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Treatment for Co-Occurring Posttraumatic Stress Disorder and Substance Use Disorders Among Veterans and Civilians: A Test of Causally Moderated Comparative Effectiveness

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Objective: The prevalence and negative sequelae of co-occurring posttraumatic stress disorder and substance use disorder (PTSD + SUD) are well documented. Findings from evidence syntheses regarding which PTSD + SUD treatments work best overall have been mixed, potentially because these treatments are not equally effective for all PTSD + SUD patient subgroups. Epidemiological and qualitative research suggest that veteran status may be related to differential PTSD + SUD treatment response. This study, applying recent quantitative methodological advances in evidence synthesis, is the first to examine the potential moderating effect of veteran status on PTSD + SUD treatment outcome. **Method:** We report secondary analyses of psychotherapy arm data ($k = 26$ randomized controlled trials; $n = 3,228$) from Project Harmony, a meta-analysis of individual PTSD + SUD patient data from sociodemographically diverse samples incorporating propensity score weighting and integrative data analysis. Outcome models (examined separately for harmonized indicators of latent PTSD, alcohol use, and drug use severity) were fit under propensity score weighting multilevel modeling. **Results:** Tests of causally moderated comparative effectiveness showed that trauma-focused psychotherapy targeting PTSD and integrated trauma-focused psychotherapy targeting PTSD and SUD were both superior to treatment as usual for alcohol use severity outcomes, and this effect was stronger for veterans than civilians. Analyses did not provide evidence for differential response to active PTSD + SUD psychotherapies, relative to treatment as usual, on PTSD or drug use severity outcomes as a function of veteran status. **Conclusions:** Findings lend support for delivering trauma-focused psychotherapies to patients with PTSD + SUD, especially veterans, and point to important future directions for inquiries into optimizing patient matching to PTSD + SUD treatment.

Clinical Impact Statement

Posttraumatic stress disorder (PTSD) and substance use disorders (SUD) frequently co-occur, especially among veterans. Research suggests that veterans do not respond as well as civilians to PTSD treatment, but differential response to treatments for PTSD with co-occurring SUD has not been tested. This study analyzed data from 3,228 patients from 26 clinical trials to compare veterans' and civilians' responses to active PTSD + SUD psychotherapies, relative to treatment as usual. Findings indicated that veterans with PTSD + SUD did not respond differently than civilians to active psychotherapies on PTSD or drug use outcomes and responded better than civilians to trauma-focused treatments on alcohol use outcomes.

Keywords: posttraumatic stress disorder, alcohol use, substance use, veterans, causal moderation analysis

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The prevalence and negative consequences of co-occurring posttraumatic stress disorder (PTSD) and substance use disorder (SUD) are well documented. After adjusting for sociodemographic factors and comorbid psychiatric disorders, lifetime SUDs are associated with 1.3 to 1.5 times greater odds of lifetime PTSD, and lifetime PTSD is associated with 1.5 times greater odds of lifetime SUD (Goldstein et al., 2016; Grant et al., 2015, 2016). Compared with PTSD or SUD alone, comorbid PTSD + SUD is associated with greater psychiatric severity, more psychosocial functioning difficulties, and higher risk for self- and other-directed violence (Blakey et al., 2022; Hellmuth et al., 2012; Mills et al., 2006; Norman et al., 2007, 2018; Simpson et al., 2019).

Fortunately, people with PTSD + SUD have several treatment options. In addition to PTSD- and SUD-targeting medications,¹ behavioral treatments for people with PTSD + SUD include trauma-focused (TF) psychotherapy targeting PTSD, cognitive-behavioral psychotherapy targeting SUD, integrated TF psychotherapy targeting PTSD + SUD (ITF), and integrated nontrauma-focused psychotherapy targeting PTSD + SUD (INTF). Given these numerous treatment approaches, the field has aimed to identify which PTSD + SUD interventions are most effective overall. Pharmacological PTSD + SUD trials are unfortunately inconclusive; specific medications have not been extensively evaluated, and previous studies have been limited by small sample sizes (Hien et al., 2024; Petrakis & Simpson, 2017; Sofuoglu et al., 2014). Considerably more research has evaluated psychotherapies for PTSD + SUD. Roberts et al. (2015) conducted a meta-analysis of 14 randomized controlled trials (RCTs) of PTSD + SUD psychotherapies. Results generally favored ITF over TF or INTF approaches, but treatment effects were small and stronger for PTSD outcomes than SUD outcomes. In an updated meta-analysis of 27 RCTs, Roberts et al. (2022) again found that ITF psychotherapy was superior to INTF psychotherapy, although ITF psychotherapy's superiority to psychotherapy for SUD was not always clinically important or statistically significant across outcome measures,

assessment time points, and ITF protocols. In a different meta-analysis of 28 RCTs, Simpson et al. (2021) found that manualized SUD psychotherapies yielded similar PTSD improvements and slightly superior SUD improvements compared with TF psychotherapies. Taken together, although there is accumulated evidence for TF, ITF, and manualized SUD psychotherapies in the treatment of PTSD + SUD, comparative efficacy findings are mixed.

One explanation for inconsistent meta-analytic findings is that treatments were not equally effective for all PTSD + SUD patient groups. Research has therefore sought to identify moderators of treatment outcome. One possible moderator of PTSD + SUD treatment effectiveness is military veteran status. Rates of both PTSD and alcohol use disorder are higher among veterans than civilians (Dworkin et al., 2018), and combat exposure has been associated with drinking to cope with PTSD symptoms (Blakey et al., 2021). Subjective experiences with substance use also differ between veterans and civilians, with veterans reporting longer periods of addiction prior to initiating recovery and greater psychosocial functioning difficulties prior to and after beginning recovery (Laudet et al., 2014). Unfortunately, investigators have encountered barriers to comparing PTSD + SUD treatment outcomes between veterans and civilians. Previous PTSD + SUD clinical trials either drew from predominantly civilian community samples or recruited all-veteran samples through the U.S. Department of Veterans Affairs (VA), thus precluding within-study comparisons of treatment response. Military history is rarely captured as a demographic characteristic in community-based trials, and the few PTSD + SUD trials that did measure veteran status were underpowered to test moderation effects

¹ Specific pharmacotherapies are recommended for alcohol use disorder (e.g., naltrexone, topiramate, acamprosate), tobacco use disorder (nicotine replacement therapies, bupropion), and opioid use disorder (methadone, buprenorphine/naloxone). The U.S. Food and Drug Administration has not approved any medications for cocaine use disorder or cannabis use disorder.

authors of the *Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure* therapy manuals published by Oxford University Press. Ismene L. Petrakis has received in-kind (medications) support for research studies from Alkermes and BioXcel Therapeutics. Ismene L. Petrakis is coeditor for the *Journal of Addiction Medicine* and associate editor for the *American Journal on Addictions*. Ismene L. Petrakis has received textbook royalties from MacGraw/Hill. Ismene L. Petrakis also reports patents and inventions: (a) Arias A., Petrakis I., and Krystal J. H., Composition and methods to treat addiction. Provisional Use Patent Application no. 61/973/961. April 2, 2014. Filed by Yale University Office of Cooperative Research. (b) Gihyun, Yoon, Petrakis I., and Krystal J. H., Compounds, Compositions and Methods for Treating or Preventing Depression and Other Diseases. U. S. Provisional Patent Application No. 62/444552, filed on January 10, 2017, by Yale University Office of Cooperative Research OCR 7088 US01. All other authors have no conflicts of interest to declare.

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(Foa et al., 2013; Petrakis et al., 2012; Simpson et al., 2015; Stappenbeck et al., 2015).

Research on treatments for PTSD without co-occurring SUD provides indirect support for a moderating role of veteran status on PTSD + SUD treatment outcome. Meta-analytic (Straud et al., 2019; Watts et al., 2013) and multisite effectiveness studies (Dillon et al., 2019; Jacoby et al., 2022) show that although both veterans and civilians benefit from TF psychotherapy, PTSD improvements are greater for civilians than veterans. Because these studies focused on treatment for PTSD without psychiatric comorbidities, however, the extent to which these findings extrapolate to PTSD + SUD treatment is unknown.

Because more than half of veterans receive care outside VA (U.S. Department of Veterans Affairs, 2022a), identifying which treatments are most helpful for veterans and civilians with PTSD + SUD could have broad implications for clinical research, practice, and policy. Such findings could also facilitate an important step toward optimizing treatment for people with PTSD + SUD. To make this contribution, however, several methodological limitations to the literature must be addressed. Certain sociodemographic characteristics associated with PTSD + SUD (e.g., male sex) are overrepresented in the veteran population, and veterans are more likely than civilians to endorse adverse childhood experiences, have higher overall trauma exposure, and smoke cigarettes—all of which are associated with greater PTSD and SUD severity (Dworkin et al., 2018; Evans et al., 2018; Hoggatt et al., 2017; Kearns et al., 2018; Lewinsohn et al., 1999; Teeters et al., 2017). Such confounding variables are typically included as covariates in single RCTs and meta-analyses, but conventional analytic adjustments do not resolve the issue that key covariates differ across studies, are influenced by study eligibility criteria, and are related to primary study outcome measures. Nor do many PTSD + SUD trials adjust for treatment attendance (Glenn et al., 2013; Marrero et al., 2020; Nock & Ferriter, 2005). This is problematic, as TF psychotherapies are associated with higher rates of dropout than non-TF psychotherapies (Varker et al., 2020), treatment attendance can influence PTSD and SUD improvements (Cooper et al., 2017; Weiss, 2004), and randomization to psychotherapy attendance is not necessarily possible.

Additionally, prior RCTs comparing PTSD + SUD treatments were not sufficiently resourced to compare all extant PTSD + SUD psychotherapies. Although evidence syntheses permit broader treatment comparisons, combining patient-level data from separate RCTs can introduce bias, as the randomization structures present within each original trial are lost when data are merged across trials. Propensity score weighting (PSW), a statistical technique used to control for selection bias in nonrandomized designs that would otherwise prohibit causal inferences, can be used to address these critical analytic limitations (Harder et al., 2010; Li et al., 2013; Rosenbaum & Rubin, 1983), thereby mimicking a fully randomized design within a comprehensive evidence synthesis (Moons, 2020).

In sum, although evidence suggests that veterans do not respond as strongly as civilians to PTSD treatment—so may therefore benefit less from PTSD + SUD treatments—such potential moderated comparative effectiveness remains unknown. Large traditional meta-analyses, while informative in many ways, have not clarified the field's understanding of which PTSD + SUD treatment approaches work best for whom. Applying PSW to manage relevant sociodemographic and clinical covariates would

offer a more rigorous approach to testing moderated comparative effectiveness of PTSD + SUD treatment approaches. In Project Harmony, a synthesis of raw data from 36 PTSD + SUD RCTs, Hien et al. (2023) combined PSW, meta-analysis of individual patient data (MIPD), and integrative data analysis to examine the efficacy of medications (PTSD targeting, SUD targeting, and placebo), psychotherapy (TF, ITF, INTF, and SUD focused), and SUD medications combined with psychotherapy, all compared with treatment as usual (TAU; nonmanualized community-based treatment, nonevidence-based treatment, or wait-list control). Findings showed that relative to TAU, comparative effect sizes for PTSD, alcohol use, and drug use severity outcomes were largest for SUD medications, TF or ITF psychotherapy, and SUD medications combined with TF psychotherapy. Moderators, however, were not explored. The present study provided an opportunity to conduct a secondary analysis of Project Harmony data examining the potential moderating effect of veteran status on PTSD + SUD treatment effectiveness.

Method

Participants and Procedure

To be included in Project Harmony (PROSPERO registration identifier CRD42019146678), studies must have (a) been RCTs of psychotherapies or pharmacotherapies targeting PTSD, alcohol or drug use, or both, (b) assessed PTSD and alcohol/drug use outcomes pre- and posttreatment, and (c) recruited adults at least 18 years old with current *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2000, 2013) diagnosis of full or subthreshold² PTSD and current SUD. Authors of RCTs meeting the inclusion criteria were invited to contribute patient-level data to Project Harmony. Only data from participants who had consented to the original RCT and to individual-level data sharing were accepted into Project Harmony. Next, original RCT arms were classified into treatment class (e.g., TF psychotherapy, INTF psychotherapy, SUD medication; Hien et al., 2022). Analyses reported in this secondary analysis are limited to the following treatment classes: TAU or else TF, ITF, INTF, and SUD psychotherapy. Excluded treatment classes (e.g., TF + SUD medications) were subject to multicollinearity between covariates in estimating PSWs due to nonrepresentation within certain conditions (e.g., conditions with no civilian men). Two data sets drawn from incarcerated samples (Zlotnick et al., 2003, 2009) were excluded given that the uniquely controlled environment of a prison setting did not align with our research question. This yielded a total secondary analysis sample drawing data from 26 (of the 36) RCTs, 53 (of the 81) treatment arms, and $n = 3,228$ (of the total $N = 4,046$) Project Harmony sample. A list of RCTs included in this secondary analysis is provided in the Supplemental Material. The analyzed sample was 46.3% veteran, 52.6% male/men, and $M_{age} = 39$ years. Additional descriptive statistics are presented in Table 1. All Project Harmony procedures were approved by the Institutional Review Boards of RTI International and Rutgers University.

² Defined as meeting all PTSD criteria except for either C or D (Hien et al., 2023).

Table 1
Sample Characteristics

Covariate	% or <i>M (SD)</i>					
	Full sample	TAU class	TF class	ITF class	INTF class	SUD class
Age in years	39.0 (11.2)	36.3 (9.8)	42.8 (12.0)	40.9 (12.4)	38.9 (11.4)	40.3 (11.9)
Veteran	46.3	39.0	67.7	55.5	48.3	24.6
Male/men	52.6	46.4	62.7	70.4	45.4	42.2
Race and ethnicity						
White	30.1	38.3	13.7	15.1	34.1	40.3
Asian	0.7	0.5	2.1	0.9	1.1	0.8
Black	24.2	18.1	29.0	33.9	17.5	26.2
Hispanic	7.3	8.3	9.1	7.2	9.1	4.2
Other	4.3	4.5	8.1	4.7	5.0	1.2
Education level						
Some college	33.3	30.8	38.0	38.2	33.2	27.2
College degree or higher	16.4	15.0	13.3	21.0	15.4	15.3
Married	18.1	18.0	21.1	22.4	16.0	16.7
Screened positive for depression at baseline	54.5	54.5	53.5	53.4	59.4	50.8
Taking nonstudy psychotropic medication at baseline	60.6	61.5	65.0	58.2	63.7	66.4

Note. TAU = treatment as usual; TF = trauma-focused psychotherapy; ITF = integrated TF psychotherapy; INTF = integrated nontrauma-focused psychotherapy; SUD = psychotherapy targeting substance use disorder.

Measures

Pretreatment Participant Demographic and Clinical Characteristics

We examined the following individual-level covariates: sex/gender,³ age, race/ethnicity, education level, proportion of intended treatment sessions attended, probable major depressive disorder at baseline, and baseline nonstudy concomitant psychotropic medication use. Whereas randomization balances these variables across treatment arms within RCTs, grouping of treatment classes across RCTs compromises original within-trial randomization structures (Brincks et al., 2018; Saavedra et al., 2021). This grouping effectively converts multiple RCTs into a single de facto quasi-experiment. We accordingly used PSW (described below) to rebalance treatment classes across covariates.

Veteran Status

Participants were coded as veterans if they participated in an RCT requiring veteran status for inclusion or endorsed combat or warzone exposure on the Life Events Checklist (Gray et al., 2004; Weathers et al., 2013), even if combat or warzone exposure was not the index event. Military trauma exposure was not required given this study's broader focus on veteran compared with civilian status.

Harmonized PTSD + SUD Outcomes

Because original RCTs used different assessments to measure PTSD, alcohol use, and drug use severity, Project Harmony applied item harmonization strategies (Bauer & Hussong, 2009) to place these different indicators of latent symptom severity on the same metric (separately for each outcome) prior to conducting moderated nonlinear factor analysis. We summarize the harmonization process for each of these symptom severity outcomes immediately below; additional details are reported elsewhere (Hien et al., 2023; Saavedra et al., 2021).

PTSD Severity. Most RCTs included in Project Harmony used the Clinician-Administered PTSD Scale (i.e., Clinician-Administered PTSD Scale-IV or Clinician-Administered PTSD Scale-5) or the PTSD Checklist (PCL, PCL-C, PCL-M, or PCL-5), with some studies using both. For a full list of assessments used in the original RCTs, see Hien et al. (2023). A harmonized measure of latent PTSD severity was calculated under the MNLFA framework (Bauer, 2017; Bauer & Hussong, 2009) from 42 PTSD severity indicators across studies that had item-level PTSD data. The resulting 42-item latent variable was jointly estimated from 21 clinical interview symptoms and 21 self-report measure symptoms (Saavedra et al., 2021).

SUD Severity. We separately analyzed latent alcohol use severity scores and latent drug use severity scores previously estimated in other Project Harmony work (see Hien et al., 2023; Saavedra et al., 2021). For alcohol use severity, data regarding the number of days of alcohol use in the past 30 days and any past-30-day alcohol use to intoxication were used to estimate a two-indicator latent severity variable. For drug use severity, binary indicators of any past-30-day use of cocaine, heroin, opioids other than heroin, sedatives, other psychostimulants, and hallucinogens were used to estimate a six-indicator latent severity variable. Alcohol and drug use indicators were determined from original patient-level data, most commonly from the Timeline Follow Back (Sobell & Sobell, 1992) or Addiction Severity Index (McLellan et al., 1992). See Hien et al. (2023) for a list of original RCT SUD assessments.

Data Analytic Plan

Propensity Weighting Models

Given the mixing-and-matching of treatment arms across clinical trials, we addressed cross-trial covariate imbalance via estimation of

³ There was variability across original RCTs included in Project Harmony in that some trials reported sex and other trials reported gender. We accordingly use the term "sex/gender" to reflect this inconsistent measurement approach in the original studies.

propensity score weights before fitting primary outcome models (Hien et al., 2023; Morgan-López et al., 2022). First, propensity score weights specific to each outcome model (i.e., PTSD severity, alcohol use severity, and drug use severity) were estimated using a multinomial logit model where, for causal estimates of Treatment \times Veteran Status interactions (Dong, 2012), separate groupings by each combination of treatment and veteran status were treated as a nominal outcome variable. We used covariates in each model that were jointly related to treatment assignment and baseline levels of the outcome, consistent with recent recommendations regarding optimal covariate selection in quasi-experiments (Cook et al., 2008, 2020; Saavedra et al., 2023; Zurovac et al., 2021). Propensity scoring models, using average treatment effects on the overlap population weighting (Li et al., 2018), were estimated with study-level fixed effects using SAS Proc GLIMMIX. Covariate balance across treatment classes was achieved for all covariates after PSW; all postweighting balance checks were below $|d|$ of .10 (see Supplemental Materials in Hien et al., 2023).

Outcome Models

We fit outcome models under PSW multilevel linear modeling using SAS Proc HPMIXED to account for random intercepts and slopes due to clustering of repeated observations within participants and participants clustered within studies. We estimated fixed-effect parameters and standard errors with a focus on (a) two-way interaction effects with both during treatment (i.e., from pre- to post-treatment) and after treatment (i.e., from posttreatment to follow-up) time phase variables (i.e., single intervention treatment effects compared with TAU) and (b) three-way interaction effects (i.e., treatment effects vs. TAU that differed by veteran status). We modeled missing data via multiple imputation for clustered data using the mice R package (van Buuren & Groothuis-Oudshoorn, 2011) with 20 imputed data sets. We then combined results across the 20 data sets using Rubin's (1976) rules for combining results in multiple imputation using SAS Proc MIANALYZE.

Results

Propensity Weighting Models

Each final PSW model included only the variables across outcomes that, prior to inclusion in PSW models, were related to treatment condition, veteran status, and the model-specific outcome (i.e., latent PTSD, alcohol use, or drug use severity) in multilevel multinomial logit models. The final PTSD severity model included baseline PTSD severity, $F(9, 3252) = 10.17, p < .001$; age, $F(9, 3252) = 22.39, p < .001$; sex/gender, $F(9, 3252) = 106.36, p < .001$; and use of nonstudy psychotropic medications, $F(9, 2902) = 3.54, p < .001$. The final alcohol use severity model included only baseline alcohol use severity, $F(9, 3279) = 90.13, p < .001$. The final drug use severity model included baseline drug use severity, $F(9, 3213) = 15.39, p < .001$; age, $F(9, 3213) = 23.42, p < .001$; sex/gender, $F(9, 3213) = 106.26, p < .001$; and use of nonstudy psychotropic medications, $F(9, 3213) = 3.36, p < .001$.

Outcomes Models

Moderation-related effects for each outcome model are presented next. All other pre- to posttreatment and posttreatment to follow-up

effects not significantly moderated by veteran status mirrored previously reported Project Harmony primary outcome analyses (Hien et al., 2023, 2024). Specifically, treatment arms included in this secondary analysis that were superior to TAU for PTSD severity outcomes were ITF ($|Cohen'sd|$ compared with TAU = 0.47) and SUD psychotherapy ($|Cohen'sd|$ compared with TAU = 0.60); for alcohol use severity outcomes, ITF ($|Cohen'sd|$ compared with TAU = 0.42) and TF ($|Cohen'sd|$ compared with TAU = 0.45). No included treatment arms were superior to TAU on drug use severity outcomes in the primary outcomes analysis (Hien et al., 2023).

PTSD Severity

Overall decreases in PTSD severity were observed within TAU during treatment (i.e., from pre- to posttreatment), $b = -.49 (.05), p < .001$, and after treatment (i.e., from posttreatment to follow-up), $b = -.11 (.02), p < .001$. No treatments showed differential effects compared with TAU by veteran status (all three-way interaction effects observed at $p > .12$).

Alcohol Use Severity

Overall decreases in alcohol use severity were observed within TAU during treatment, $b = -.34 (.02), p < .001$. Two Treatment \times Veteran Status interactions emerged as significant (see Figure 1). TF psychotherapies yielded greater reductions in alcohol use severity for veterans than civilians, $b = -.78 (.16), t = -4.74, p < .001$. ITF psychotherapies also yielded greater decreases in alcohol use severity for veterans than civilians, $b = -.51 (.17), t = -3.00, p = .002$.

Drug Use Severity

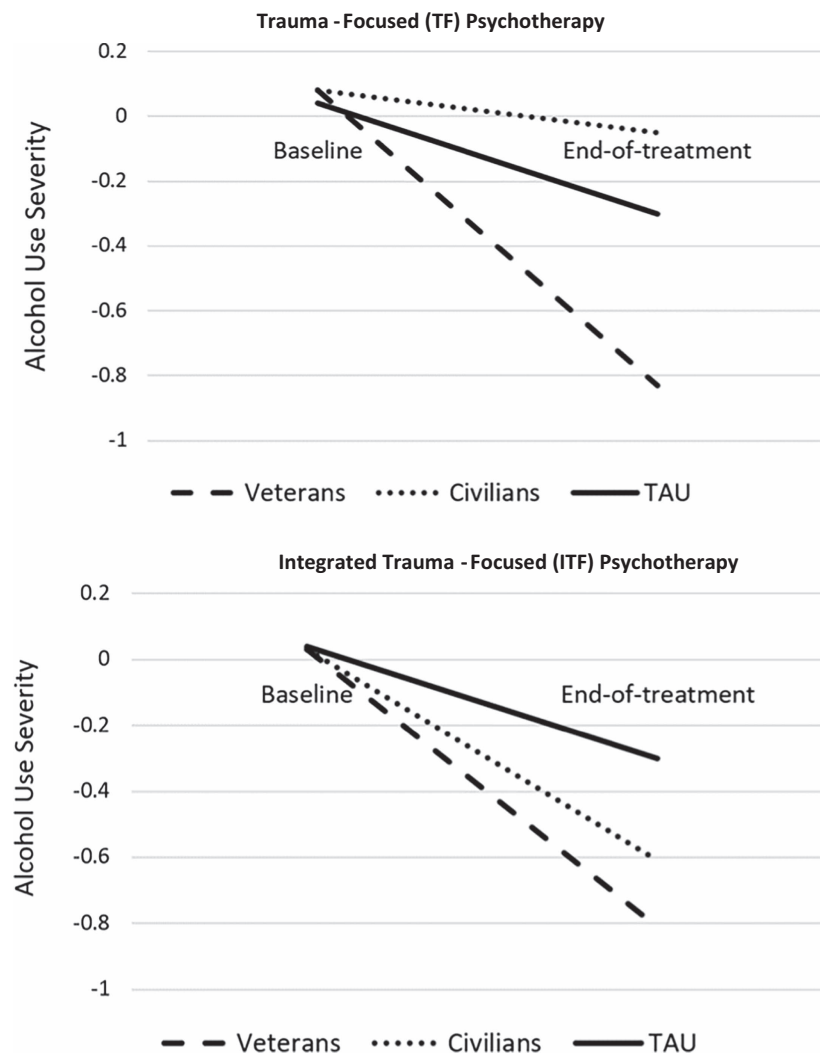
Overall decreases in drug use severity were observed within TAU during treatment, $b = -.50 (.03), p < .001$. ITF psychotherapy showed greater decreases in drug use severity, $b = -.26 (.14), t = -1.83, p = .06$, but this effect did not differ by veteran status ($p = .37$).

Discussion

Although several PTSD + SUD treatment options exist, moderators of treatment outcomes remain largely unknown. It is important to consider whether veteran status moderates PTSD + SUD treatment response given that veterans have higher lifetime prevalence of PTSD and certain SUDs compared with civilians (Boden & Hoggatt, 2018), often seek community (non-VA) mental health care (U.S. Department of Veterans Affairs, 2022a), and may not respond as well as civilians to treatment for PTSD only (Dillon et al., 2019; Jacoby et al., 2022; Straud et al., 2019). Recent quantitative methodological advances in evidence synthesis and management of confounding variables have not yet been applied to address critical limitations of previous PTSD + SUD meta-analyses. This Project Harmony secondary analysis study combined integrative data analysis, MIPD, and PSW to test whether veteran status was a causal moderator of comparative PTSD + SUD treatment effectiveness separately on PTSD, alcohol use, and drug use severity outcomes.

Models of latent alcohol use severity outcomes showed that TF and ITF were both superior to TAU and that this effect was stronger for veterans than civilians. One potential explanation is that VA RCTs, unlike most community-based settings, occur within a comprehensive, integrated health care system. Such wraparound services available at

Figure 1
Comparative Latent Alcohol Use Severity Treatment Outcomes by Veteran Status



Note. TF and ITF psychotherapies led to greater pre- to posttreatment reductions in alcohol use severity, compared with TAU in the overall sample, for veterans than civilians. *Y*-axis reflects the standardized score estimated under moderated nonlinear factor analysis (see Hien et al., 2023). All simple slopes had a small to large effect size except for TF psychotherapy for civilians ($d = -0.14$). TAU = treatment as usual.

many VA RCT sites might have better enabled veteran participants to benefit from TF psychotherapies. For example, veterans receiving treatment through VA RCTs may also have had prior or concurrent access to SUD care, as VA policy enables veterans with PTSD + SUD to get treatment for both disorders (National Academies of Sciences, Engineering, and Medicine, 2018), and the VA/Department of Defense Clinical Practice Guidelines (U.S. Department of Veterans Affairs & U.S. Department of Defense, 2023) recommend still delivering TF psychotherapy when patients with PTSD have co-occurring SUD. It is also possible that VA-based study therapists had more experience using TF psychotherapies given VA's evidence-based psychotherapies training initiative (Karlin & Cross, 2014), which could have contributed to veterans' superior RCT alcohol use

outcomes. However, another explanation is that VA-enrolled RCT participants may have been enrolled in other programs mandating abstinence (e.g., to receive housing support, vocational rehabilitation) and requiring regular substance use testing, influencing study data. As our analyses could not disentangle the effects of other VA service utilization and associated factors from veteran status, additional studies of PTSD + SUD treatments delivered to veterans in community settings would be helpful.

Contrary to the literature on treatment for PTSD without co-occurring SUD, latent PTSD severity outcome models did not show differential response to TF psychotherapies, compared with TAU, as evidenced by nonsignificant Treatment \times Veteran Status interaction terms. This finding is encouraging for VA and community

clinicians, as it suggests their veteran patients with comorbid PTSD + SUD would still benefit from TF/ITF psychotherapies. Whereas the PTSD-only treatment literature points to differential treatment response as a function of veteran status, our findings from a large ($n = 3,228$) MIPD sample indicate that veterans with PTSD + SUD are equally as likely as civilian adults to benefit from active psychotherapies. For VA practitioners and decision-makers, these findings support ongoing efforts to provide TF treatment to veterans and invest in training providers to deliver it. Community clinicians serving veterans with PTSD + SUD might also consider pursuing training in TF psychotherapies, ideally with support from clinic leadership (e.g., training time and registration fees, supervision and consultation, treatment manuals, and patient forms). Multiple TF and ITF psychotherapy trainings are available through federal (e.g., VA), university, and nonprofit sources, often at discounted or no cost.

Drug use severity outcome models also failed to detect Treatment \times Veteran Status interaction effects. Several factors may have influenced this finding. For example, unlike harmonization of alcohol use severity, which used continuous past-30-day drinking days and number of days to intoxication as the latent indicators, drug use severity was harmonized based on dichotomized indicators of any drug use across specific substances, which could have limited power. In addition, most original RCTs targeted alcohol use disorder as the single or primary SUD co-occurring with PTSD, and, therefore, treatment may have focused on alcohol use instead of other SUDs. Moreover, consequences incurred from illicit drug use (e.g., on employment, career, housing) may differ by veteran status and could have impacted the data. Additional studies evaluating treatments in veteran and civilian samples with PTSD and drug use disorders would help sharpen the field's understanding of PTSD + SUD treatment effects on drug use severity outcomes.

Our findings point to specific recommendations for PTSD + SUD practice and policy, that is, regarding improving models for integrated PTSD + SUD care. Although PTSD and SUD care is not integrated at all VA facilities, the VA is well positioned to do so (e.g., shared electronic health record system) and has established policy to provide veterans with PTSD + SUD integrated care (e.g., Veterans Health Administration Directive 1160.04, which requires VA facilities to designate a PTSD + SUD team or specialist to support the provision of concurrent, trauma-informed, integrated treatment for veterans diagnosed with PTSD + SUD; U.S. Department of Veterans Affairs, 2022b). PTSD and alcohol misuse screening made easier through integrated assessments built into the VA's electronic medical record system additionally increase the likelihood that veterans with PTSD + SUD will be identified and referred for treatment. However, several cross-facility barriers such as resource limitations, knowledge gaps, and inconsistent policy implementation need to be addressed before fully integrated care in VA can be achieved (Tiet et al., 2024). Of course, these barriers to care also apply to community-based settings, especially community care settings staffed by clinicians with comparatively less familiarity or comfort treating veterans (Tanielian et al., 2014; Vest et al., 2018, 2019).

Clinicians, patients, and policymakers should be encouraged by this study's findings, but several limitations should be acknowledged. Although RCT-specific eligibility criteria facilitated accurate veteran status coding for many participants, we relied on self-reported trauma types to code veteran status for most community-based RCTs. It is possible that some community RCT participants were veterans but did

not experience military combat or exposure to a warzone so were inaccurately coded as civilians in analyses. Incorporating military history into standard demographic assessments would better allow the field to explore which PTSD + SUD (and other) treatments work best for whom. Nor did we examine the effects of military era on outcomes, although PSW adjusting for age mitigates this limitation. We did not include Project Harmony patient data from medication treatment arms due to multicollinearity issues that precluded making reliable estimates of effects. The comparatively limited understanding of pharmacotherapeutic approaches to PTSD + SUD treatment, relative to the psychotherapy evidence base, remains a challenge for the field. Although the meta-analytic sample was diverse in many ways, not all identities of people with PTSD + SUD may have been represented. Another limitation is that our findings may not extend to trauma survivors with SUD and co-occurring disorders other than PTSD. As trauma exposure is a transdiagnostic risk factor for multiple other mental health conditions (e.g., anxiety-related disorders, mood disorders, and psychotic disorders; Hogg et al., 2023), our synthesis's focus on full or subthreshold PTSD may be considered another limitation.

This study advances the field's understanding of PTSD + SUD treatment and veteran care in several ways. For example, it is the first to examine veteran status as a potential moderator of comparative PTSD + SUD treatment outcome. Other strengths include using a large sample and quantitative methodological advances combining PSW, integrative data analysis, MIPD, and a causal moderation framework. This allowed for simultaneous evaluation of multiple active treatments relative to a TAU comparator as well as superior management of confounding variables relative to traditional evidence synthesis methodologies. Taken together, this study provides a strong foundation for future inquiries into optimally serving veteran and civilian patients with PTSD + SUD.

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