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Does trauma-focused exposure therapy exacerbate symptoms among patients with comorbid PTSD and substance use disorders?

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Abstract

Background: Although exposure-based therapy is a well-established, effective treatment for post-traumatic stress disorder (PTSD), some practitioners report reluctance to implement it due to concerns that it may exacerbate symptoms of PTSD and commonly comorbid disorders, such as substance use disorders (SUD).

Aim: This study compared the exacerbation of psychological symptoms among participants with comorbid PTSD and SUD who received either SUD treatment alone or SUD treatment integrated with exposure therapy for PTSD.

Method: Participants (N = 71) were treatment-seeking, military Veterans with comorbid PTSD and SUD who were randomized to 12 individual sessions of either (1) an integrated, exposure-based treatment (Concurrent Treatment of PTSD and Substance Use Disorders using Prolonged Exposure; COPE); or (2) a non-exposure-based, SUD-only treatment (Relapse Prevention; RP). We examined between-group differences in the frequency of statistically reliable exacerbations of PTSD, SUD and depression symptoms experienced during treatment.

Results: At each of the 12 sessions, symptom exacerbation was minimal and generally equally likely in either treatment group. However, an analysis of treatment completers suggests that RP

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Conflicts of interest. The last three authors (T.K., K.B. and S.B.) are also co-authors of the COPE therapy manuals.

Ethical statements. The authors assert that all procedures contributing to this work comply with the ethical standards of the local Institutional Review Board, and with the Helsinki Declaration of 1975 and its most recent revision. The procedures and measures used in this study were approved by the local institutional review board.

participants experienced slightly more exacerbations of PTSD symptoms during the course of treatment.

Conclusions: This study is the first to investigate symptom exacerbation throughout trauma-focused exposure therapy for individuals with comorbid PTSD and SUD. Results add to a growing literature which suggests that trauma-focused, exposure-based therapy does not increase the risk of symptom exacerbation relative to non-exposure-based therapy.

Keywords

combined treatment; depression; post-traumatic stress disorder; substance use; therapy outcome; Veteran

Introduction

Post-traumatic stress disorder (PTSD) has a lifetime prevalence of 6.8% in the general population (Kessler et al., 2005). Among military Veterans, rates range from 8 to 20%, depending upon the sample, measures and criteria used (Hoge et al., 2004; Miller et al., 2012; Wisco et al., 2014). Substance use disorders (SUDs) are often comorbid with PTSD in both veterans (Wisco et al., 2014) and the general population (Kessler et al., 2005), with comorbidity estimates ranging from 26 to 52% of cases (Roberts et al., 2015). One common pathway to comorbid PTSD and SUD begins with individuals with PTSD using substances to 'self-medicate' distressing symptoms, such as sleep impairment, negative affect and intrusive memories (Jacobsen et al., 2001). Substance withdrawal symptoms may also exacerbate PTSD symptoms and trigger further substance use (Jacobsen et al., 2001). These maladaptive cycles appear to worsen the course of both illnesses, compared with either disorder alone (McCauley et al., 2012; Najt et al., 2011; Schäfer and Najavits, 2007).

The negative prognosis for individuals with both PTSD and SUD prompted the development of treatments that address both conditions simultaneously (Norman and Hamblen, 2017; Simpson et al., 2017; van Dam et al., 2012). Meta-analytic work indicates that integrated interventions are more effective than single-disorder treatments for PTSD or SUD symptoms, when they include trauma-focused exposure therapy (Roberts et al., 2015). Additionally, most patients prefer integrated compared with single-disorder treatments (Back et al., 2014b).

Despite decades of evidence supporting the use of exposure-based treatments for PTSD (Powers et al., 2010), many therapists do not use exposure therapy when treating PTSD (Becker et al., 2004; Larsen et al., 2016; Meyer et al., 2014; van Minnen et al., 2010). Studies suggest that this may be due to widespread concerns that trauma-focused exposure therapy could produce symptom exacerbation or drop out (Foa et al., 2007; Larsen et al., 2016). In addition, concerns regarding patients' psychiatric comorbidities and emotional fragility are frequently endorsed reasons for excluding patients from exposure therapy or trauma-focused therapies (Leeman et al., 2017; Meyer et al., 2014).

Despite these concerns, particularly about patients with comorbidities, there are relatively few published studies evaluating exposure therapy outcomes in individuals with comorbid

SUD. Expert recommendations in the earlier stages of treatment development were to treat SUD prior to PTSD (i.e. sequential treatment; Foa and Rothbaum, 1998; McCauley et al., 2012; Nace, 1988), due in part to concerns that intense emotions elicited by exposure therapy would provoke an increase in substance use (i.e. the 'Pandora's box' hypothesis; Becker et al., 2004; Souza and Spates, 2008; van Minnen et al., 2010). Therefore, most clinical trials (74%) investigating the efficacy of treatments for PTSD have excluded patients with comorbid SUD (Leeman et al., 2017; van Minnen et al., 2012). However, more recent studies have provided some insight on response to trauma-focused exposure therapy among individuals with comorbid PTSD and SUDs.

Specifically, there have been several randomized controlled trials (RCTs) for treatments of comorbid PTSD and SUD, in which exposure-based therapy for PTSD was administered either alongside, or integrated with, psychotherapy for SUD (Mills et al., 2012; Coffey et al., 2016; Sannibale et al., 2013; Ruglass et al., 2017). Overall, data suggest that these concurrent or integrated treatments produce improvements in both PTSD and SUD symptoms. The outcomes from these RCTs directly contradict the Pandora's box hypothesis (Souza and Spates, 2008), that the use of trauma-focused exposure therapy in patients with comorbid PTSD and SUD exacerbates substance use.

However, following the standard methodology of RCTs, these studies have primarily relied on mean-based statistics. While this provides critical information about the overall efficacy of a given treatment in a population, reliance on means does not provide information about individual change, including the prevalence of reliable symptom exacerbation among study participants. It is possible for a subgroup of participants to experience reliable increases in symptoms, even if the overall means indicate a decrease in symptoms. In fact, recent methodological research has found that generalizing group-level averages to individuals may be 'worryingly imprecise' (p. 1, Fisher et al., 2018). Therefore, these prior RCTs have not fully addressed the common concern voiced among clinicians (e.g. Becker et al., 2004; van Minnen et al., 2010) that trauma-focused exposure-based therapy could provoke increases in substance use among patients with comorbid SUD. Furthermore, data suggest that at least some patients with comorbid PTSD and SUD may be experiencing symptom exacerbation during exposure-based therapy for PTSD.

For example, two separate studies evaluating session-to-session change on an individual level (using reliable change analyses; e.g. Foa et al., 2002; Larsen et al., 2016) have found that some PTSD patients (20% or less) experience exacerbation in symptoms of PTSD and depression symptoms during exposure-based therapy for PTSD. Importantly, both studies found that exacerbation rates were no different in exposure-based and non-exposure-based therapies for PTSD. However, these studies included few or no patients with a comorbid SUD (< 5% in Larsen et al., 2016; 0% in Foa et al., 2002). Therefore, we know that a subset of patients receiving psychotherapy for PTSD (both exposure-based and not) experience symptom exacerbation, but we have almost no data on exacerbation rates among patients receiving psychotherapy for comorbid PTSD and SUDs.

Additionally, exacerbation could potentially be occurring among patients with comorbid PTSD and SUD because higher drop-out rates have been noted across several RCTs in this

population. A recent meta-analysis examining psychotherapy outcomes for comorbid PTSD and SUD found consistently high therapy drop-out rates in this patient population (30–50% for most studies; Roberts et al., 2015). Furthermore, this meta-analysis found that, 'fewer individuals assigned to [exposure-based] trauma focused intervention than control group completed treatment … suggesting that such interventions may not always be well tolerated' (p. 34, Roberts et al., 2015). Clients who terminate treatment prematurely do not benefit from the full dosage of treatment, and may experience inferior outcomes (e.g. Pekarik, 1992). It is possible that the high drop-out rates in participants with comorbid PTSD and SUD are fuelled by symptom exacerbation. These data therefore highlight the need to evaluate symptom exacerbation among patients receiving trauma-focused, exposure therapy for comorbid PTSD and SUD.

Furthermore, laboratory-based studies have found that individuals with comorbid PTSD and SUD experience increases in substance cravings and distress in response to listening to a personalized trauma script, in comparison with a neutral script (Coffey et al., 2002, 2006). Although this reactivity decreases after repeated exposure to trauma scripts (Coffey et al., 2006), this evidence suggests that there could be a temporary increase in symptoms at the onset of imaginal exposure in a population with comobird PTSD and SUD. It is unclear whether the observed increases in distress and substance craving reactivity in the laborotory would be associated with reliable exacerbation in PTSD symptoms and increases in substance use after imaginal exposure is initiated. Prior studies among PTSD patients suggest that there is no increased risk of symptom exacerbation during initiation of imaginal exposure relative to other types of psychotherapy (Foa et al., 2002; Larsen et al., 2016), but this has not been examined among patients with comorbid PTSD and SUD diagnoses.

One emerging exposure-based treatment for comorbid PTSD and SUD is called Concurrent Treatment of PTSD and Substance Use Disorders using Prolonged Exposure (COPE; Back et al., 2014a). Overall outcome data suggest that COPE can improve symptoms of both SUD and PTSD among civilian and military individuals with both diagnoses (Back et al., 2019; Hien et al., 2016; Mills et al., 2012, 2016; Persson et al., 2017; Ruglass et al., 2017). Only one of these studies (Mills et al., 2016) has evaluated symptom exacerbation based on reliable change analyses. This study observed no reliable and clinically significant exacerbation of symptoms, when examining relaible change from before to after treatment. However, the authors did not examine the presence of symptom exacerbation during the process of completing COPE, and prior research suggests that symptom exacerbation (if present) would probably occur closer to the onset of exposure therapy (e.g. Coffey et al., 2002, 2006).

The present study is the first to examine exacerbation of psychological symptoms based on session-to-session changes during COPE. This study will specifically evaluate exacerbation of psychological symptoms (i.e. PTSD, depression and substance use) among Veterans receiving COPE (Back et al., 2014b) compared with SUD-only treatment [Relapse Prevention (RP); Carroll, 1998]. Based on previous research supporting the efficacy of COPE for reducing PTSD and SUD symptoms, and prior research demonstrating low rates of symptom exacerbation during PTSD-only treatment trials (Foa et al., 2002; Larsen et al., 2016), we hypothesized that rates of symptom exacerbation would be comparable between

an exposure-based, integrated treatment (COPE) and a non-exposure-based, SUD-only treatment (RP).

Methods

Participants

Veterans with current PTSD and SUD diagnoses were recruited from Veterans Affairs (VA) treatment clinics and advertisements as part of a randomized controlled trial sponsored by the National Institute on Drug Abuse (NIDA). Inclusion criteria were: (1) status as a Veteran, Reservist, or National Guard member of the US Armed Forces, (2) age between 18 and 65 years, (3) current *Diagnostic and Statistical Manual for Mental Disorders*, Fourth Edition (DSM-IV; APA, 2000) diagnosis of PTSD and SUD, (4) Clinician-Administered PTSD Scale (CAPS) score ≥ 50, (5) substance use within the last 90 days, and (6) fluency in English. Participants taking psychotropic medications had to be stabilized on the medication for at least 4 weeks to be included in the study. Exclusion criteria were: (1) current or history of psychosis or bipolar disorders, (2) current suicidal or homicidal ideation with intent, (3) current eating disorder, (4) ongoing PTSD or SUD treatment, and (5) severe cognitive impairment (Mini Mental Status Exam ≤ 21). See Table 1 for sample demographics.

Procedures

The present study examined exacerbation during treatment.[1] Participants were pre-screened by telephone or in person, and then completed a baseline assessment to determine study eligibility. Veterans meeting inclusion criteria (N = 81 out of 175 who were pre-screened) were randomized using a 2:1 ratio[2] to COPE (n = 54) or RP (n = 27). Because this study evaluated the frequencies of between-session symptom exacerbations, the final dataset for this study included participants who completed at least two sessions of treatment (N = 71; COPE, n = 49; RP, n = 22).

All procedures were approved by the local VA Research and Development committee as well as the Institutional Review Board (IRB) at the affiliated university. Procedures complied with the Helsinki Declaration of 1975, and its most recent revision. All study participants signed an IRB approved informed consent prior to completing any study procedures, and participants were compensated for each assessment.[3]

Treatments

Concurrent Treatment of PTSD and Substance Use Disorders using Prolonged Exposure (COPE) is a manualized, integrated, cognitive behavioural therapy for comorbid PTSD and SUD that consists of 12 weekly, individual, 90-minute sessions (Back et al., 2014a).

[1]For a full report of the overall outcomes from this randomized clinical trial, see additional publications (Back et al., 2019; Jarnecke et al., 2019).
[2]The 2:1 randomization ratio was used due to ethical concerns. Researchers wished to minimize the extent to which they delayed the receipt of an evidence-based treatment for PTSD to a vulnerable population (i.e. patients with comorbid PTSD and SUD).
[3]Participants were compensated for the completion of study assessments in the form of cash, gift cards, or VA vouchers. Participants received $60 for the baseline assessment, increasing compensation for completion of assessments at each therapy session (starting at $10 and increasing to $50 by the last session), and $50 for each follow-up assessment, for a total of up to $400 for completion of all study assessments.

Sessions 1 and 2 focus primarily on psychoeducation related to PTSD and SUD, methods for coping with cravings, awareness of triggers for use, and rationale for *in vivo* and imaginal exposure. *In vivo* exposures (sessions 3 to 12) and imaginal exposures (sessions 4 to 12) are key components of the therapy, and were integrated with SUD coping skills throughout the remaining sessions of treatment. (See Supplementary Material for information on anxiety activation and habituation during COPE.)

Relapse Prevention (RP) is a manualized cognitive behavioural therapy for SUD that consists of 12 weekly, individual, 90-minute sessions (Carroll, 1998; Kadden et al., 1995). Each session focuses on a topic related to common issues experienced in recovery from alcohol or drug use disorders (e.g., managing cravings and thoughts about using alcohol/drugs, drink/drug refusal skills, planning for emergencies, and anger management). The goal of treatment is to master the coping skills necessary to manage high-risk situations, and to reduce or abstain from substance use.

Treatment was delivered by masters- or doctoral-level clinicians who completed a multi-day training workshop and received weekly supervision. All therapy sessions were recorded. Approximately 25% of the sessions were randomly selected and evaluated to ensure fidelity. Therapists scored in the range of good to very good on average on a version of the Yale Adherence and Competence Scale (Nuro et al., 2005) adapted to this study.

Measures

Participants completed a large assessment battery.[4] Measures relevant to the present study included the Mini International Neuropsyhiatric Interview (baseline), the Clinician Administered PTSD Scale (baseline and last session), the PTSD Symptom Checklist (baseline and each session), the Timeline Follow-back assessment (baseline and each session), and the Beck Depression Inventory-II (baseline and each session).

Mini International Neuropsychiatric Interview (MINI)

The MINI is a structured diagnostic interview designed to assess DSM-IV psychiatric disorders (Sheehan et al., 1998). The MINI was used to assess all psychiatric disorders at baseline except PTSD, which was assessed with the CAPS. The MINI has demonstrated adequate test-retest and inter-rater reliability for most disorders (Sheehan et al., 1998).

Clinician Administered PTSD Scale (CAPS)

The CAPS is a clinician-rated semi-structured interview designed to diagnose past-month DSM-IV PTSD (Blake et al., 1995). To ensure competency, all raters completed a CAPS training, co-rated an interview with an expert trainer, and administered and co-rated a CAPS interview monitored by an expert trainer. The CAPS has adequate internal consistency, inter-rater reliability, and test-retest reliability (Orsillo, 2002).

[4]For a full description of all measures completed by participants in the study, see additional publication (Back et al., 2019).

Timeline Follow-Back (TLFB)

The TLFB is a retrospective assessment of daily substance use (Sobell and Sobell, 1992). The TLFB was used to assess frequency and quantity of substance use at baseline and at each weekly treatment session. The TLFB has demonstrated good psychometric properties, including convergent and discriminant validity, test-retest reliability, and agreement with urine assays and collateral informants (Fals-Stewart et al., 2000). The investigated items in the present study were the per cent days of use, for alcohol and for any psychoactive substance.

PTSD Checklist-Military Version (PCL-M)

The PCL-M is a 17-item self-report questionnaire in which participants indicate the extent to which they have been bothered by each of 17 DSM-IV PTSD symptoms on a scale from 1 (not at all) to 5 (extremely; Bliese et al., 2008; Weathers et al., 1993; Wilkins et al., 2011). The PCL-M has demonstrated good internal consistency, test-retest reliability, and convergent validity (Wilkins et al., 2011), as well as good internal consistency in the present sample ($\alpha = 0.86$).

Beck Depression Inventory - 2nd Edition (BDI-II)

The BDI-II is a 21-item self-report measure designed to assess the cognitive, affective, behavioural, motivational and somatic symptoms of depression (Beck et al., 1996). The BDI-II has demonstrated excellent test-retest reliability over a 1-week interval, internal consistency, and convergent and discriminant validity (Beck et al., 1996), as well as excellent internal consistency in the present sample ($\alpha = 0.92$).

Data analysis

Our primary research objective was to assess the frequency of reliable increases in symptoms (i.e. symptom exacerbation) during exposure-based therapy, compared with non-exposure therapy. We therefore used reliable change analyses, rather than group-mean analyses, to address our primary research question. The statistical strategy used to examine reliable change is a well-established technique that has been used by several other researchers examining symptom exacerbation among patients receiving exposure-based therapy for PTSD (e.g. Foa et al., 2002; Jayawickreme et al., 2014; Larsen et al., 2016).

Cut-offs for reliable exacerbation

Reliable exacerbation was defined as a between-session worsening in symptoms that exceeded the standard error of the difference (SE_D) between two measurement administrations, or the fluctuation expected to occur due to measurement error (Foa et al., 2002). Calculating the SE_D requires psychometric data, including test-retest reliability, and the standard deviation (SD) at the initial and final test. Jacobsen and Truax's (1991) formula assumes the SD will not change between the initial and final test, so estimates the final SD with the intial SD value (Maassen, 2004). When the psychometric study reported only the initial SD (i.e. for the PCL-M), we followed the formula outlined by Jacobsen and Truax (1991) ($SE_D = \sqrt{\{2[(SD^2)(1 - r)]\}}$). However, following recommendations of Maassen (2004), when the initial and final SD were both available (i.e. for the BDI and TLFB), we

pooled these to provide a more precise estimate of the SE_D ($SE_D = \sqrt{[(SD_1^2 + SD_2^2)(1 - r)]}$). See Table 2 for SE_D calcualtions for each measure. The unit of each SE_D estimate reflects the unit used by the scale, which is total points for sum scores on the PCL and BDI-II, and per cent days for the TLFB outcomes.

Symptom exacerbation analyses

Because analyses evaluated the frequency of between-session symptom exacerbations, participants who completed at least two therapy sessions were included in the final dataset (COPE, $n = 49$; RP, $n = 22$). Minimal missing data (<1% missing questionnaire items) on individual PCL and BDI-II items were imputed carrying the last observation forward. Although individual questionnaire items were imputed in a few cases to calculate questionnaire sum scores, we did not impute data for missing assessments (i.e. drop-outs). At each assessment timepoint, we evaluated only participants with available data for that timepoint.

We first examined between-group differences (COPE *versus* RP) in symptom exacerbation at each session during treatment. This approach, with pair-wise rather than list-wise deletion, allowed us to examine all available data at each treatment session. We used chi-squared analyses to determine whether the likelihood of reliable exacerbation differed between groups. When expected values were too low for chi-squared tests, we used Fisher's exact test of independence (Larntz, 1978).

We then evaluated treatment completers to determine whether there were between-group differences in the frequency of symptom exacerbations. Finally, we conducted exploratory analyses within each treatment group to evaluate whether experiencing at least one exacerbation during treatment was associated with higher symptom severity and/or greater likelihood of meeting diagnostic/cut-off criteria at the end of treatment (session 12). Specifically, we evaluated PTSD diagnosis with the CAPS, and at-risk alcohol use with the National Institute on Alcohol Abuse and Alcoholism criteria (NIAAA, 2016).

Results

Preliminary analyses

Among the participants who dropped out prior to completing at least two sessions of therapy ($N = 10$), drop-out was reported for the following reasons: unable to contact/unknown ($n = 2$), therapy/study not a good fit ($n = 2$), relocated and declined to continue the study ($n = 1$), transportation issues ($n = 3$), unusual [personal] event ($n = 1$), and assigned to RP but requested to receive trauma-focused exposure therapy ($n = 1$).

Of those who did not complete treatment ($N = 39$), drop-out was reported for the following reasons: unable to contact/unknown ($n = 17$), therapy/study not a good fit ($n = 4$), relocated and declined to continue ($n = 4$), transportation issues ($n = 6$), required a higher level of care ($n = 1$), unusual [personal] event ($n = 1$), needed psychiatric consultation ($n = 1$), assigned to RP but requested to receive trauma-focused exposure therapy ($n = 2$), and did not want to talk about the trauma anymore ($n = 3$).[5]

Among participants who attended at least one treatment session ($N = 74$), there were no between-group differences in drop out prior to completing the 12-session treatment protocol ($\chi^2(1) < .001$, $p > .99$; 55% completed COPE; 57% completed RP). In the final sample for exacerbation analyses ($N = 71$ participants who completed at least two therapy sessions), there were no between-group differences on any of the baseline measures (BDI-II, $t(69) = .10$, $p = .92$; PCL, $t(69) = -0.08$, $p = .93$; CAPS, $t(69) = -1.39$, $p = .17$; TLFB-Any, $t(69) = -1.26$, $p = .21$; TLFB-Alochol $t(69) = -1.33$, $p = .19$). Expert-level independent assessors rated treatment adherence as good to very good, although there was some slight variance in the implementation of the treatment protocol due to the complex subject population; most, but not all, COPE patients received the standard eight sessions of imaginal exposure (mode = 8, mean = 7.21, $SD = 1.60$).

Session-by-session exacerbation analysis

Chi-squared (or Fisher's exact) tests were performed to evaluate differences between COPE and RP in the frequency of symptom exacerbation on each outcome between each treatment session. Among these 44 analyses, only one significant difference emerged (see Table 3). From session 10 to 11, participants were more likely to experience reliable exacerbation of PTSD symptoms if they were in RP rather than COPE (Fisher's exact test, $p = .006$, 31% in RP *versus* 0% in COPE). Given the number of analyses conducted, this single statistically significant result should be interpreted with caution.[6]

Completers exacerbation analysis

We then evaluated treatment completers (i.e. participants who completed all 12 sessions). We totalled the number of exacerbations on each outcome across all 12 sessions. There were no between group differences in the average number of exacerbations for depression symptoms ($t(39) = -1.08$, $p = .29$), the per cent of days using any psychoactive substance ($t(39) = -1.16$, $p = .25$), or the per cent of days using alcohol ($t(39) = -1.06$, $p = .29$). However, there was a trend for participants receiving COPE to experience slightly fewer exacerbations of PTSD symptoms (COPE; mean = 1.04, $SD = 1.04$), compared with participants receiving RP (RP; mean = 1.77, $SD = 1.17$; $t(39) = -2.03$, $p = .05$, $d = .67$).

We then evaluated whether participants who experienced *any* exacerbation in symptoms during therapy had worse outcomes for the primary diagnoses (PTSD and SUD) at the end of treatment. We began by evaluating PTSD outcomes in both groups. Among participants receiving COPE, 61% ($n = 17$) of treatment completers experienced at least one exacerbation of PTSD symptoms, and 18% ($n = 5$) met criteria for PTSD at the end of treatment. Experiencing an exacerbation in PTSD at any point during treatment was not associated with a greater likelihood of PTSD diagnosis at the end of treatment (Fisher's exact test, $p = .12$), although it was associated with higher PTSD symptom severity at the end of treatment (session 12 PCL total, $t(26) = -2.18$, $p = .04$, $d = .88$; mean = 29.91 *vs* 43.76). However, participants who experienced one or more PTSD exacerbations during

[5]Additionally, one participant had missing assessment data for session 12 (due to completing sessions 11 and 12 on the same day), but did not drop out of treatment.

[6]We chose not to use a correction for inflated type I error across multiple tests because we wished to maximize the sensitivity of our analyses, and ensure the likelihood of detecting any between-group differences in symptom exacerbation, if present.

COPE still showed statistically significant improvement on PTSD symptoms over the course of treatment (session 1 to 12; $t(16) = 2.49$, $p = .02$, $d = .60$, mean = 53.29 to 43.76).

Among participants receiving RP, 92% ($n = 12$) of treatment completers experienced at least one exacerbation of PTSD symptoms, and 62% met criteria for PTSD at the end of treatment. Experiencing an exacerbation in PTSD symptoms at any point during treatment was not associated with a greater likelihood of PTSD diagnosis at the end of treatment (Fisher's exact test, $p > .99$).[7] Participants who experienced one or more PTSD exacerbations during RP showed no significant change in PTSD symptoms over the course of RP (session 1 to 12; $t(11) = 1.85$, $p = .09$, mean = 60.67 to 53.75).

Because alcohol use disorder was the most common substance use disorder in the sample (see Table 1), we evaluated whether any exacerbation in alcohol use during treatment increased risk for meeting the NIAAA criteria for at-risk alcohol use, defined as more than 14 drinks per week for men, and more than seven drinks per week for women (NIAAA, 2016). This was assessed using the average number of alcoholic beverages per week, according to the TLFB assessment at session 12. In the COPE group, 46% ($n = 13$) experienced an exacerbation in alcohol use symptoms at some point during treatment, and 18% ($n = 5$) met NIAAA criteria for at-risk drinking at the end of treatment. COPE participants who experienced an exacerbation in alcohol use symptoms at any point during treatment were not at greater risk for meeting NIAAA criteria at the end of treatment (Fisher's exact test, $p = .15$), although this group did exhibit more frequent alcohol use at session 12 (per cent days alcohol used, $t(17.05) = -2.78$, $p = .01$, $d = 1.08$; mean = 8 *vs* 34%). Participants who experienced one or more alcohol use exacerbations during COPE showed no significant change in frequency (per cent days) of alcohol use over the course of treatment (session 1 to 12; $t(12) = 0.41$, $p = .69$, mean = 38% days used to 34% days used).

In the RP group, 54% ($n = 7$) experienced an exacerbation in alcohol use symptoms at some point during treatment, and 15% ($n = 2$) met NIAAA criteria for at-risk drinking at the end of treatment. RP participants who experienced an exacerbation in alcohol use symptoms at any point during treatment were not at greater risk for meeting NIAAA criteria at the end of treatment (Fisher's exact test $p = .46$), and showed no statistically significant difference in alcohol use at session 12 (per cent days alcohol used, $t(7.38) = -2.16$, $p = .07$; mean = 7 *vs* 43%).[8] Participants who experienced one or more alcohol use exacerbations during RP showed no significant change in frequency (per cent days) of alcohol use over the course of treatment (session 1 to 12; $t(6) = 1.99$, $p = .09$, mean = 66% days used to 43% days used).

Discussion

This study compared rates of symptom exacerbation among Veterans who received an integrated, exposure-based treatment for comorbid PTSD and SUD (COPE), or a non-exposure-based, SUD-only treatment (RP). As opposed to prior research, which has

[7] All but one participant in the RP group experienced an exacerbation in PTSD symptoms at some point during treatment, thus we were unable to use a *t*-test to evaluate to evaluate differences in post-treatment PTSD symptom severity.

[8] This independent samples *t*-test was performed with a Welch-Satterthwaite correction, due to heterogeneous variances (Levene's test, $p < .05$).

primarily focused on exacerbation of PTSD and depression symptoms in participants with PTSD only (e.g. Foa et al., 2002; Jayawickreme et al., 2014; Larsen et al., 2016), the current study evaluated exacerbation of PTSD, depression and substance use symptoms in participants with comborid diagnoses of PTSD and SUD. A session-by-session analysis found no increased risk for exacerbation of PTSD, substance use or depression for participants receiving COPE as opposed to RP. Notably, this included no increased risk after sessions in which *in vivo* and imaginal exposures were initiated in COPE (sessions 3 and 4, respectively). Overall, we found no evidence that integrating exposure therapy for PTSD with cognitive behavioural treatment for SUD increases risk for symptom exacerbation. These findings are consistent with prior research among participants receiving prolonged exposure for PTSD without SUD (Foa et al., 2002; Larsen et al., 2016). In samples with both PTSD and SUD, studies have found that COPE is effective for treating both diagnoses simultaneously (e.g. Brady et al., 2001; Mills et al., 2012; Ruglass et al., 2017). However, these studies did not use individual change analyses to evaluate the proportion of patients who experience reliable symptom exacerbation during the course of therapy.

In the present study, having an exacerbation in PTSD during treatment did not increase the risk for PTSD diagnosis at the end of treatment, although it was associated with higher PTSD symptom severity at the end of treatment. Similarly, an exacerbation in alcohol use during treatment did not increase the risk for meeting NIAAA criteria for at-risk drinking at the end of treatment, but it was associated with more frequent alcohol use at the end of treatment. These are the first data available examining the association of symptom exacerbation and treatment outcomes among patients with comorbid PTSD and SUD receiving exposure-based therapy. In prior studies of PTSD patients without SUD, the findings have been mixed, with some results showing that PTSD exacerbation increases the severity of PTSD symptoms and likelihood of diagnosis at the end of treatment (Larsen et al., 2016) and others suggesting that it does not (Foa et al., 2002). However, in the present study and in these previous studies, the findings document a consistent pattern showing that those who receive trauma-focused exposure therapy, who experience increased PTSD symptoms at some point during treatment, still experience significant improvements in PTSD symptoms by the end of treatment.

Although results from this study are comparable to prior studies in many ways, it is also important to note that the overall frequencies of symptom exacerbations in this study were higher than those in prior research on prolonged exposure therapy protocols. For example, in this study 61% of COPE patients and 92% of RP patients experienced an exacerbation of PTSD symptoms at some point during treatment. On the other hand, other studies have found between 0% (Jayawickreme et al., 2014) and 20% (Larsen et al., 2016; Mills et al., 2016) of patients experience a reliable exacerbation of symptoms during prolonged exposure (PE). The discrepancies in rates of PTSD exacerbation during PE-based protocols (including PE and COPE) could be due to any of several key differences between studies. First, in the present study we collected data at each session, so we were able to evaluate exacerbation on a more sensitive, session-by-session basis. Larsen *et al.* evaluated exacerbation on a bi-weekly basis (starting with session 4), and Mills *et al.* and Jayawickreme *et al.* evaluated exacerbation from pre- to post-treatment. The higher rates in the present study may be related to more frequent, and thus more sensitive, evaluation of symptom exacerbation

during the course of treatment. Another key difference between these studies is the more complex patient population (i.e. comorbid PTSD/SUD *versus* PTSD-only; except for Mills et al., 2016). The chronic substance use and/or acute withdrawal from substances may make comorbid PTSD/SUD patients more likely than PTSD-only patients to experience certain symptom exacerbations, such as hyper-arousal. To best examine whether patients with comorbid PTSD/SUD experience more frequent exacerbations than PTSD-only patients, future studies could compare rates of PTSD exacerbation during prolonged exposure among patients with and without a comorbid SUD.

Overall, the findings from this study have important implications for clinicians as well as implications for the provision of clinical care. Although, relative to other therapeutic techniques, providers endorse greater hesitancy and more barriers to using prolonged exposure therapy for PTSD (Becker et al., 2004; van Minnen et al., 2010), the current results suggest that symptom exacerbation is not unique to exposure-based treatment. In the present study, equal (or in some cases, slightly more) patients who received RP (without exposure therapy for PTSD) experienced symptom exacerbation. Thus, the evidence suggests that symptom exacerbation may be a phenomenon common to multiple therapeutic approaches (also see Larsen et al., 2016). If providers and/or patients misattribute the cause of exacerbation to the type of psychotherapy (i.e. exposure), it is possible that therapy could be unnecessarily delayed or prematurely terminated. Premature termination of exposure therapy may then, in turn, contribute to overall avoidance behaviour and work against long-term treatment goals. Data from the present study and prior research (Foa et al., 2002; Larsen et al., 2016) suggest that exposure therapy does not increase risk for drop-out or result in long-term worsening of symptoms. To reduce the risk of terminating exposure-based therapy prematurely, it may be helpful to educate providers on the typical frequency of exacerbation across therapy modalities, and also to inform patients early in treatment to expect that symptoms could worsen before improving. Prior therapy manuals and treatment dissemination efforts have employed these techniques with success (e.g. Gros, 2014; Gros et al., 2017), although further research is needed to isolate the impact of this specific educational information on providers' and patients' success in completing exposure therapy (or other forms of treatment) despite symptom exacerbation.

Several study limitations should be noted. First, findings should be interpreted with some caution due to the high drop-out in both treatment groups (43–45%). However, these are the first data available examining the association of symptom exacerbation and treatment outcomes among patients with comorbid PTSD and SUD receiving exposure-based therapy. Furthermore, according to the available data, relatively few participants dropped out of treatment due to explicit concerns about exposure therapy ($n = 3$ dropped out due to not wishing to discuss the trauma further). Interestingly, some patients were dropped from the study ($n = 2$) due to requests to switch to trauma-focused exposure therapy. However, self-reported reasons for drop-out may be influenced by a desire to please therapists and researchers. To better address the question of whether drop-out is associated with the use of exposure-based therapy, we compared drop-out rates in exposure-based therapy (COPE) with drop-out rates in the non-exposure therapy control group (RP). We found that drop-out rates in COPE (45%) were not statistically different from drop-out rates in RP (43%). Thus, data do not support the hypothesis that drop-out can be attributed to trauma-focused

exposure therapy, specifically. Furthermore, the overall high drop-out rates in the present study are consistent with drop-out rates in the broader literature on psychotherapy among patients with comorbid PTSD and SUD (30–50% in most studies; Roberts et al., 2015).

Additionally, the sample consisted of military Veterans, who were mostly male with a history of combat trauma. More research is needed to determine whether the findings extend to other populations. Furthermore, the sample size in this study was somewhat limited, which could have limited statistical power. It is also important to note that this study examined symptom exacerbation in a population during an integrated protocol for treating both PTSD and SUD (COPE). The focus in early treatment sessions on cognitive behavioural skills for managing cravings and thoughts about using may have mitigated the potential for increased substance use after beginning exposure-based trauma work. It therefore remains unclear whether patients with comorbid PTSD and SUD would exhibit SUD exacerbation during standard prolonged exposure therapy for PTSD (in the absence of additional skills training for managing SUD symptoms). Finally, although we isolated explicit trauma-focused exposure therapy procedures in our comparison of COPE with RP, patients receiving RP may have incidentally experienced an increase in exposure to trauma-related cues as a function of reducing substance use. This would be consistent with theoretical models suggesting that substances may be used for self-medication (Jacobsen et al., 2001) and avoidance of unpleasant emotional experiences (Stewart et al., 1998). This potential increase in exposure to trauma-related memories in RP could have contributed to similarities in symptom exacerbation rates between our treatment groups.

Overall, findings from this study add to a growing literature demonstrating that exposure-based treatments for PTSD do not increase the risk for symptom exacerbation. Among studies that have investigated symptom exacerbation during the use of prolonged exposure for PTSD, the present study is the first to examine exacerbation of SUD symptoms, and report on exacerbation in a sample of patients with PTSD and comorbid SUD throughout treatment. Findings suggest that trauma-focused exposure therapy can be used safely and effectively in patients with comorbidities such as alcohol and drug use disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Demographic characteristics of the sample ($N = 71$)

	Mean (*SD*)	Range
Age	40.94 (10.72)	22–62
Years of education	14.08 (2.04)	8–18
	Category	**Percentage (*n*)**
Gender		
	Male	88.7% (63)
	Female	11.3% (8)
Race		
	White	62.0% (44)
	Black	35.2% (25)
	Multi-racial or other	2.8% (2)
Ethnicity		
	Hispanic	4.2% (3)
	Non-Hispanic	95.8% (68)
Marital status		
	Single, never married	28.2% (20)
	Married	26.8% (19)
	Separated	7.0% (5)
	Widowed	1.4% (1)
	Divorced/annulled	36.6% (26)
Military branch		
	Army	56.3% (40)
	Navy	11.3% (8)
	Marines	16.9% (12)
	Air Force	9.9% (7)
	National Guard	5.6% (4)
Deployment		
	OIF/OEF/OND	60.6% (43)
	Other	36.6% (26)
	Missing	2.8% (2)
Current substance use disorder		
	Alcohol	90.1% (64)
	Cocaine	19.7% (14)
	Opioid	11.3% (8)
	Marijuana	8.5% (6)
	Sedative, hypnotic, or anxiolytic	1.4% (1)
	Poly-substance	1.4% (1)

Diagnostic results combine abuse and dependence diagnoses from DSM-IV-TR criteria into one category to be consistent with substance use disorders in the DSM-5.

Table 2.

Calculations of cut-offs for reliable exacerbation of symptoms

Measure	Source	SE_D formula*	Calculation	1-week SE_D
PCL	Adkins et al. (2008)	$\sqrt{(2((SD^2)(1-r))}$	$\sqrt{(2((10.8^2)(1-.87))}$	5.51 points
BDI	Beck et al. (1996)	$\sqrt{((SD1^2 + SD_2^2)(1-r))}$	$\sqrt{((10.46^2 + 10.38^2)(1-.93)}$	3.90 points
TLFB-Alcohol	Present study**	$\sqrt{((SD1^2 + SD_2^2)(1-r))}$	$\sqrt{((35.74^2 + 33.96^2)(1-.86))}$	18.45% days
TLFB-Any	Present study**	$\sqrt{((SD1^2 + SD_2^2)(1-r))}$	$\sqrt{((37.66^2 + 36.08^2)(1-.87))}$	18.80% days

*The formulas used to calculate SE_D differ based on the available psychometric information for the scale. When the *SD*s for both time points of the test-retest reliability were available, these were pooled to provide a more accurate estimate of the SE_D (Maassen, 2004). When the *SD* was only available for the first time point, we used the SE_D formula outlined by Jacobsen and Truax (1991), which assumes that the *SD* does not change between the initial and final test.

**Although studies support the validity of using a 7-day window forthe TLFB (Hoeppner et al., 2010; Toll et al., 2006), psychometric data for the 1-week test-retest reliability of the 7-day TLFB (as used in the present study) were not available. We therefore followed Maassen's (2004) recommendations for using one's own dataset to estimate the SE_D. We used assessments from sessions 1 and 2 to calculate test-retest reliability (and *SD*s) for the TLFB because there was no significant change between these two sessions on per cent days (a) using any psychoactive substance (TLFB-Any; $t(70) = .720$, $p = .474$) or (b) using alcohol (TLFB-Alcohol; $t(70) = 1.033$, $p = .305$). Test-retest reliability was high for each outcome (TLFB-Any, $r(69) = .87$, $p < .001$; TLFB-Alcohol, $r(69) = .86$, $p < .001$).

Table 3.

Per cent of participants with reliable exacerbation, and relative risk for exacerbation, in COPE and RP

			BDI		PCL		TLFB Alcohol		TLFB Any substance	
	Group	Sample size	Per cent with exacerbation	Relative risk	Per cent with exacerbation	Relative risk	Per cent with exacerbation	Relative risk	Per cent with exacerbation	Relative risk
Session 2	COPE	49	18.37	1.35	12.24	0.90	6.12	1.35	8.16	1.80
	RP	22	13.64		13.64		4.55		4.55	
Session 3	COPE	47	8.51	0.30†	4.26	0.30	8.51	0.60	8.51	0.60
	RP	21	28.57		14.29		14.29		14.29	
Session 4	COPE	45	20.00	1.90	11.11	1.29	15.56	0.74	13.33	0.63
	RP	19	10.53		26.32		21.05		21.05	
Session 5	COPE	44	15.91	0.85	13.64	1.09	6.82	1.09	6.82	0.55
	RP	16	18.75		12.50		6.25		12.50	
Session 6	COPE	41	19.51	0.49	9.76	0.37	2.44	0.37	2.44	0.37
	RP	15	40.00		26.67		6.67		6.67	
Session 7	COPE	38	13.16	0.39	18.42	1.38	2.63	0.39	2.63	0.39
	RP	15	33.33		13.33		6.67		6.67	
Session 8	COPE	36	22.22	3.33	16.67	2.50	8.33	1.25	8.33	1.25
	RP	15	6.67		6.67		6.67		6.67	
Session 9	COPE	35	11.43	0.53	8.57	0.60	11.43	0.80	11.43	0.80
	RP	14	21.43		14.29		14.29		14.29	
Session 10	COPE	31	16.13	0.75	9.68	0.68	9.68	0.27†	9.68	0.27†
	RP	14	21.43		14.29		35.71		35.71	
Session 11	COPE	29	6.90	0.30	0.00	0.00**	3.45	0.45	3.45	0.45
	RP	13	23.08		30.77		7.69		7.69	
Session 12	COPE	28	17.86	2.32	10.71	0.70	10.71	NA	14.29	NA
	RP	13	7.69		15.38		0.00		0.00	

PCL-M, PTSD Checklist, Military Version; BDI-II, Beck Depression Inventory, Second Edition; TLFB, Time Line Follow-Back; COPE, Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure; RP Relapse Prevention; Per cent with exacerbation = percent of participants in each treatment arm who experienced a reliable level of symptom exacerbation.

† $p < .10$

* $p < .05$

** $p < .01$.