Integrated exposure based therapy for co-occurring post traumatic stress disorder and substance dependence: A randomized controlled trial

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ABSTRACT

Context: There is concern that exposure therapy, an evidence-based cognitive-behavioral treatment for posttraumatic stress disorder (PTSD), may be inappropriate for patients with co-occurring substance dependence (SD).

Objective: To determine whether an integrated treatment for PTSD and SD, Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure (COPE), can achieve greater reductions in PTSD and SD symptom severity compared to treatment as usual (TAU) for SD.

Design, Setting, and Patients: A randomized controlled trial of 103 participants who met DSM-IV-TR criteria for both PTSD and SD. Participants were recruited from 2007-2009 in Sydney, Australia, and randomized to one of two conditions. The treatment group received COPE plus TAU (COPE+TAU; *n*=55) and the control group received TAU alone (*n*=48). Outcomes were assessed at 9-months post-baseline, and interim measures collected at 6-weeks and 3-months post-baseline.

Interventions: COPE consists of 13 individual 90-minute sessions (i.e., 19.5 hours) with a clinical psychologist. It represents an integration of existing evidence based manualized cognitive behavioral treatments for PTSD and SD, comprising psychoeducation, motivational enhancement, and cognitive behavioral therapy for PTSD and SD, including imaginal and *in vivo* exposure.

Main outcome measures: Change in PTSD symptom severity as measured by the Clinician Administered PTSD Scale (CAPS; scale range 0-240), and change in severity of SD as measured by the number of dependence criteria met according to the Composite International Diagnostic Interview version 3.0 (CIDI; range 0-7), from baseline to 9-month follow-up. A change of 15 points on the CAPS scale and 1 dependence criteria on the CIDI were considered to be clinically significant.

Results: From baseline to 9-month follow-up, significant reductions in PTSD symptom severity were found for both the treatment (mean difference -38.24, 95%CI: -47.93 - -28.54) and control group (mean difference -22.14, 95%CI: -30.33 - -13.95), however, the treatment group demonstrated a

significantly greater reduction in PTSD symptom severity compared to the control group (mean difference -16.09, 95%CI: -29.00 to -3.19). No significant between group difference was found in relation to improvement in severity of SD (0.43 v 0.52; IRR 0.85, 95%CI: 0.60 - 1.21), nor were there any significant between group differences in relation to changes in substance use, depression or anxiety.

Conclusions: Among patients with PTSD and SD, the combined use of COPE+TAU, compared with TAU alone, resulted in improvement in PTSD symptom severity without an increase in severity of SD.

Trial registration: Registration number ISRCTN12908171; URL: http://www.controlled-trials.com/ISRCTN12908171/mills

INTRODUCTION

Prolonged exposure (PE) therapy, a cognitive-behavioral therapy (CBT) involving exposure to memories and reminders of past trauma, has long been regarded as a "gold standard" treatment for post traumatic stress disorder (PTSD). While there are other evidence based treatments for PTSD such as eye movement desensitization and reprocessing (EMDR) therapy, there is more empirical evidence for the efficacy of PE than any other treatment [1]. Indeed, the International Consensus group on Depression and Anxiety recommend PE as the most appropriate form of psychotherapy for PTSD [2], and it was the only treatment for PTSD endorsed in a US Institute of Medicine study as evidence based [3]. The efficacy of PE in reducing PTSD symptom severity has been demonstrated among persons from a number of populations, who have been exposed to a wide variety of trauma types [4]. There is, however, a notable absence of research examining the efficacy of PE among individuals with co-occurring PTSD and substance dependence (SD).

Epidemiologic and clinical research has demonstrated that trauma exposure among individuals with SD is almost universal, and up to 62% suffer from comorbid PTSD [5,6]. Similarly, up to 65% of patients with PTSD have been found to have a comorbid substance use disorder [7,8]. While PTSD is pervasive across all drug classes, there is some evidence to suggest that individuals with opiate, sedative and stimulant use disorders are at greatest risk [5]. Thus, there is a clear need for PTSD treatment in this population. Until recently, however, many experts and clinicians considered the use of PE among individuals with SD to be inappropriate unless a lengthy period of abstinence had been achieved [9,10]. Based on early case reports it was widely believed that the intense emotions elicited during PE could place individuals at increased risk for relapse [9]. There is, however, an absence of evidence to support or refute this recommendation, as most PTSD treatment trials have excluded individuals with SD [11]. Although a small number of pilot studies have examined the efficacy of integrated treatment programs (which address both PTSD and SD at the same time) which incorporate PE [12-14], these treatments have not yet been examined in a large randomized controlled trial. The aim of the

present study was to address this gap in the literature by conducting the first randomized controlled trial of an integrated treatment for PTSD and SD that incorporates PE.

METHODS

Design

Participants were randomly assigned to one of two conditions. The treatment condition consisted of an integrated treatment for PTSD and SD, called Concurrent Treatment of PTSD and Substance Use Disorders with Prolonged Exposure (COPE), plus treatment as usual (TAU) for substance use. The control condition consisted of TAU for SD only. Block randomization was conducted in groups of 10, stratified according to sex, by a person independent of the research. It was hypothesized that participants randomized to the treatment group would demonstrate greater reductions in PTSD and SD symptom severity compared to those randomized to the control group. Participants were interviewed upon entry to the study and primary outcome measures assessed at 9-months post-baseline. Two interim measures of outcome were also obtained, at 6-weeks and 3-months post-baseline, in order to monitor participants status and increase the likelihood of retention at 9-months. Ethical approval was granted by the Human Ethics Review Committees of the University of New South Wales and the Northern Sydney Central Coast Area Health Service.

Recruitment

Participants were recruited between April 2007-June 2009 from substance use treatment services, media advertisements and practitioner referrals within the greater Sydney region, Australia. Inclusion criteria were past-month DSM-IV-TR diagnoses of PTSD and SD, age of 18 years or over, and fluency in English. Individuals were excluded from participating if they were currently suicidal (expressed suicidal ideation accompanied by a plan and intent), had a recent history of self-harm (past 6 months), had current active symptoms of psychosis, or suffered cognitive impairment severe enough to impede treatment.

Structured interviews

All participants were administered a structured, face-to-face interview at baseline. The primary outcomes, severity of PTSD and severity of SD (as indicated by the number of dependence criteria met), were assessed using the Clinician-Administered PTSD Scale (CAPS; range 0-240 with higher scores indicating more severe PTSD) [15] and the Composite International Diagnostic Interview version 3.0 (CIDI; range 0-7 dependence criteria with higher scores indicating more severe SD) [16], respectively.

The interview also assessed demographic characteristics; lifetime and current use of heroin, other opiates, amphetamines, cocaine, hallucinogens, benzodiazepines, alcohol, cannabis and inhalants using the Opiate Treatment Index [17]; DSM-IV-TR diagnoses of current SD for main drug of concern (using the CIDI [16]) ; trauma history using the CIDI version 2.1 [18]; DSM-IV-TR diagnoses of PTSD in the past month using the CAPS [15]; depression using the Beck Depression Inventory-II (BDI-II; range 0-63 with higher scores indicating more severe depression) [19]; state and trait anxiety using the State-Trait Anxiety Inventory (STAI; range 20-80 with higher scores indicating more severe anxiety) [20]; the possible presence of borderline personality disorder (BPD) using the International Personality Disorder Examination Questionnaire [21]; and history of attempted suicide. To assess SD treatment history participants were asked whether they had commenced any of the follow-up forms of treatment for their substance use: substitution pharmacotherapies (including methadone, buprenorphine, Suboxone, and naltrexone maintenance); outpatient or inpatient detoxification; residential rehabilitation; and outpatient counseling. To assess PTSD treatment history, participants were asked whether they had ever commenced any of the follow-up forms of treatment for their PTSD: inpatient hospitalization; outpatient counseling or psychotherapy, and medication (such as antidepressants).

The sections of the assessment pertaining to current drug use, SD, PTSD, depression, and anxiety were re-administered at each follow-up interview. Participants were also asked whether they had

been exposed to any further traumatic events, had experienced any suicidal ideation or attempted suicide, or undergone any treatment over the follow-up period. Participants were paid A$30 for completing each interview. Interviews were administered by two trained research officers who were blind to group allocation.

Interventions

COPE

COPE is a modified version of Concurrent Treatment of PTSD and Cocaine Dependence (CTPCD) [22]. The version of COPE used in the present study represents an integration of existing evidence based manualized CBT interventions for PTSD and SD [23-25]. The intervention consists of 13, individual, 90-minute sessions (i.e., 19.5 hours) delivered by a clinical psychologist and combines CBT for PTSD and SD. Although designed to be delivered weekly, flexibility is permitted. Treatment components include: motivational enhancement and CBT for substance use (Sessions 1-4 and throughout); psychoeducation relating to both disorders and their interaction (Sessions 1-4); *in vivo* exposure (Sessions 5-12); imaginal exposure (Sessions 6-12); and cognitive therapy for PTSD (Sessions 8-12). The final session (Session 13) is dedicated to providing a review of the treatment, devising an after care plan, and termination.

COPE was delivered by two clinical psychologists employed on the project who received fortnightly supervision for the duration of the study. All treatment sessions were recorded. Ten percent of participants were randomly selected to have their sessions rated for treatment fidelity (i.e., compliance with the treatment manual) by an independent assessor. Fidelity was rated on 53 (16.4%) out of a total of 323 sessions conducted as part of the study. Average fidelity ratings were high with a mean score of 4.13 (SD 0.95) out of a possible score of 5 indicating strong adherence to the treatment manual.

TAU

Both the treatment and control groups were able to engage in TAU for SD. As such, participants could access any type of substance use treatment currently available in the community, including outpatient counseling, inpatient or outpatient detoxification, residential rehabilitation and pharmacotherapies (e.g., methadone, buprenorphine, Suboxone, naltrexone).

Sample size calculations

Power analysis on the primary outcome variables (i.e., change in CAPS score and number of dependence criteria met) was conducted using RMASS2. The target sample size (*n*=150) was conservatively designed to have 90% power to detect a time-averaged difference between groups of 5 points on the CAPS scale, and 0.5 points in severity of SD, at α=.05. The final sample size was 103 due to a lower than expected recruitment rate. The final sample size had 80% power to detect a difference between groups of 10 points on the CAPS scale at 9-month follow-up, but only 60% power to detect a 1 point difference in the number of dependence criteria met at 9-month follow-up, at α=.05. A difference of 15 points on the CAPS scale is considered to be clinically significant [26]. With regard to severity of SD, we considered a one unit change in the number of DSM-IV-TR criteria met to be clinically significant as research has demonstrated a one unit change to be associated with level of impairment, mental health, and risk of attempted suicide [27,28].

Missing data

Missing data analysis revealed 18.7% missing data across the follow-up period. According to the results of Little's missing completely at random (MCAR) test the data could be considered to be MCAR (χ^2=14.28, df 36, *p*=1.000). In order to satisfy the intention-to-treat (ITT) requirement that analyses be undertaken on all participants, missing data were imputed using multiple imputation (MI). MI allows for the uncertainty about the missing data by creating several different plausible imputed data sets and appropriately combining results obtained from each of them [29,30]. MI is recommended over single imputation techniques as the missing values for each participant are predicted from his or her own observed values, and the estimates produced take into account the

uncertainty of the imputation process [29]. As the pattern of missing data was non-monotone the Markov Chain Monte Carlo (MCMC) method of MI was utilized [30]. As suggested by Schafer and Graham [29], five imputations were used. Imputations were constrained to plausible values for the scales used.

Statistical analyses

Two-sided analyses were conducted with PASW Statistics 20 using a predetermined alpha level of $p<.05$. Baseline differences between groups were examined using *t*-tests for normally distributed measures, Mann-Whitney *U*-tests for non-normally distributed data, and chi-squared for categorical variables. Chi-squared and linear regression analyses were undertaken to ascertain whether there were any between group differences in exposure to TAU for SD over the follow-up period.

ITT analyses were conducted for all outcomes. Primary unadjusted analyses were undertaken comparing the treatment and control groups. Secondary analyses were undertaken adjusting for covariates found to be unbalanced between groups (i.e., history of childhood trauma, history of childhood sexual abuse, percentage of time spent in TAU during the study).

Outcomes were examined using a series of binomial logistic, linear and Poisson distributed generalized estimating equations (GEE) for categorical, continuous and count data, respectively. Analyses were undertaken using an exchangeable correlation matrix. Linear and Poisson models utilized data from all time points (baseline and each follow-up). These models tested whether the scores obtained at each time point differed significantly between the two groups, whether the change in scores from baseline to 9-month differed for each group, and whether the degree of change between baseline and 9-month differed between the two groups. Binomial models did not include baseline data for the dependent variables as these values were constant and hence the models could not converge. Thus the binomial models examined whether the scores obtained at each time point differed significantly between the two groups. Results are reported as the unstandardized mean difference with 95% confidence intervals (95%CI) for linear models, odds

ratios (OR) with 95%CI for binomial logistic models, and incident rate ratios (IRR) with 95%CI for Poisson models.

RESULTS

Sample recruitment and retention

Over one-third (*n*=103, 37.1%) of the 334 individuals assessed were eligible to participate (Figure 1). The primary reasons for exclusion were not meeting criteria for a diagnosis of PTSD (*n*=111, 52.9%) or no substance use in the preceding month (*n*=82, 39.0%); 14 people (6.7%) were currently suicidal or self-harming, 2 people (1.0%) exhibited cognitive impairment severe enough to impede treatment, and 1 person (0.5%) was under 18 years of age. The majority of individuals who were eligible agreed to participate (*n*=103, 83.1%). Written informed consent was obtained from all participants prior to participation.

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A total of 74, 82 and 77 participants were re-interviewed at 6-weeks, 3-months and 9-months post-baseline respectively, representing 71.8%, 79.6% and 74.8% of participants enrolled in the study at baseline (Figure 1). Ninety-three participants (90.3%) completed at least one of the three follow-up interviews; 57 (55.3%) completed all three follow-up interviews. Detail regarding the pattern of follow-up data collected is provided in eFigure 1.

Study retention was not related to randomization. There were no significant differences between the treatment and control groups in the likelihood of completing interviews at 6-weeks (*n*=37, 67.3% v *n*=37, 77.1%; OR 0.61, 95%CI: 0.25-1.47), 3-months (*n*=41, 74.5% v *n*=41, 85.4%; OR 0.50, 95%CI: .18-1.37) or 9-months (*n*=39, 70.9% v *n*=38, 79.2%; OR .64, 95%CI: .26-1.59); or the number of follow-up interviews completed (Median 3.0 v 3.0; U=1142.5, *p*=.193).

Patterns of study retention were largely unrelated to current substance use, severity of SD, the types of trauma exposed to, age of first trauma exposure, or the severity of PTSD (eTable 1); however, participants who completed the 6-week follow-up were more likely to have experienced sexual molestation (*n*=54, 73.0% v *n*=14 48.3%; OR 2.89, 95%CI: 1.19-7.05) compared to those who did not complete the 6-week follow-up. Participants who completed the 3-month follow-up were more likely to have experienced rape (*n*=60, 73.2% v *n*=10, 47.6%; OR 3.00, 95%CI: 1.12-8.04) and less likely to have used inhalants in the month prior to baseline (*n*=3, 3.7% v *n*=4, 19.0%; OR 0.16, 95%CI: 0.03-0.79) compared to those who did not complete the 3-month follow-up. Participants who completed the 9-month follow-up were also more likely to have experienced rape (*n*=57, 74.0% v *n*=13, 50.0%; OR 2.85, 95%CI: 1.13-7.17) compared to those who did not complete the 9-month follow-up. None of the substance use, trauma or PTSD variables examined were related to the number of follow-up interviews completed (eTable 1).

Baseline sample characteristics

There were no significant differences between the treatment and control groups in demographic characteristics, lifetime or current substance use, severity of SD, or history of substance use treatment (Tables 1 & 3). Poly-substance use was the norm, with participants using a median of 4.0 different drug classes in the preceding month, most commonly benzodiazepines, cannabis, and alcohol, followed by heroin, amphetamines, other opiates, cocaine, hallucinogens, and inhalants. The most commonly reported main drug of concern was heroin (*n*=22, 21.4%), followed by cannabis (*n*=20, 19.4%), amphetamines (*n*=18, 17.5%), benzodiazepines (*n*=16, 15.5%), alcohol (*n*=12, 11.7%), cocaine (*n*=7, 6.8%), other opiates (*n*=5, 4.9%), and hallucinogens (*n*=1, 1.0%). The distribution of main drug of concern did not differ according to group ($\chi^{2=}$8.03, df 8, *p*=.431).

The treatment and control groups were similar in terms of trauma history (Table 1), however, participants randomized to the control group were more likely to have experienced childhood sexual abuse compared to participants randomized to the treatment group. All participants had

experienced multiple traumas and met criteria for current PTSD. There were no significant differences between groups in PTSD, depression or anxiety symptomology (Table 3).

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Treatment Exposure

COPE treatment

Forty-five participants (81.8%) randomized to the treatment group attended at least one session. Of those randomized to receive COPE, the median number of sessions attended was 5 (range 0-13). Thirty participants (54.5%) attended sessions in which imaginal or *in vivo* exposure were covered (*n*=22, 40.0% imaginal, *n*=28, 50.9% *in vivo*). Participants attended a median of 0 sessions which covered imaginal exposure (range 0-7) and 1 covering *in vivo* exposure (median 0-8). Ten participants (18.2%) attended all 13 sessions.

Although the 13 session intervention was designed to be delivered weekly, appointment scheduling and treatment retention was made difficult by the chaotic lifestyle that is associated with SD and comorbidity. There was, therefore, considerable variability in the time taken to deliver the COPE treatment, ranging from 0-271 days (median 71 days). Twenty-two (40.0%) participants randomized to COPE were still receiving COPE treatment after 3 months.

TAU for SD

The majority of both the treatment and control groups were enrolled in TAU for SD at study entry (*n*=44, 80.0% v *n*=42, 87.5%; OR 0.57, 95%CI: 0.19-1.68). The type of TAU enrolled in at baseline did not differ significantly between the two groups (χ^2=7.00, df 4, *p*=.136). The most common treatment enrolled in for the treatment group was detoxification (*n*=28, 50.0%) followed by maintenance

277 therapies (*n*=12, 21.8%), and residential rehabilitation (*n*=4, 7.3%). The most common treatment
278 enrolled in for the control group was detoxification (*n*=29, 60.4%) followed by maintenance
279 therapies (*n*=7, 14.6%), residential rehabilitation (*n*=3, 6.5%), and outpatient counseling (*n*=3, 6.3%).

280 Percentage of time spent in treatment over the follow-up period was analyzed instead of days in
281 treatment to control for differences in time to follow-up. As shown in Table 2, the treatment group
282 spent significantly less time in TAU compared to the control group over the entire 9-month follow-up
283 period, however, there were no differences between groups in the percentage of time spent in
284 treatment between follow-up points.

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288 **Primary treatment outcome analysis**

289 ***PTSD***

290 There was a significant group x time interaction in relation to PTSD symptom severity (χ^2=5.38, df 1,
291 *p*=.022). From baseline to 9-month follow-up, significant reductions in PTSD symptom severity were
292 found for both the treatment (mean difference -38.24, 95%CI: -47.93 - -28.54) and control group
293 (mean difference -22.14, 95%CI: -30.33 - -13.95), however, the treatment group demonstrated a
294 significantly greater reduction in PTSD symptom severity compared to the control group (mean
295 difference -16.09, 95%CI: -29.00 to -3.19; Table 3). At 9-month follow-up, PTSD symptom severity
296 was significantly lower in the treatment group compared to the control group (52.89 v 67.23; mean
297 difference -14.34, 95%CI: -26.94 - -1.75). Although the prevalence of PTSD diagnosis at 9-month
298 follow-up appears to be significantly lower in the treatment group compared to the control group
299 (*n*=31, 56.4% v *n*=38, 79.2%; OR 0.32, 95%CI: 0.13-0.81; Table 4), the group x time interaction in
300 relation to PTSD diagnosis was not significant (χ^2=0.30, df 1, *p*=.583).

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Substance use and dependence

The group x time interactions in relation to rates of substance use (χ^2=0.00, df 1, *p*=.998) and the number of drug classes used (χ^2=0.10, df 1, *p*=.755) were not significant indicating that the prevalence of abstinence and number of drug classes used over the follow-up period did not differ between the treatment and control groups. Although the majority of participants in both the treatment and control groups continued to use substances at 9-month follow-up (*n*=45, 81.8% v *n*=35, 72.9%; Table 4), both the treatment and control group demonstrated significant reductions in the number of drug classes used from baseline to 9-month follow-up (Tables 3). The degree of improvement in number of drug classes used did not differ significantly between groups (0.57 v 0.60; IRR 0.96, 95%CI: 0.69-1.34).

The group x time interactions in relation to rates of SD (χ^2=0.00, df 1, *p*=.997) and severity of SD (χ^2=2.09, df 1, *p*=.0.152) were not significant indicating that the prevalence of SD and degree of change in severity of SD over the follow-up period did not differ between the treatment and control groups. By the 9-month follow-up, rates of SD had dropped to 45.4% (*n*=25) in the treatment group and 56.2% (*n*=27) in the control group, however, the difference between groups was not significant (OR 0.64, 95%CI: 0.28-1.48;Table 4). Both the treatment and control group also demonstrated significant reductions in severity of dependence from baseline to 9-month follow-up (Table 3), however, the degree of change did not differ significantly between groups (0.43 v 0.52; IRR 0.85, 95%CI: 0.60-1.21).

Depression and anxiety

The group x time interactions in relation to severity of depression (χ^2=1.31, df 1, *p*=.263) and anxiety (χ^2=2.69, df 1, *p*=.103) were not significant indicating that severity of depression and anxiety did not differ between the treatment and control groups over the follow-up period. Both the treatment and control group demonstrated significant reductions in severity of depression from baseline to 9-month follow-up (Table 3), however, the degree of change did not differ significantly between groups (-11.64 v -6.90; mean difference -4.73, 95%CI: -11.76 - 2.29). There was also no significant difference between the treatment and control groups in the degree of change in severity of anxiety from baseline to 9-month follow-up (-8.25 v -2.91; mean difference -5.34, 95%CI: -12.47 - 1.80; Table 3).

Secondary treatment outcome analysis

Secondary analyses were undertaken adjusting for covariates found to be unbalanced between groups (i.e., history of childhood trauma, history of childhood sexual abuse, percentage of time spent in TAU during the study). The results of these analyses (presented in eTables 2 & 3) were consistent with those of the unadjusted analyses.

Serious adverse events

Two participants from the treatment group (3.6%) and five participants from the control group (10.4%) attempted suicide during the study (OR 0.32, 95%CI: 0.06-1.76). While it is possible that these attempts were related to participation in the study, all seven individuals reported that this was not the case and elected to remain involved with the study. Additionally, one participant from the treatment group (1.8%) died as a result of a pre-existing medical condition.

COMMENT

Findings from the present study provide support for the efficacy of integrated exposure based therapies for the treatment of PTSD among patients with SD. Consistent with our hypothesis, participants randomized to receive COPE+TAU demonstrated significantly greater reductions in PTSD

symptom severity compared to participants randomized to receive TAU alone (mean difference -16.09). This difference also represents a clinically significant difference [26]. It is important to note that most participants randomized to receive COPE+TAU continued to use substances throughout the study. These findings challenge the widely held view that patients need to be abstinent before any trauma work, let alone PE, is commenced [10]. Whilst we agree that patients need to show some improvement in their substance use and an ability to employ alternative coping strategies before initiating PE, findings from the present study demonstrate that abstinence is not required.

Our second hypothesis, that individuals randomized to receive COPE+TAU would demonstrate significantly greater reductions in severity of SD, was not confirmed. Both groups demonstrated significant reductions in severity of SD, but the difference between groups was not significant. This may be due to a lack of statistical power as the final sample size had only 60% power to detect a 1 point difference in the number of dependence criteria met across the 9-month follow-up. Comparable reductions in severity of depression and anxiety were also observed between groups. Further research with larger samples that are sufficiently powered to detect differences in these domains is needed. It is important to note, however, that studies examining the temporal sequencing of changes in PTSD and SD symptoms have shown that improvements in PTSD symptoms are associated with subsequent improvements in SD, but the reciprocal relationship is not observed [31,32]. These findings highlight the importance of treating PTSD in order to improve SD outcomes for individuals with this comorbidity.

The improvements in PTSD, SD and depression observed in the present study are consistent with the findings of Brady and colleagues' pilot study of an earlier version of the COPE treatment [13]. Brady and colleagues did not utilize a control group, however, similar within group pre- to post-treatment effects were observed in both studies. These similarities are encouraging given that Brady and colleagues examined outcomes for treatment completers only (i.e., patients who completed 10 of 16 sessions), and the baseline severity of PTSD symptoms in their study was considerably lower than

that of participants randomized to receive COPE+TAU in the present study (mean CAPS scores of 45.2 v 91.1). The present findings add to that of Brady and colleagues by demonstrating the efficacy of COPE using a more conservative ITT approach, in a substantially more disabled sample. It should be noted however, that while those randomized to receive COPE+TAU demonstrated significantly greater improvements in PTSD, at the end of the study 56.4% continued to meet diagnostic criteria for PTSD. Further analysis of this data will examine the characteristics of this group and the importance of particular treatment components to inform further development of the intervention.

The overall lack of between-group differences found in the present study is similar to the findings of Triffleman and colleagues' [12] examination of Substance Dependency-Post-Traumatic Stress Disorder Therapy (SDPT), an integrated 40-session therapy for PTSD and SD which includes *in vivo* (but not imaginal) exposure. SDPT was compared with Twelve-Step Facilitation Therapy, an evidence based treatment for SD which does not address trauma, among a sample of 19 methadone-maintained patients. As in the present study, both groups demonstrated significant improvements in PTSD and SD symptoms, however, no between-group differences were found in relation to PTSD or SD outcomes. Like the present study, the lack of differences observed by Triffleman and colleagues [12] may also be due to insufficient power.

Aside from measures of treatment outcome, treatment retention is an important indicator of a treatment's acceptability and utility. Consistent with the findings of Brady and colleagues [13], the present study demonstrated high treatment dropout rates, with participants attending a median of 5 of the 13 sessions offered. While higher retention rates would be optimal, it is important to note that low attendance in addiction treatment has been identified as a pervasive clinical challenge, particularly in cases where there is comorbidity [33,34]. High dropout rates and attrition have been observed across treatment settings, interventions, and substances of abuse . Indeed, treatment retention in the present study is comparable to those of studies of integrated PTSD treatments for SD patients which are not trauma-focused, studies of treatments for SD alone, and studies of

treatments for other mental health disorders [32,35]. For example, in Hien and colleagues' [32] examination of Seeking Safety (a non-trauma focused integrated treatment for SD and PTSD), 82% of participants attended at least one session with a mean of 6 (of a possible total of 12 sessions) completed. Only 12% of the sample completed all 12 sessions. The corresponding figures for the present study were 82% attendance, for a median of 5 sessions, with 18% completing all 13 sessions. Given that the treatment aims to address two disorders characterized by extreme avoidance among individuals with severe and chronic symptomology (in addition to many other current life stressors that make it difficult for them to engage in treatment), it is imperative that future research incorporate and examine methods to improve retention in treatment. Based on observations made in the present study, it appears that the provision of ancillary support services that provide concurrent case management may be useful.

The characteristics of the sample lend support to the generalizability of the findings. Participants had experienced a wide range of traumas, were using a variety of substances, and suffered significant comorbidity including likely BPD; features that are typical of patients with PTSD and SD [5,36] . However, the findings cannot be generalized to those who are under the age of 18, not fluent in English, currently suicidal, self-harming, psychotic, or those with severe cognitive impairment, as these individuals were excluded from study participation.

A number of other limitations should also be noted. Firstly, the study relied on measures of self-report alone. There is much controversy regarding the reliability and validity of self-reported drug use, however, there is an extensive literature documenting its reliability and validity [37]. Overall, agreement between self-report and biomarkers is high; indeed, where there are discrepancies this tends to be where respondents report drug use that has failed to be detected by the biological measures [37]. Sherman and Bigelow [38] suggest that drug use reported by those seeking treatment is likely to be highly valid, given that they are seeking treatment for that drug use and have no need to conceal their use. Two studies examining self-reported substance use among PTSD patients found

participants' responses to be highly valid, with less than 10% of cases not reporting substance use detected by urine screens [39,40].

Secondly, although the effects observed remained after controlling for between group differences in exposure to TAU, and the prevalence of childhood sexual abuse and childhood trauma, the outcomes observed may have been influenced by confounding factors not measured by the present study. It could also be argued that the differences observed may be attributed to more general therapist effects (i.e., the treatment group received up to 13 sessions with a therapist that the control group did not). Thus, although the present study provides evidence in support of COPE, it does not speak to its efficacy in comparison to other treatments. Further research examining the efficacy of COPE relative to other active treatments of equivalent duration is necessary.

With regard to the analyses, one should also bear in mind that in order to satisfy the ITT requirement that outcome data be analyzed for all participants, missing data were imputed. Although the methods used in the present study are considered optimal and take into account the uncertainty surrounding the imputation process, the actual values for missing participants remain unknown. The analyses were also based on a predetermined alpha level of $\alpha < .05$ and adjustments were not made to take into account multiple comparisons.

In conclusion, the present study provides evidence in support of integrated treatment for PTSD and SD utilizing PE. The COPE treatment was found to be efficacious in reducing PTSD symptom severity when combined with TAU, however, no other between group differences were observed in relation to severity of SD, substance use, depression or anxiety. Contrary to popular belief, participants randomized to receive the exposure based intervention did not demonstrate poorer substance use outcomes relative to the TAU control group. The complex trauma, substance use and psychiatric presentations commonly found among individuals with PTSD and SD should not be a deterrent to providing trauma-focused treatment.

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Study concept and design: Mills, Teesson, Baker, Hopwood, Sannibale, Back, Brady.

Acquisition of data: Barrett, Merz, Rosenfeld, Ewer.

Analysis and interpretation of data: Mills, Teesson, Baker, Hopwood, Sannibale, Back, Brady.

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Statistical analysis: Mills, Barrett, Ewer.

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Study supervision: Mills, Teesson, Baker, Hopwood, Sannibale, Back, Brady. Clinical supervision was provided by Dr's Kim Felmingham and Catherine Cahill.

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587 **Table 1:** Baseline characteristics according to group.

	Treatment (n=55)	Control (n=48)	Total (n=103)	Test statistics for between group comparisons
Demographics				
Mean age (SD)	33.4 (7.4)	33.5 (8.6)	33.7 (7.9)	t= -.17, df 101, p = .868
No. female (%)	33 (60.0)	31 (64.6)	64 (62.1)	OR 0.82, 95%CI: 0.37-1.83
No. Australian born (%)	47 (85.5)	40 (83.3)	87 (84.5)	OR 1.18, 95%CI: 0.40-3.42
No. Aboriginal or Torres Strait Islander (%)	2 (3.6)	4 (8.3)	6 (5.8)	OR 0.42, 95%CI: 0.07-2.37
Median years of school completed (range)	10 (7-12)	10 (7-12)	10 (7-12)	U=1316, p= .978
No. completed tertiary education (%)	40 (72.7)	36 (75.0)	76 (73.8)	OR 0.89, 95%CI: 0.37-2.15
No. unemployed (%)	42 (76.4)	39 (81.3)	81 (78.6)	OR 0.75, 95%CI: 0.29-1.94
No. prison history (%)	17 (30.9)	19 (39.6)	36 (35.0)	OR 0.68, 95%CI: 0.30-1.54
Substance use				
Median age of first intoxication (range)	13 (7-29)	13 (6-27)	13 (6-29)	U=1286.0, p =.821
No. history of injecting drug use (%)	43 (78.2)	39 (81.2)	82(79.6)	OR 0.83, 95%CI: 0.31-2.18
No. prior substance use treatment (%)	50 (90.9)	46 (95.8)	96 (93.2)	OR 0.44, 95%CI: 0.08-2.35
Trauma exposure				
No. experienced (%):				
- Physical assault	52 (94.5)	44 (91.7)	96 (93.2)	OR 1.58, 95%CI: 0.34-7.42
- Threatened or held captive	50 (90.9)	42 (87.5)	92 (89.3)	OR 1.43, 95%CI: 0.41-5.02
- Witness injury or death	46 (83.6)	35 (72.9)	81 (78.6)	OR 1.90, 95%CI: 0.73-4.94
- Sexual assault [a]	42 (76.4)	38 (79.2)	80 (77.7)	OR 0.85, 95%CI: 0.33-2.16
- Accident or disaster	40 (72.7)	28 (58.3)	68 (66.0)	OR 1.90, 95%CI: 0.83-4.35

- Tortured	15 (27.3)	10 (20.8)	25 (24.3)	OR 1.43, 95%CI: 0.57-3.56
- Combat experience	1 (1.8)	1 (2.1)	2 (1.9)	OR 0.87, 95%CI: 0.05-14.30
- Other	39 (70.9)	31 (64.6)	70 (68.0)	OR 1.34, 95%CI: 0.58-3.06
Median no. of trauma types experienced (range)	6.0 (2-9)	5.5 (2-10)	6.0 (2-10)	U=1100.5, .140
Median age at first trauma (range)	10 (1-44)	7 (2-28)	8 (1-44)	U=1087.0, .122
No. experienced trauma during childhood (%)	38 (69.1)	41 (85.4)	79 (76.7)	OR 0.38, 95%CI: 0.14-1.02
No. experienced childhood sexual abuse (%)	25 (45.5)	32 (66.7)	57 (55.3)	OR 0.42, 95%CI: 0.19-0.93 *
PTSD				
No. delayed onset [b] (%)	14 (25.5)	11 (22.9)	25 (24.3)	OR 1.15, 95%CI: 0.46-2.84
Median duration of trauma symptoms in years (range)	9 (.25-36)	12 (.08-40)	10 (.08-40)	U=1085.5,p=.121
No. prior PTSD treatment (%)	17 (30.9)	19 (39.6)	36 (35.0)	OR 0.68, 95%CI: 0.30-1.54
Other mental health				
No. screened positive for BPD [d] (%)	38 (69.1)	37 (77.1)	75 (72.8)	OR 0.67, 95%CI:0.28-1.61
No. attempted suicide (%):				
- Lifetime	32 (58.2)	22 (45.8)	54 (52.4)	OR 1.64, 95%CI: 0.75-3.59
- Past year	6 (10.9)	4 (8.3)	10 (9.7)	OR 1.35, 95%CI: 0.36-5.09

588 * $p<.05$

589 [a] Sexual assault includes rape and sexual molestation

590 [b] symptoms had their onset more than 6 months following trauma exposure.

591 [d] BPD = Borderline Personality Disorder.

592 Table 2. Comparisons between the treatment and control groups of percentage of time spent in TAU for SD over the follow-up period.

	Treatment (n=55) Mean (95%CI)	**Control (n=48) Mean (95%CI)**	**Total (n=103) Mean (95%CI)**	**Difference between treatment and control groups Mean difference (95%CI)**
Cumulative (i.e., since baseline)				
6-weeks	50.48 (40.50 - 60.46)	59.93 (49.54 - 70.32)	54.88 (47.69 - 62.07)	7.38 (-23.91 - 5.01)
3-months	57.01 (46.64 - 67.38)	66.51 (56.47 - 76.55)	61.44 (54.19 - 68.69)	7.43 (-24.05 - 5.07)
9-months	54.67 (43.85 - 65.49)	69.42 (59.50 - 79.34)	61.54 (53.84 - 69.24)	7.35 (-29.15 - -0.33)*
Since last interview				
6-weeks	50.48 (40.50 - 60.46)	59.93 (49.54 - 70.32)	54.88 (47.69 - 62.07)	7.38 (-23.91 - 5.01)
3-months	50.69 (39.54 - 61.84)	61.37 (49.83 - 72.91)	55.67 (47.63 - 63.71)	8.24 (-26.82 - 5.48)
9-months	52.91 (41.29 - 64.53)	67.71 (56.36 - 79.06)	59.81 (51.42 - 68.20)	8.19 (-30.85 - 1.25)

593 * $p < .05$

594

595

596 Table 3. Unadjusted comparisons between the treatment and control groups on continuous measures of outcome

	Baseline	**6-weeks**	**3-months**	**9-months**	**Within group difference between baseline and 9 month follow-up** [a]	**Between group difference between baseline and 9 month follow-up** [b]
					IRR (95%CI)	**IRR (95%CI)**
No. of drug classes used						
Mean (95%CI) [c]						
COPE + TAU (*n*=55)	3.71	2.04	2.07	2.13	0.57	0.96
	(3.32 - 4.10)	(1.57 - 2.51)	(1.62 - 2.52)	(1.68 - 2.58)	(0.46 - 0.72)***	(0.69 - 1.34)
TAU only (*n*=48)	3.81	2.26	2.31	2.28	0.60	
	(3.40 - 4.22)	(1.67 - 2.85)	(1.80 - 2.82)	(1.71 - 2.85)	(0.47 - 0.76)***	
Between group difference at	0.97	0.90	0.89	0.94		
each interview IRR (95%CI) [b]	(0.84 - 1.13)	(0.65 - 1.26)	(0.65 - 1.22)	(0.67 - 1.30)		
No. of dependence criteria met						

Mean (95%CI) [c]						
COPE + TAU (*n*=55)	5.33	2.62	2.49	2.27	0.43	0.85
	(5.09 - 5.57)	(1.68 - 3.56)	(1.75 - 3.23)	(1.58 - 2.96)	(0.31 - 0.58)***	(0.60 - 1.21)
TAU only (*n*=48)	5.58	2.96	3.41	2.98	0.52	
	(5.36 - 5.80)	(2.22 - 3.70)	(2.70 - 4.12)	(2.27 - 3.69)	(0.41 - 0.66)***	
Between group difference at	0.95	0.88	0.73	0.76		
each interview IRR (95%CI) [b]	(0.90 - 1.01)	(0.57 - 1.37)	(0.50 - 1.05)	(0.51 - 1.14)		
					Mean difference (95%CI)	**Mean difference (95%CI)**
CAPS						
Mean (95%CI) [d]						
COPE + TAU (*n*=55)	91.13	68.93	67.85	52.89	-38.24	-16.09
	(87.03 - 95.23)	(60.15 - 77.71)	(59.93 - 75.77)	(43.72 - 62.06)	(-47.93 - -28.54)****	(-29.00 - -3.18)*
TAU only (*n*=48)	89.38	75.93	73.38	67.23	-22.14	Ref
	(84.70 - 94.06)	(69.03 - 82.83)	(66.79 - 79.97)	(59.21 - 75.25)	(-30.33 - -13.95)****	
Mean between group	1.75	-7.00	-5.53	-14.34		

difference at each interview (95%CI) [b]	(-4.41 - 7.92)	(-18.96 - 4.96)	(-15.12 - 4.05)	(-26.94 - -1.75)*		
BDI						
Mean (95%CI) [c]						
COPE + TAU (*n*=55)	36.07 (33.17 - 38.97)	27.70 (22.55 - 32.85)	29.74 (25.74 - 33.74)	24.44 (19.29 - 29.59)	-11.64 (-17.08 - -6.19)****	-4.73 (-11.76 - 2.29)
TAU only (*n*=48)	31.69 (28.08 - 35.30)	25.39 (21.82 - 28.96)	25.94 (21.71 - 30.17)	24.78 (20.15 - 29.41)	-6.90 (-10.84 - -2.97)**	Ref
Mean between group difference at each interview (95%CI) [b]	4.38 (-0.20 - 8.97)	2.31 (-3.86 - 8.48)	3.80 (-1.81 - 9.40)	-0.35 (-7.72 - 7.03)		
STAI-S						
Mean (95%CI) [c]						
COPE + TAU (*n*=55)	54.69 (51.16 - 58.22)	49.24 (43.85 - 54.63)	49.89 (45.83 - 53.95)	46.44 (42.09 - 50.79)	-8.25 (-13.64 - -2.86)**	-5.34 (-12.47 - 1.80)
TAU only (*n*=48)	50.42	47.35	48.64	47.50	-2.91	Ref

	(46.89 - 53.95)	(43.29 - 51.41)	(44.19 - 53.09)	(43.15 - 51.85)	(-7.16 - 1.34)
Mean between group difference at each interview (95%CI) [b]	4.27 (-0.66 - 9.21)	1.89 (-4.03 - 7.81)	1.25 (-4.65 - 7.15)	-1.06 (-7.55 - 5.43)	

* $p < .05$ ** $p < .001$ *** $p < .0001$

[a] Reference category is baseline interview.

[b] Referent category is the control group.

[c] Group x time interaction effect not significant at $p < .05$.

[d] Group x time interaction effect significant at $p = .022$.

602 Table 4. Unadjusted comparisons between the treatment and control groups on categorical
603 measures of outcome

	Baseline n (%)	6-weeks n (%)	3-months n (%)	9-months n (%)
% abstinent [a]				
COPE + TAU (*n*=55)	0 (0)	12 (21.8)	10 (18.2)	10 (18.2)
TAU only (*n*=48)	0 (0)	15 (31.3)	12 (25.0)	13 (27.1)
Between group difference at each interview OR (95%CI) [b]	N/A	0.59 (0.24 - 1.46)	0.70 (0.24 - 1.99)	0.59 (0.21 - 1.65)
% diagnosis of substance dependence [a]				
COPE + TAU (*n*=55)	55 (100)	26 (47.3)	26 (47.3)	25 (45.4)
TAU only (*n*=48)	48 (100)	28 (58.3)	28 (58.3)	27 (56.2)
Between group difference at each interview OR (95%CI) [b]	N/A	0.64 (0.25 - 1.63)	0.62 (0.25 - 1.54)	0.64 (0.28 - 1.48)
% diagnosis of PTSD [a]				
COPE + TAU (*n*=55)	55 (100)	48 (87.3)	47 (85.4)	31 (56.4)
TAU only (*n*=48)	48 (100)	45 (93.8)	43 (89.6)	38 (79.2)
Between group difference at each interview OR (95%CI) [b]	N/A	0.41 (0.06 - 2.63)	0.68 (0.19 - 2.44)	0.32 (0.13 - 0.81)*

604 * $p < .05$.

605 [a] Group x time interaction effect not significant at $p < .05$.

606 [b] Referent category is the control group.