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Concurrent treatment of substance use disorders and PTSD using prolonged exposure: A randomized clinical trial in military veterans

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HIGHLIGHTS

- Posttraumatic stress disorder (PTSD) is common among individuals with addiction.
- Rates of PTSD and addiction are particularly high among military veterans.
- This study tested an integrated treatment for both disorders in military veterans.
- The treatment included Prolonged Exposure (PE) for PTSD.
- The treatment was effective and significantly reduced PTSD and substance use severity.

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ABSTRACT

Objective: A substantial amount of individuals with substance use disorders (SUD) also meet criteria for posttraumatic stress disorder (PTSD). Prolonged Exposure (PE) is an effective, evidence-based treatment for PTSD, but there is limited data on its use among individuals with current alcohol or drug use disorders. This study evaluated the efficacy of an integrated treatment that incorporates PE (*Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure* or COPE) among veterans.

Method: Military veterans (N = 81, 90.1% male) with current SUD and PTSD were randomized to 12 sessions of COPE or Relapse Prevention (RP). Primary outcomes included the Clinician Administered PTSD Scale (CAPS), PTSD Checklist-Military version (PCL-M), and the Timeline Follow-back (TLFB).

Results: On average, participants attended 8 out of 12 sessions and there were no group differences in retention. Intent-to-treat analyses revealed that COPE, in comparison to RP, resulted in significantly greater reductions in CAPS (d = 1.4, $p < .001$) and PCL-M scores (d = 1.3, p = .01), as well as higher rates of PTSD diagnostic remission (OR = 5.3, $p < .01$). Both groups evidenced significant and comparable reductions in SUD severity during treatment. At 6-months follow-up, participants in COPE evidenced significantly fewer drinks per drinking day than participants in RP (p = .05).

Conclusions: This study is the first to report on the use of an integrated, exposure-based treatment for co-occurring SUD and PTSD in a veteran sample. The findings demonstrate that integrated, exposure-based treatments are feasible and effective for military veterans with SUD and PTSD. Implications for clinical practice are discussed.

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1. Introduction

Substance use disorders (SUD) and posttraumatic stress disorder (PTSD) are two of the most prevalent psychiatric disorders in the United States. In the general population, lifetime estimates are approximately 29.1% for alcohol use disorder, the most common SUD (Grant et al., 2015), and 8.3% for PTSD (Kilpatrick et al., 2013). Among military personnel and veterans, rates of SUD and PTSD are 2–4 times higher than in the general population (Hoge, 2015; Petrakis, Rosenheck, & Desai, 2011; Stein et al., 2017; Teeters, Lancaster, Brown, & Back, 2017).

Research demonstrates high rates of comorbidity between SUD and PTSD. Epidemiologic data indicate that individuals with, as compared to without, an SUD are 6.5 times more likely to have comorbid PTSD (Mills, Teeson, Ross, & Peters, 2006). Comorbid SUD/PTSD is associated with substantial psychiatric comorbidity (e.g., depression), medical problems, vocational impairment, increased violence, and poor treatment outcomes (Barrett, Teeson, & Mills, 2014; Simpson, Lehavot, & Petrakis, 2017; Stein et al., 2017).

Integrated treatments, in which both disorders are addressed concurrently, may help optimize outcomes. *Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure* (COPE) is an integrated treatment that utilizes Prolonged Exposure (PE; Foa, Hembree, & Rothbaum, 2007) in combination with cognitive behavioral therapy for SUD. Previous studies of COPE among civilians demonstrate efficacy in reducing SUD and PTSD severity (Brady, Dansky, Back, Foa, & Carroll, 2001; Mills et al., 2012; Persson et al., 2017; Ruglass et al., 2017). Despite extensive research demonstrating the ability of PE to significantly reduce PTSD severity (Powers, Halpern, Ferenschak, Gillihan, & Foa, 2010; Resick, Williams, Suvak, Monson, & Gradus, 2012), some clinicians are reluctant to engage in exposure-based trauma work with SUD patients (Norman & Hamblen, 2017) and the vast majority of randomized controlled trials of treatments for PTSD exclude participants with SUD (Leeman et al., 2017). Accumulating evidence demonstrates, however, that PE is safe and associated with significant reductions in SUD severity, even among individuals with complex trauma histories (Foa et al., 2013, 2017; Mills et al., 2012; Norman et al., 2016; Peck, Schumacher, Stasiewicz, & Coffey, 2018; Persson et al., 2017; Ruglass et al., 2017). Further support is provided by recent meta-analyses and critical reviews of the literature demonstrating that exposure-based, integrated treatment results in significant improvements in SUD and PTSD (Roberts, Roberts, Jones, & Bisson, 2015; Simpson et al., 2017).

Given the sustained military operations in Afghanistan and Iraq, and the disproportionately high rates of SUD and PTSD among veterans, the current study addresses a clinically important need by evaluating, for the first time, the efficacy of COPE among military veterans. An active treatment control group was used to control for time and therapeutic attention. We hypothesized that the integrated treatment would reduce self-report and clinician-rated PTSD symptoms, as well as SUD severity (i.e., percent days using and abstinence rates) significantly more than the control group at the end of treatment (session 12).

2. Material and methods

2.1. Participants

Participants were treatment-seeking, U.S. military veterans primarily recruited from newspaper and internet advertisements (e.g., Craigslist). Inclusion criteria included: 1) military veteran, 2) 18–65 years old, 3) met DSM-IV diagnostic criteria for current PTSD and score ≥ 50 on the DSM-IV Clinician Administered PTSD Scale (CAPS; Blake et al., 1995); and 4) met DSM-IV diagnostic criteria for current SUD and endorsed alcohol or drug use in the past 90 days. Exclusion criteria included: 1) psychiatric conditions that may require a higher level of care, 2) current enrollment in another treatment for SUD or PTSD, and 3) severe cognitive impairment as evidenced by the Mini Mental Status Examination (MMSE; Folstein, Folstein, & McHugh, 1975). Psychotropic medications were required to be stabilized for four weeks prior to enrollment.

2.2. Procedures

Interested individuals provided written informed consent and completed a baseline assessment. Eligible individuals were randomized (2:1) to receive 12 individual, 90-min sessions of COPE or Relapse Prevention (RP). Twice as many participants were randomized to COPE as this was a hybrid Stage Ib/Stage II project (Rounsaville, Carroll, & Onken, 2006). A biostatistician not directly involved in the study conducted the randomization. Participants were urn randomized (Wei & Lachin, 1988) and stratified to condition by SUD severity (high/low) and psychotropic medication (yes/no). RP participants were offered PTSD treatment referrals at session 12. Evaluators, blind to treatment condition, conducted assessments at baseline, week 6, week 12, and 3- and 6-months follow-up. Participants were compensated for their time and completing assessments ($60 for baseline, ~$50 for weekly assessments, $150 for follow-up visits). All study procedures were approved by the affiliated Institutional Review Board. Fig. 1 illustrates the study design and participant flow.

2.3. Treatment conditions

COPE (Back et al., 2014) employs imaginal and in vivo exposures to treat PTSD (Foa et al., 2007). Sessions 1–2 target psychoeducation about the interrelationship between SUD and PTSD, coping with cravings, substance- and trauma-related triggers, and the rationale for PE. In vivo exposures (sessions 3–12) and imaginal exposures (sessions 4–11) are key components. Abstinence is strongly encouraged, but not required to participate in COPE.

RP (Kadden et al., 1992) teaches skills to help manage cravings and high-risk situations that commonly precipitate substance use. RP was selected as the control condition because it is a manualized, evidence-based treatment often used in VA healthcare settings. The control condition in this study is, however, likely more rigorous than clinical practice in that it is protocol-driven and therapists received weekly supervision. Study therapists were instructed not to focus on PTSD or trauma-related symptoms during RP.

Treatment was provided by six masters- or doctoral-level clinicians who completed a 3-day training which covered content from both interventions. Study therapists attended weekly supervision during the trial. Completion of at least one pilot case of COPE (all 12 sessions) was required before being assigned a randomized case. COPE and RP were administered by the same clinicians to reduce potential therapist-related confounds. Sessions were videotaped and approximately 25% were randomly selected and evaluated using an adaptation of the Yale Adherence and Competence Scale (Carroll et al., 2000) that was modified to address components of the interventions used in this study. Adherence and competency ratings (0 = not at all, 1 = poor, 2 = adequate, 3 = very good, 4 = excellent) were in the "very good" range (M = 3, SD = 0.3), which is similar to prior studies. Holder et al. (2018) found that therapist fidelity rating scores in the "good" range (i.e., 5 on a scale of 1 to 7) were associated with significantly greater reductions in PTSD symptom severity than those scoring below average (< 4 on same scale). Another study found that clinicians delivering cognitive behavioral treatment for PTSD had fidelity ratings in the "good to excellent" range (i.e., 4 on a scale of 1 to 5), which met the certification criteria for achieving competence (Lu et al., 2012).

2.4. Assessments

Demographic information was collected via a self-report measure at baseline. The Life Events Checklist (Gray, Litz, Hsu, & Lombardo, 2004)

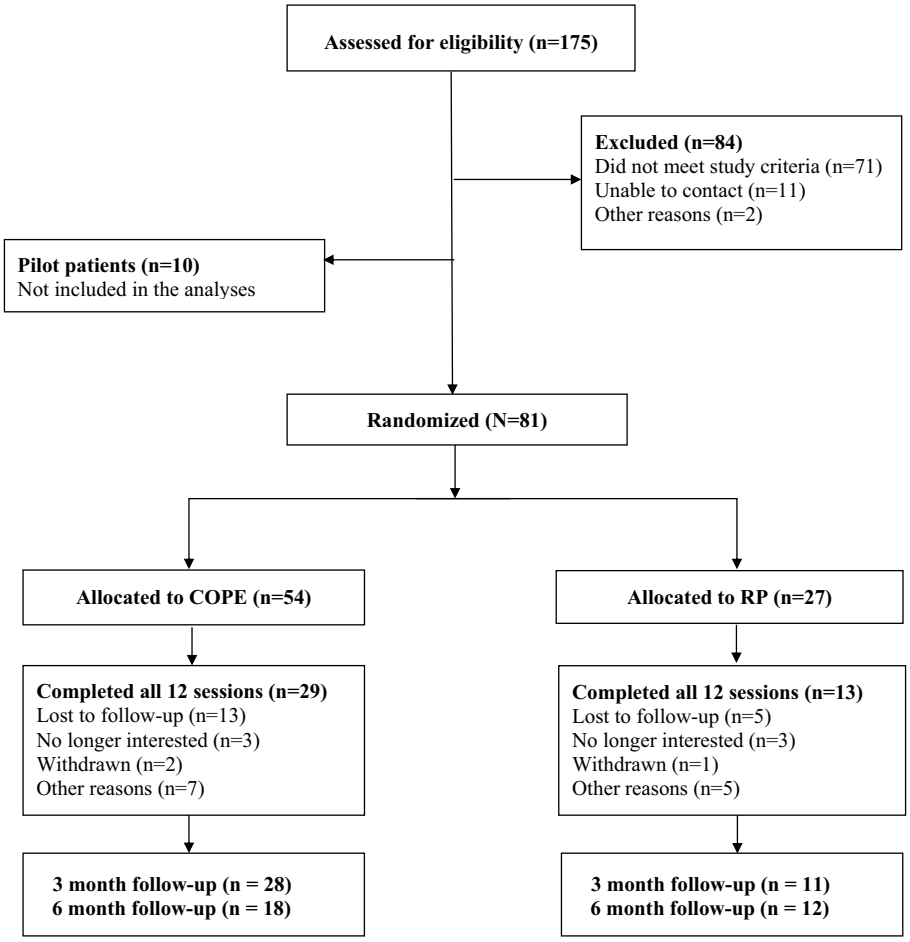

Fig. 1. Flow of participants through the study.

assessed lifetime exposure to traumatic events. The Deployment Risk and Resilience Inventory (DRRI; Vogt et al., 2013) assessed deployment-related trauma exposure. PTSD diagnosis and severity were evaluated using the DSM-IV CAPS, a clinical interview considered a gold standard for PTSD assessment (Blake et al., 1995). The PCL-M (Weathers, Litz, Huska, & Keane, 1994), a self-report measure, was administered weekly.

DSM-IV diagnoses for SUD were evaluated using the MINI International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). The Timeline Follow-back (TLFB; Sobell & Sobell, 1992), a calendar-based instrument, was administered weekly as an interview by study staff to measure substance use quantity and frequency. The Addiction Severity Index (ASI; McLellan, Luborsky, Woody, & O'Brien, 1980) assessed alcohol and drug use severity. Breathalyzer tests measured blood alcohol concentration (BAC) before each therapy session (> 0.01 g/dl was considered positive). Urine drug screen (UDS) tests (CLIAwaived Inc.) were administered weekly to assess for the presence of cocaine, marijuana, benzodiazepines, opioids, and amphetamines.

Major depressive episode (MDE) was assessed at baseline using the MINI. The Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996), a self-report measure, was administered weekly. Several items on the ASI inquire about lifetime suicidal ideation and attempts (McLellan et al., 1980). Finally, the Helping Alliance Questionnaire (HAQ-II; Luborsky et al., 1996), scaled 1–6 with higher scores reflecting a stronger perceived alliance, was administered at sessions 6 and 12.

2.5. Statistical analyses

Baseline characteristics were compared across treatment groups using independent-samples *t*-tests, Fisher's exact tests, and chi-square tests. Intent-to-treat (ITT) data included all randomized participants and all available data from those participants. Completer analyses utilized data from participants who attended all 12 sessions. Abstinence was assessed by the proportion of participants who attained abstinence 1) during the last two weeks of treatment, and 2) for three consecutive weeks at any time during treatment as measured by the TLFB (Carroll et al., 2014). These were compared across groups using chi-square test of independence and binary logistic regression to obtain odds ratios (ORs) and associated 95% confidence intervals (CIs).

Change in PTSD, SUD and depression severity as a function of treatment group was examined via a series of random intercept and slope multilevel models, utilizing robust maximum likelihood (MLR). Two-part modeling was used to examine SUD outcomes due to the presence of zero-inflated data (Olsen & Schafer, 2001). In this approach, one part of the model captures the likelihood of using (dichotomous, 0 = no use, 1 = use) and the other part captures frequency of use (e.g., percent days using).

A series of unconditional models using all data points were fit to determine whether a single linear change model or a piecewise model with separate intercepts and slopes for treatment and follow-up best approximated the data. The best-fitting unconditional models were established, and effect of treatment was examined in conditional models including group (0 = COPE, 1 = RP) and group by session interaction terms. Due to baseline differences, MDE was included as a covariate. We report unstandardized regression coefficients; estimated within-group change from baseline to session 12; estimated between-group differences at baseline, sessions 6 and 12; 95% CIs; and effect sizes as the regression coefficients standardized to the baseline SD of

Table 1
Baseline Demographic and Clinical Characteristics by Treatment Group.

	COPE (N = 54)		RP (N = 27)		Total (N = 81)	
	Mean	SD	Mean	SD	Mean	SD
Characteristic						
Age (years)	39.7	11.0	41.9	10.3	40.4	10.7
Education (years)	14.0	2.1	13.8	1.8	13.9	2.0
Average years of military service	10.1	8.7	9.2	6.2	9.8	7.9
	N	%	N	%	N	%
Sex (male)	50	92.6	23	85.2	73	90.1
Race/Ethnicity						
Caucasian/White	37	68.5	12	44.4	49	60.5
African American/ Black	16	29.6	14	51.9	30	37.0
More than one race/ Other	1	1.9	1	3.7	2	2.5
Hispanic ethnicity	2	3.7	1	3.7	3	3.7
Relationship status						
Single/Never married	15	27.8	8	29.6	23	28.4
Married	14	25.9	6	22.2	20	24.7
Separated/Widowed	4	7.4	4	14.8	8	9.9
Divorced/Annulled	21	38.9	9	33.3	30	37.0
Employment[a]						
Unemployed	18	34.0	12	44.4	30	37.5
Employed	22	41.5	7	25.9	29	36.3
Retired/Disabled	11	20.8	7	25.9	18	22.5
Student	2	3.8	1	3.7	3	3.8
Served in OEF/OIF/ OND[a]	37	68.5	14	53.8	51	64.6
Military-related index trauma[a]	44	83.0	20	76.9	64	81.0
Substance use						
Alcohol use disorder only	33	61.1	18	66.7	51	63.0
Alcohol and drug use disorder	15	27.8	7	25.9	22	27.2
Drug use disorder only	6	11.1	2	7.4	8	9.9
Cigarette smoker	32	59.3	14	51.9	46	56.8
Goal of abstinence[a]	26	50.0	17	65.4	43	55.1
History of addiction treatment	38	70.4	19	70.4	57	70.4
History of mental health treatment[a]	39	73.6	20	74.1	59	73.8
History of chronic pain treatment	35	64.8	14	51.9	49	60.5
Psychotropic medication[a]	34	65.4	17	63.0	51	64.6
Current major depression[b]	21	38.9	3	11.1	24	29.6
Lifetime suicidal ideation	26	48.1	8	29.6	34	42.0
Lifetime suicide attempt	16	29.6	6	22.2	22	27.2

Note. COPE = Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure; RP = Relapse Prevention; OEF = Operation Enduring Freedom; OIF = Operation Iraqi Freedom; OND = Operation New Dawn.

[a] Some information was missing for one to three participants.

[b] Significantly higher proportion of participants meeting criteria for current major depression in COPE group, Fisher's exact p = .01.

each outcome in the total sample (Feingold, 2009). Minimal missingness (< 1%) observed for individual items on the PCL-M and BDI-II were imputed using last observation carried forward. All statistical tests were two-sided with $\alpha = 0.05$.

3. Results

3.1. Baseline and clinical characteristics

Participants were mostly male with an average age of 40.4 years (see Table 1). The majority served in Operation Enduring Freedom, Operation Iraqi Freedom or Operation New Dawn (OEF/OIF/OND), with an average of 9.8 years of military service. The average number of trauma types experienced was 8.4 (SD = 2.7) and 81.0% reported a military-related index trauma (see Table 2). The average baseline CAPS score was 79.8, indicating severe to extreme PTSD symptomatology (Weathers et al., 2001). Most (90.0%) met criteria for an alcohol use disorder and 55% endorsed a treatment goal of abstinence, as compared to reduced use. At the baseline visit, all but one participant had a negative breathalyzer test and 74.1% had a negative UDS test. Among those with a positive UDS test at baseline, the most common drug detected was marijuana (55.6%). Significantly more participants in COPE met criteria for current MDE, and there were no other group differences in baseline or clinical characteristics.

Table 2
Lifetime traumatic events and combat-related experiences.

Lifetime traumatic events	% yes (N)
Natural disaster	63.5 (47)
Fire or explosion	54.7 (41)
Transportation accident (e.g., car accident, train wreck)	73.3 (55)
Serious accident at work, home or during recreation	47.9 (35)
Exposure to toxic substances	39.2 (29)
Physical assault (e.g., being attacked, hit, beaten up)	69.7 (53)
Assault with a weapon (e.g., shot, stabbed, threatened with a knife, gun, bomb)	66.7 (50)
Sexual assault (e.g., rape, attempted rape, made to perform sexual act through force or threat of harm)	24.7 (18)
Other unwanted or uncomfortable sexual experience	25.0 (18)
Combat or war-zone exposure	82.4 (61)
Captivity (e.g., kidnapped, held hostage, prisoner of war)	6.9 (5)
Life-threatening illness or injury	38.2 (29)
Severe human suffering	22.7 (17)
Sudden violent death of someone close (e.g., suicide, homicide)	24.7 (20)
Sudden unexpected death of someone close	58.1 (43)
Serious injury, harm or death you caused to someone	44.4 (32)
Other very stressful event or experience	44.4 (28)
Combat-related traumatic events during deployment	% yes (N)
Went on combat patrols or mission	73.0 (54)
Encountered land or water mines	58.1 (43)
Received hostile incoming fire (e.g., artillery, rockets, mortars, bombs)	78.4 (58)
Received hostile “friendly fire”	33.8 (25)
Was in vehicle (e.g., tank, helicopter, truck) that was under fire	56.8 (42)
Unit was attacked by terrorists or civilians	68.5 (50)
Part of land/naval artillery unit that fired on enemy	41.9 (31)
Part of assault on entrenched or fortified positions	37.8 (28)
Part of an invasion involving land or naval forces	44.6 (33)
Unit suffered causalities from battle	51.4 (38)
Witnessed someone from unit seriously wounded or killed	60.8 (45)
Witnessed enemy troops being seriously wounded or killed	62.2 (46)
Was wounded or injured in combat	28.8 (21)
Fired weapon at the enemy	58.1 (43)
Killed someone in combat	49.3 (37)

Note. Some events/experiences included missing values. Percentages reflect the proportion of participants completing each item who endorsed it positively.

3.2. Retention

Participants attended an average of 8 sessions [M = 8.8 for COPE (SD = 4.1) vs. 7.4 for RP (SD = 5.0); p = .21]. Over half (53.7%) completed all 12 sessions of COPE and 48.1% completed all 12 sessions of RP (p = .64). Previous studies report the percentage who attended at least 8 out of 12 sessions (Brady et al., 2001), which was 63% in this study (COPE = 66.7% vs. RP = 55.6%, p = .33). Divorced/annulled participants were more likely than married individuals to complete 12 sessions (p = .03). No other baseline differences between completers and non-completers were observed.

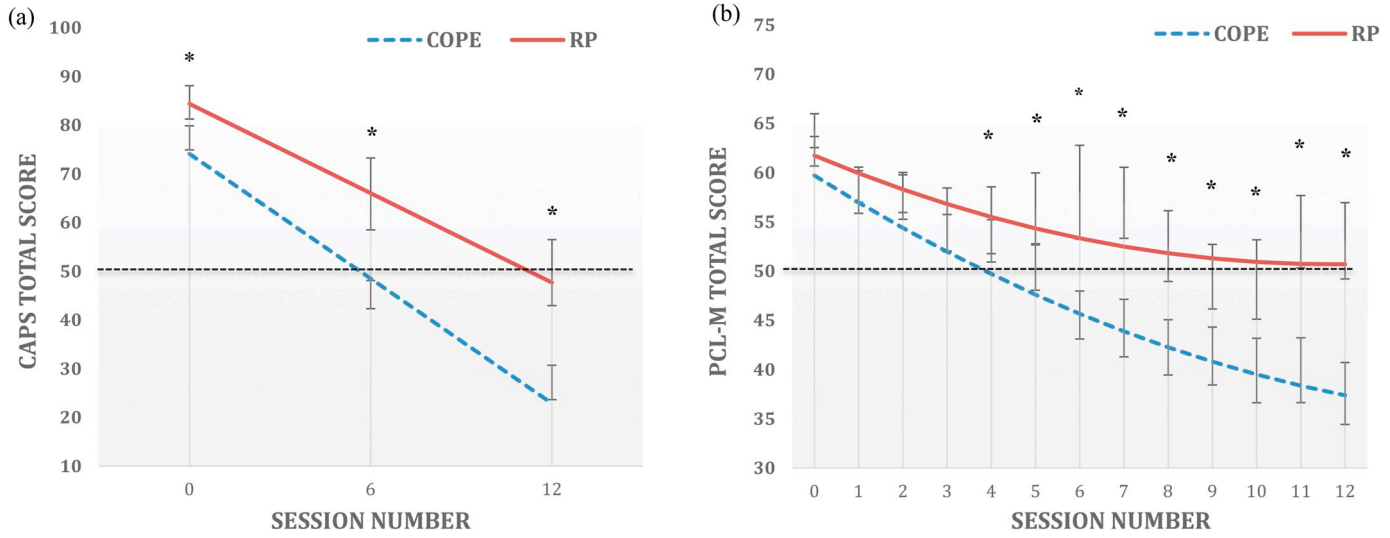

Fig. 2. Change in (a) Clinician Administered PTSD Scale (CAPS) and (b) PTSD Checklist-Military (PCL-M) from baseline to end of treatment by group.

3.3. PTSD diagnostic remission and severity

In the ITT sample, a significantly higher proportion of participants in COPE, as compared to RP, achieved diagnostic remission and no longer met criteria for PTSD [59.3% vs. 22.2%, $p = .002$; OR = 5.3; 95% CI (1.8, 15.7)]. Similarly, among completers, rates of PTSD diagnostic remission were significantly higher in COPE than RP [82.8% vs. 38.5%, $p = .004$; OR = 7.7; 95% CI (1.8, 33.6)]. PTSD severity improved in both groups (see Fig. 2); however, participants in COPE improved significantly more on the CAPS [$M_{\text{within-group}\Delta} = -51.2$; 95% CI (−59.7, −42.8)] and PCL-M [$M_{\text{within-group}\Delta} = -22.3$; 95% CI (−29.3, −15.3)] than participants in RP [CAPS $M_{\text{within-group}\Delta} = -35.9$; 95% CI (−48.8, −23.0) and PCL-M $M_{\text{within-group}\Delta} = -10.9$; 95% CI (−18.0, −3.9)]. At session 12, COPE participants scored approximately 25.6 points lower on the CAPS ($d = 1.4$) and 13.3 points lower on the PCL-M ($d = 1.3$) than RP participants (see Table 5).

PTSD treatment gains were maintained during follow-up with only slight decay at 3-months [CAPS, $M_{\text{within-group}\Delta} = 7.6$ ($SD = 22.3$); PCL-M, $M_{\text{within-group}\Delta} = 3.3$ ($SD = 11.2$)], and 6-months follow-up [CAPS, $M_{\text{within-group}\Delta} = 4.1$ ($SD = 33.6$); PCL-M, $M_{\text{within-group}\Delta} = 2.4$ ($SD = 12.0$)], with no significant group differences.

3.4. Substance use severity

Substance use decreased significantly in both groups (see Table 3), with improvement occurring more rapidly early in treatment ($M_{\Delta} = -29.3\%$, -36.5% for any substance use and alcohol use, respectively). In the ITT sample, 40.7% of participants in COPE and 25.9% in RP reported abstinence during the last two weeks of treatment. Similarly, 42.6% of participants in COPE and 25.9% in RP reported three consecutive weeks of abstinence during treatment. Among completers, the findings were slightly higher for the last two weeks of abstinence (COPE = 51.7%, RP = 38.5%) and three consecutive weeks of abstinence (COPE = 51.7%, RP = 30.8%). BAC tests were positive in approximately 1.5% of COPE and 2.5% of RP participants across treatment sessions, with no between group differences. UDS tests were positive for any drug in approximately 16.2% of COPE and 19.1% of RP participants across all treatment sessions, which was not significantly different by group.

Reductions in substance use were generally maintained during follow-up in both groups. In comparison to end of treatment, the average number of standard drinks per drinking day was similar at 3-months [$M_{\text{within-group}\Delta} = -0.09$ ($SD = 3.5$)] and 6-months follow up [$M_{\text{within-group}\Delta} = 0.5$ ($SD = 3.6$)]. At 3-months there was a trend ($p = .07$) and at 6-months a significant group difference in the average number of drinks per drinking day (COPE $M = 4.5$ vs. RP $M = 8.3$, $p = .05$).

3.5. Therapeutic alliance

Patients rated the therapeutic alliance positively at sessions 6 (COPE $M = 5.3$, RP $M = 5.5$) and 12 (COPE $M = 5.2$, RP $M = 5.4$). Positive perceptions of therapeutic alliance were also reported by therapists at sessions 6 (COPE $M = 5.0$, RP $M = 4.9$) and 12 (COPE $M = 5.2$, RP = 5.0). No group differences in therapeutic alliance were observed.

3.6. Depression

Depression improved in both groups (see Table 4) with a trend toward greater improvement in COPE ($p = .07$) on the BDI-II [COPE, $M_{\text{within-group}\Delta} = -16.0$; 95% CI (−21.4, −10.6); RP, $M_{\text{within-group}\Delta} = -9.4$; 95% CI (−15.3, −3.6)]. At session 12, the BDI-II score was significantly lower in COPE than RP ($p = .01$).

3.7. Adverse events

Three serious adverse events occurred during the study: 1) one COPE participant was hospitalized for suicidal ideation, 2) one RP participant made a suicide attempt, and 3) one individual who had not yet completed the baseline assessment, and therefore had not been randomized, died unexpectedly due to cardiac problems. None of these events were deemed study related.

4. Discussion

This is the first study to evaluate the efficacy of an integrated, exposure-based treatment for co-occurring SUD and PTSD among military veterans. To date, prior studies of integrated treatments for SUD/PTSD, including prior studies of COPE, have focused on non-veteran samples. In this study, the majority of participants were OEF/OIF/OND veterans with military-related traumas. The findings from this study provide critical information to help inform clinical practice guidelines regarding the treatment of comorbid SUD and PTSD, two of the most common mental health disorders afflicting our nation's military veterans.

As hypothesized, COPE was associated with significantly greater reduction in PTSD severity and higher rates of PTSD diagnostic remission than RP. Among participants who completed COPE, 83% no longer met criteria for PTSD, and among the more conservative ITT sample,

Table 3
Raw Scores on Primary and Secondary Outcomes by Treatment Group[a].

Measure	COPE			RP		
	n	Mean	*SD*	*n*	Mean	*SD*
CAPS Total[b]						
Baseline	54	77.4	18.1	27	84.7	17.8
Midtreatment	41	45.2	18.5	15	65.9	28.6
Posttreatment	30	27.2	19.4	14	49.7	25.3
CAPS Re-experiencing						
Baseline	54	22.8	7.6	27	21.6	7.7
Midtreatment	41	11.7	6.5	15	15.6	10.3
Posttreatment	30	5.6	7.1	14	14.6	10.7
CAPS Avoidance/Numbing						
Baseline	54	31.5	9.1	27	35.2	7.1
Midtreatment	41	16.8	9.4	15	27.8	13.9
Posttreatment	30	10.8	9.7	14	24.0	13.4
CAPS Hyperarousal						
Baseline	54	26.0	6.0	27	27.3	5.8
Midtreatment	41	17.0	8.0	15	22.9	7.4
Posttreatment	30	11.7	8.2	14	19.1	6.0
PCL-M Total[b]						
Baseline	54	62.2	11.0	27	64.3	8.9
Midtreatment	41	45.5	15.6	15	58.0	18.5
Posttreatment	30	37.6	17.2	14	53.1	14.5
PDU Any Substance[c]						
Baseline	48	52.8	33.7	25	54.1	32.2
Midtreatment	25	33.6	26.2	10	43.3	26.1
Posttreatment	14	43.3	26.7	9	42.3	36.2
PDU Any Alcohol[c]						
Baseline	44	53.6	30.4	25	46.0	31.5
Midtreatment	23	34.0	24.7	9	37.0	17.8
Posttreatment	14	41.3	22.8	9	39.1	36.0
Drinks Per Drinking Day[c]						
Baseline	44	8.5	7.0	25	9.7	6.7
Midtreatment	23	4.8	3.5	9	5.4	3.3
Posttreatment	14	4.6	3.6	9	5.0	4.1
BDI-II[d]						
Baseline	54	29.2	12.3	25	29.6	9.7
Midtreatment	41	19.5	11.7	15	26.2	13.7
Posttreatment	30	13.0	11.0	14	19.4	12.3
ASI – Alcohol Composite						
Baseline	54	0.37	0.26	27	0.37	0.29
Midtreatment	39	0.23	0.19	15	0.34	0.28
Posttreatment	29	0.17	0.18	14	0.23	0.17
ASI – Drug Composite						
Baseline	54	0.04	0.06	27	0.09	0.12
Midtreatment	39	0.04	0.07	15	0.06	0.09
Posttreatment	29	0.02	0.04	14	0.03	0.06
ASI – Psychiatric Composite						
Baseline	54	0.56	0.22	27	0.54	0.15
Midtreatment	39	0.41	0.17	15	0.66	0.74
Posttreatment	29	0.27	0.21	14	0.35	0.22

Note. COPE = Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure; RP = Relapse Prevention; CAPS = Clinician-Administered PTSD Scale; PCL-M = PTSD Checklist-Military; PDU = percent days using; BDI-II = Beck Depression Inventory-II; ASI = Addiction Severity Index.

[a] Posttreatment *ns* include participants who did not complete all 12 sessions but completed assessments.

[b] Diagnositc cut off for the DSM-IV CAPS and PCL total scores = 50.

[c] Among participants reporting substance use during period covered by a given assessment.

[d] Data is missing on baseline scores for two participants.

59% of COPE participants no longer met criteria for PTSD. These outcomes are similar or higher than diagnostic remission rates observed in PTSD-only patients (no comorbid SUD) treated with cognitive behavioral therapies (Hoffman et al., 2018). Based on this and other studies examining exposure-based treatments in comorbid populations, the presence of a current SUD should not be regarded as a contraindication to receiving exposure-based treatment for PTSD (Brady et al., 2001; Foa et al., 2013; Foa et al., 2017; Mills et al., 2012; Najavits, Krinsley, Waring, Gallagher, & Skidmore, 2018; Norman & Hamblen, 2017; Persson et al., 2017; Ruglass et al., 2017; Simpson et al., 2017). Although the greatest reductions in PTSD symptoms were observed in the COPE group, participants in the RP group also reported improvements in PTSD, and approximately 22% of the ITT sample who received RP no longer met criteria for PTSD. This finding is consistent with previous investigations (e.g., Simpson et al., 2017), and may be due, in part, to the fact that manualized RP therapy, provided by a well-trained clinician receiving weekly expert supervision can address negative emotions, cognitions and behaviors that overlap with PTSD symptoms. Although PTSD was not discussed during RP therapy sessions, the cognitive-behavioral skills learned in RP could conceivably generalize to PTSD-related symptoms.

The trauma history of participants in this study is notable. Most participants endorsed a variety of military-related and non-military related traumatic events with exposure to an average of 8 different types of traumas. Previous studies of COPE among civilians with complex trauma histories have also found substantial pre- to post-treatment reductions in SUD and PTSD. Mills et al. (2012) evaluated COPE among 103 outpatients in Australia who were mostly female, heroin injection drug users with childhood trauma (79%) and exposure to an average of 6 different trauma types. Mills et al. (2012) found that COPE, in comparison to treatment as usual in the community, significantly reduced PTSD symptoms and yielded comparable SUD outcomes. In a more recent, open-label study of COPE among women with alcohol use disorder and PTSD in Sweden, Persson et al. (2017) found that COPE led to significant reductions in both SUD and PTSD severity, despite the fact that almost all of the women (91%) reported childhood trauma and exposure to an average of 7 different trauma types. Taken together, the findings indicate that integrated, exposure-based treatment is effective in reducing SUD and PTSD severity across multiple types of traumas, including military-related events.

Contrary to our hypothesis, both treatment groups evidenced significant and comparable reductions in substance use during treatment. One possible explanation for why the COPE group did not demonstrate significantly greater reductions in SUD outcomes, as compared to the RP group, is that the COPE group received approximately half the amount of the RP intervention. That is, approximately 45 min of each COPE session was dedicated to substance use, while the full 90 min of each RP session was dedicated to substance use. Despite this, significant group differences emerged with COPE participants consuming fewer drinks per drinking day (approximately 4 fewer drinks per day) than RP participants at the final time point. On the one hand, the lack of group differences in SUD outcomes during treatment may be seen as disappointing. On the other hand, this finding may be viewed as encouraging in that a 12-session integrated SUD/PTSD treatment resulted in as much reduction in SUD severity as an evidence-based, SUD-only treatment, while also conferring the additional benefit of reducing PTSD severity. This highlights a major advantage of integrated treatments in efficiently addressing two disorders in the same amount of time. Reductions in SUD observed in the current study were similar to findings from previous studies of COPE in civilians (Mills et al., 2012; Ruglass et al., 2017) and comparable to findings observed in randomized controlled trials of SUD-only patients (Anton et al., 2006; Dutra et al., 2008). The findings from this study converge with those of previous investigations (Coffey, Stasiewicz, Hughes, & Brimo, 2006; Foa et al., 2013; Mills et al., 2012; Norman et al., 2016; Peck et al., 2018; Persson et al., 2017; Ruglass et al., 2017) and show that PE delivered in the context of an integrated or comprehensive SUD treatment is beneficial, even among individuals who continue to use substances. The findings also highlight that there is room for improvement, particularly with regard to SUD outcomes, and suggest that the addition of

Table 4
Conditional Intent-to-Treat Models of PTSD Symptoms and Substance Use.

PTSD symptoms	CAPS total score		CAPS Re-experiencing		CAPS avoidance/numbing		CAPS hyperarousal		PCL-M	
	B	*SE*	*B*	*SE*	*B*	*SE*	*B*	*SE*	*B*	*SE*
Intercept (Baseline)	74.1***	2.7	21.7***	1.1	34.9***	1.3	18.0	0.9	59.7***	1.75
Group	10.3*	4.4	−0.6	1.8	6.6**	2.1	1.9	1.5	2.0	2.61
Session (linear)	−4.3***	04	−1.4***	0.1	−1.9***	0.2	−0.9***	0.1	−2.8***	0.48
Session^2 (quadratic)	–	–	–	–	–	–	–	–	0.1*	0.03
Group by session	1.3*	0.6	0.8***	0.2	0.8*	0.3	0.5**	0.2	1.0*	0.39

Substance use	Any substance use		Any alcohol use		PDU any substance		PDU Alcohol		Drinks per drinking day	
	B	*SE*	*B*	*SE*	*B*	*SE*	*B*	*SE*	*B*	*SE*
Threshold/Intercept	−3.7***	0.9	−3.0***	0.7	52.5***	5.2	53.0***	5.4	6.9	0.6
Group	0.3	1.2	0.6	1.0	3.0	7.1	−4.1	7.1	1.8	1.2
Session (linear)	−0.7***	0.1	−0.8***	0.1	−4.0*	1.4	−4.8**	1.2	−0.7***	0.2
Session^2 (quadratic)	0.0***	0.0	0.0***	0.0	0.2*	0.1	0.3**	0.1	0.1***	0.0
Group by session	0.0	0.2	0.1	0.1	−0.7	0.9	0.3	0.7	−0.1	0.1

Depression	BDI-II	
	B	*SE*
Intercept	26.5***	1.8
Group	2.2	2.6
Session (linear)	−1.3***	0.2
Session^2	–	–
Group by session	0.6[a]	0.3

Note. Continuous outcomes are modeled among those reporting any use. Intercepts and session slopes are adjusted for current major depressive episode at baseline. Substance/alcohol use (0 = no use, 1 = any use). Treatment condition (0 = COPE, 1 = RP). PTSD = posttraumatic stress disorder; CAPS = Clinician Administered PTSD Scale; PCL-M = PTSD Checklist-Military; PDU = percent days use; BDI-II = Beck Depression Index-II; SE = standard error.

* $p < .05$.
** $p < .01$.
*** $p < .001$.
[a] $p = .07$.

pharmacotherapies or other interventions to further reduce craving and substance use may be benefit some patients with SUD/PTSD.

Participants in this study completed an average of 8 therapy sessions, with no difference by treatment condition; this highlights that the addition of exposure-based trauma work does not lead to increased dropout. The majority of available COPE sessions (73.7%) and RP sessions (61.7%) were attended. Completion rates and attendance in this study were similar to or higher than previous studies of non-exposure based, integrated treatments (Hien et al., 2009; Myers, Browne, & Norman, 2015; Najavits et al., 2018) as well as exposure-based, integrated treatments (Coffey et al., 2016; Foa et al., 2013; Mills et al., 2012; Peck et al., 2018; Ruglass et al., 2017; Schacht, Brooner, King, Kidorf, & Peirce, 2017). Improvements in retention observed in the current study may be due, in part, to modifications made to the treatment protocol. Most notably, the current version of the COPE therapy manual (Back et al., 2014), which was utilized in this study, initiates in vivo and imaginal exposures earlier in treatment (sessions 3 and 4, respectively), which is earlier than exposures were initiated in previous studies (e.g., Brady et al., 2001; Mills et al., 2012). The higher retention may also be due to the study sample which consisted of military veterans who often receive multiple services at the VA hospital (e.g., primary care, housing, occupational assistance), which allows research staff to schedule study visits around veterans' other VA appointments. In addition, transportation problems are mitigated in this population, as veterans may be reimbursed by the VA for transportation costs to and from appointments, or offered transportation via a VA shuttle bus. Nonetheless, there remains significant room for improving retention in this population, as 54% of the COPE group and 48% of the RP group attended all 12 sessions of treatment. Retention of patients with either PTSD *or* SUD, conditions frequently characterized by avoidance coping, is challenging and it becomes even more challenging when both conditions are present. Previous examination of dropout from COPE reveals that the highest probability of dropout occurs between sessions 9 and 10 (Szafranski et al., 2017), and that a substantial proportion of individuals (40%–68%) who drop out before completing all 12 sessions evidence clinically significant improvement and/or met good end-state functioning with regard to SUD, PTSD, and depression prior to dropping out (Szafranski et al., in press). Thus, it may not always be the case that dropout is due to a worsening or lack of symptom improvement (Szafranski, Smith, Gros, & Resick, 2017), and more research in this area is needed.

Several limitations warrant consideration. The sample size was small, which may have underpowered the analyses. Although the percentage of women in the study is representative of women in the U.S. military service (Department of Defense (DoD), 2015), the small number of women limited our ability to evaluate gender differences. Despite these limitations, this study is the first to examine COPE in a military population and has several key strengths including the use of a randomized between-groups experimental design, comparison of two evidence-based treatments matched on time and therapeutic attention, intent-to-treat design, validated assessments, and inclusion of a substantial proportion of minority individuals (37% African American). Furthermore, minimal exclusion criteria were used and the sample is representative of real-world practice.

In summary, in this sample of veterans with extensive military-related trauma, COPE resulted in significantly greater reductions in PTSD severity, higher rates of PTSD diagnostic remission, and comparable reductions in SUD, as compared to RP. Importantly, there were no treatment group differences in measures of therapeutic alliance, retention, or number of adverse events. In conjunction with a growing

Table 5
Intent-to-Treat Differences (RP - COPE) on Primary and Secondary Outcomes at Baseline, Mid-, and Posttreatment.

Measure	*B* [95% CI]	*p*	ES [95% CI]
CAPS-Total			
Baseline	10.3 [1.7, 18.9]	0.02	0.6 [0.1, 1.0]
Midtreatment	18.0 [8.6, 27.4]	< 0.001	1.0 [0.5, 1.5]
Posttreatment	25.6 [11.3, 49.0]	< 0.001	1.4 [0.6, 2.2]
CAPS-Re-experiencing			
Baseline	−0.6 [−4.1, 2.8]	0.73	−0.1 [−0.5, 0.4]
Midtreatment	4.2 [0.2, 8.1]	0.04	0.6 [0.0, 1.2]
Posttreatment	8.9 [3.3, 14.6]	0.00	1.2 [0.4, 1.9]
CAPS-Avoidance/Numbing			
Baseline	6.6 [2.5, 10.6]	0.00	0.7 [0.3, 1.2]
Midtreatment	11.2 [6.1, 16.2]	< 0.001	1.2 [0.7, 1.8]
Posttreatment	15.8 [7.6, 24.0]	< 0.001	1.8 [0.8, 2.7]
CAPS-Hyperarousal			
Baseline	1.9 [−0.9, 4.8]	0.19	0.3 [−0.3, 0.7]
Midtreatment	4.6 [2.1, 7.1]	< 0.001	0.8 [0.8, 1.3]
Posttreatment	7.3 [3.8, 10.9]	< 0.001	1.3 [0.7, 2.0]
PCL-M			
Baseline	2.0 [−3.1, 7.1]	0.44	0.2 [−0.6, 1.3]
Midtreatment	6.8 [−0.6, 14.2]	0.07	0.7 [0.2, 1.3]
Posttreatment	13.3 [4.0, 22.7]	0.01	1.2 [0.4, 2.2]
PDU Any Substance			
Baseline	3.0 [−11.0, 16.9]	0.68	0.1 [−0.3, 0.5]
Midtreatment	−0.9 [−13.2, 11.3]	0.88	−0.0 [−0.4, 0.3]
Posttreatment	−4.8 [−22.3, 12.7]	0.59	−0.1 [−0.6, 0.4]
PDU Alcohol			
Baseline	−4.1[−18.0, 9.7]	0.56	−0.1 [−0.5, 0.3]
Midtreatment	−2.3 [−14.1, 9.5]	0.71	−0.1 [−0.4, 0.3]
Posttreatment	−0.5 [−15.7, 14.7]	0.95	−0.0 [−0.5, 0.4]
Drinks Per Drinking Day			
Baseline	1.8 [−0.6, 4.2]	0.15	0.4 [−0.2, 1.0]
Midtreatment	1.1 [−0.5, 2.7]	0.18	0.3 [−0.1, 0.6]
Posttreatment	0.4 [−1.3, 2.1]	0.64	0.1 [−0.3, 0.5]
BDI-II			
Baseline	2.2 [−2.8, 7.3]	0.38	0.2 [−0.2, 0.6]
Midtreatment	5.1 [0.4, 9.9]	0.04	0.4 [0.0, 0.9]
Posttreatment	9.0 [2.2, 15.7]	0.01	0.8 [0.2, 1.4]

Note. Models are adjusted for current major depressive episode at baseline. RP = Relapse Prevention. COPE = Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure; CAPS = Clinician-Administered PTSD Scale; CI = confidence interval; PCL-M = PTSD Checklist-Military; PDU = percent days using; BDI-II = Beck Depression Index-II.

body of literature on integrated treatments for SUD/PTSD, the findings raise important questions for clinical practice and future research in VA healthcare settings. First, it is recommended that all veterans with SUD be assessed for trauma exposure and PTSD. Veterans with both SUD and PTSD should be offered integrated, exposure-based treatment to address both conditions concurrently. Veterans wishing to receive integrated treatment should initiate treatment promptly; PTSD treatment should not be delayed until abstinence has been achieved. Although abstinence is the safest option, a significant proportion of veterans with SUD/PTSD do not endorse a goal of abstinence (Lozano et al., 2015) and PTSD treatment should not be delayed because of this. Future research is needed to identify ways to further increase treatment retention and reduce substance use in order to yield long-term positive outcomes in both SUD and PTSD.

Fig. 2a2b: raw mean scores, standard errors, and mean estimated effect of the treatment condition by session interaction in predicting PTSD symptoms from baseline (time 0) to session 12. Dashed lines indicate standard cut-off scores of 50 for severity and diagnostic thresholds. Asterisks indicate significant group differences ($p < .05$).

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