse prognosis at baseline, had a larger treatment effect.

In this analysis, we had to use the control group event rate as a convenient surrogate of the prognosis of the enrolled population. However, we acknowledge that this surrogate is subject to measurement error and mathematical coupling, and identifying specific prognostic factors is clearly preferred.[19]

Clinically, findings of this study suggest that psychotherapies that deliberately focus on processing traumatic memories are more effective than other approaches that do not support patients in explicitly examining their traumatic experiences. As such, consistent with practice guidelines,[25] and in settings where these treatment options are available, trauma focused psychotherapies should continue to be considered a first-line option. Moreover, given that patient characteristics were not associated with treatment effects, trauma focused treatments should be considered regardless of age, sex, military status, or severity of PTSD. Beyond referring patients for trauma focused psychotherapy, the lack of findings related to therapy characteristics, referrals can take into account patient preferences as to the frequency of sessions, format of intervention, duration of treatment, or whether the therapy is offered virtual or in person.

Strengths and Limitations

This study draws on the presence of a comprehensive repository of PTSD trials that is federally funded and freely available to researchers. This repository followed rigorous methodology in selecting and appraising trials and is continuously updated following guidance of key stakeholders and a technical expert panel. The analysis followed modern frameworks for exploring heterogeneity in complex interventions such as the TIP framework. Limitations of this work include ecologic bias, which affects analyses that are based on study level variables. For example, our conclusions about sex being a statistically nonsignificant effect modifier are limited by this bias because the repository only provides the mean proportion of females per trial. Conversely, our conclusions about study level characteristics such as risk of bias and whether the treatment was trauma focused are not affected by ecologic bias.

CONCLUSION

In summary, the findings of these meta-regression analyses using a rigorous repository of 199 eligible PTSD trials enrolling over 8000 patients confirms that trauma focused psychotherapies are considered the first-line intervention in improving PTSD remission. Although SSRIs/SNRIs were associated with clinically meaningful change in symptoms, they did not exhibit benefit in improving remission. The findings that patient characteristics or treatment context were not associated with the magnitude of treatment effect suggest that they are likely less relevant in selecting an appropriate treatment and referring clinicians can tailor the approach based on patient values, preferences, and logistics.

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **CBT,** cognitive behavioral therapy; **CPT,** cognitive processing therapy; **EMDR,** eye movement desensitization and restructuring; **OR,** odds ratio; **PTSD,** posttraumatic stress disorder; **SNRI,** serotonin and norepinephrine reuptake inhibitors; **SSRI,** selective serotonin reuptake inhibitors; **TIP,** theme, intensity, platform

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