

Integrated Exposure-Based Therapy for Co-occurring Posttraumatic Stress Disorder and Substance Dependence

A Randomized Controlled Trial

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PROLONGED EXPOSURE 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 posttraumatic stress disorder (PTSD). Although there are other evidence-based treatments for PTSD, such as eye movement desensitization and reprocessing therapy, there is more empirical evidence for the efficacy of prolonged exposure than for any other treatment.¹ Indeed, the International Consensus Group on Depression and Anxiety recommends prolonged exposure 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 prolonged exposure 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

See also p 714 and Patient Page.

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

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

Design, Setting, and Participants Randomized controlled trial enrolling 103 participants who met *DSM-IV-TR* criteria for both PTSD and substance dependence. Participants were recruited from 2007-2009 in Sydney, Australia; outcomes were assessed at 9 months postbaseline, with interim measures collected at 6 weeks and 3 months postbaseline.

Interventions Participants were randomized to receive COPE plus usual treatment (n=55) or usual treatment alone (control) (n=48). COPE consists of 13 individual 90-minute sessions (ie, 19.5 hours) with a clinical psychologist.

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 substance dependence 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 criterion on the CIDI were considered clinically significant.

Results From baseline to 9-month follow-up, significant reductions in PTSD symptom severity were found for both the treatment group (mean difference, -38.24 [95% CI, -47.93 to -28.54]) and the control group (mean difference, -22.14 [95% CI, -30.33 to -13.95]); however, the treatment group demonstrated a significantly greater reduction in PTSD symptom severity (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 substance dependence (0.43 vs 0.52; incidence rate ratio, 0.85 [95% CI, 0.60 to 1.21]), nor were there any significant between-group differences in relation to changes in substance use, depression, or anxiety.

Conclusion Among patients with PTSD and substance dependence, the combined use of COPE plus usual treatment, compared with usual treatment alone, resulted in improvement in PTSD symptom severity without an increase in severity of substance dependence.

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efficacy of prolonged exposure among individuals with co-occurring PTSD and substance dependence.

Epidemiologic and clinical research has demonstrated that trauma exposure among individuals with substance dependence is almost universal, and up to 62% experience comorbid PTSD.^{5,6} Similarly,

up to 65% of patients with PTSD have been found to have a comorbid substance use disorder.^{7,8} Although PTSD is perva-

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sive 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 prolonged exposure therapy among individuals with substance dependence 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 prolonged exposure therapy could place individuals at increased risk for relapse.⁹ There is, however, an absence of evidence to support or refute this recommendation, because most trials of PTSD treatment have excluded individuals with substance dependence.¹¹ Although a small number of pilot studies have examined the efficacy of integrated treatment programs (which address both PTSD and substance dependence at the same time) that incorporate prolonged exposure,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 what is to our knowledge the first randomized controlled trial of an integrated treatment for PTSD and substance dependence that incorporates prolonged exposure therapy.

METHODS

Design

Participants were randomly assigned to 1 of 2 conditions. The treatment condition consisted of an integrated treatment for PTSD and substance dependence, called Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure (COPE), plus usual treatment for substance dependence. The control condition consisted of usual treatment for substance dependence 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 substance dependence symptom sever-

ity compared with those randomized to the control group. Participants were interviewed on entry to the study, and primary outcome measures were assessed at 9 months postbaseline. Two interim measures of outcome were also obtained at 6 weeks and 3 months postbaseline 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. Written informed consent was obtained from all participants prior to participation.

Recruitment

Participants were recruited between April 2007 and June 2009 from substance use treatment services, media advertisements, and practitioner referrals within the greater Sydney region, Australia. Inclusion criteria were past-month *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision) (*DSM-IV-TR*) diagnoses of PTSD and substance dependence, age 18 years or older, 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 experienced 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 substance dependence (as indicated by the number of dependence criteria met), were assessed using the Clinician-Administered PTSD Scale (CAPS) (range, 0-240; higher scores indicate more severe PTSD)¹⁵ and the Composite International Diagnostic Interview version 3.0 (CIDI) (range, 0-7 dependence criteria; higher scores indicate more severe substance dependence),¹⁶ respectively.

The interview also assessed demographic characteristics; lifetime and cur-

rent use of heroin, other opiates, amphetamines, cocaine, hallucinogens, benzodiazepines, alcohol, cannabis, and inhalants using the Opiate Treatment Index¹⁷; *DSM-IV-TR* diagnoses of current substance dependence for main drug of concern (using the CIDI¹⁶); trauma history using the CIDI version 2.1¹⁸; *DSM-IV-TR* diagnoses of PTSD in the past month using the CAPS¹⁵; depression using the Beck Depression Inventory II (range, 0-63; higher scores indicate more severe depression)¹⁹; state and trait anxiety using the State-Trait Anxiety Inventory (range, 20-80; higher scores indicate more severe anxiety)²⁰; the possible presence of borderline personality disorder using the International Personality Disorder Examination Questionnaire²¹; and history of attempted suicide.

To assess history of treatment for substance dependence, participants were asked whether they had commenced any of the following forms of treatment for their substance use: substitution pharmacotherapies (including methadone, buprenorphine, buprenorphine plus naloxone, 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 following 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, substance dependence, PTSD, depression, and anxiety were readministered 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 had undergone any treatment over the follow-up period. Participants were paid A\$30 (US \$30.75) for completing each interview. Interviews were administered by 2 trained research officers blinded to group allocation.

Interventions

COPE Treatment. COPE is a modified version of Concurrent Treatment of

PTSD and Cocaine Dependence.²² The version of COPE used in the present study represents an integration of existing evidence-based manualized CBT interventions for PTSD and substance dependence.²³⁻²⁵ The intervention consists of 13 individual 90-minute sessions (ie, 19.5 hours) delivered by a clinical psychologist. 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 of therapy.

COPE was delivered by 2 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 (ie, compliance with the treatment manual) by an independent assessor. Fidelity was rated for 53 of a total of 323 sessions (16.4%) conducted as part of the study. Average fidelity ratings were high, with a mean score of 4.13 (SD, 0.95) of a possible score of 5 indicating strong adherence to the treatment manual.

Usual Treatment. Both the treatment and the control group were able to engage in usual treatment for substance dependence. 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 (eg, methadone, buprenorphine, buprenorphine plus naloxone, naltrexone).

Sample Size Calculations

Power analysis on the primary outcome variables (ie, change in CAPS score and number of dependence cri-

teria met) was conducted using RMASS2 (Phar Lap Software Inc). 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 substance dependence, at $\alpha=.05$. The final sample size was 103 because of 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 $\alpha=.05$. A difference of 15 points on the CAPS scale is considered clinically significant.²⁶ With regard to severity of substance dependence, we considered a 1-unit change in the number of *DSM-IV-TR* criteria met to be clinically significant, because research has demonstrated a 1-unit change to be associated with level of impairment, mental health, and risk of attempted suicide.^{27,28}

Missing Data

Analysis of missing data revealed 18.7% missing data across the follow-up period. According to the results of the Little missing completely at random test, the data could be considered to be missing completely at random ($\chi^2_{36}=14.28, P>.99$). To satisfy the intention-to-treat (ITT) requirement that analyses be undertaken on all participants, missing data were imputed using multiple imputation, which allows for the uncertainty about the missing data by creating several different plausible imputed data sets and appropriately combining results obtained from each.^{29,30} Multiple imputation is recommended over single-imputation techniques because 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 Because the pattern of missing data was nonmonotone, the Markov chain Monte Carlo method of multiple imputation was used.³⁰ As suggested by Schafer and Graham,²⁹ 5 imputations were used. Impu-

tations were constrained to plausible values for the scales used.

Statistical Analyses

Two-sided analyses were conducted with IBM SPSS Statistics 20 using a predetermined α level of $P<.05$. Baseline differences between groups were examined using *t* tests for normally distributed measures, Mann-Whitney *U*-tests for nonnormally distributed data, and χ^2 test for categorical variables. χ^2 and linear regression analyses were undertaken to ascertain whether there were any between-group differences in exposure to usual treatment for substance dependence over the follow-up period.

Intention-to-treat 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 (ie, history of childhood trauma, history of childhood sexual abuse, percentage of time spent in usual treatment during the study).

Outcomes were examined using a series of binomial logistic, linear, and Poisson-distributed generalized estimating equations for categorical, continuous, and count data, respectively. Analyses were undertaken using an exchangeable correlation matrix. Linear and Poisson models used data from all points (baseline and each follow-up). These models tested whether the scores obtained at each point differed significantly between the 2 groups, the change in scores from baseline to 9 months differed for each group, and the degree of change between baseline and 9 months differed between the 2 groups. Binomial models did not include baseline data for the dependent variables, because these values were constant and hence the models could not converge. Thus, the binomial models examined whether the scores obtained at each point differed significantly between the 2 groups. Results are reported as the unstandardized mean difference with 95% CIs for linear models, odds ratios (ORs) with 95% CIs for binomial logistic models, and incidence rate ratios (IRRs) with 95% CIs for Poisson models.

RESULTS

Sample Recruitment and Retention

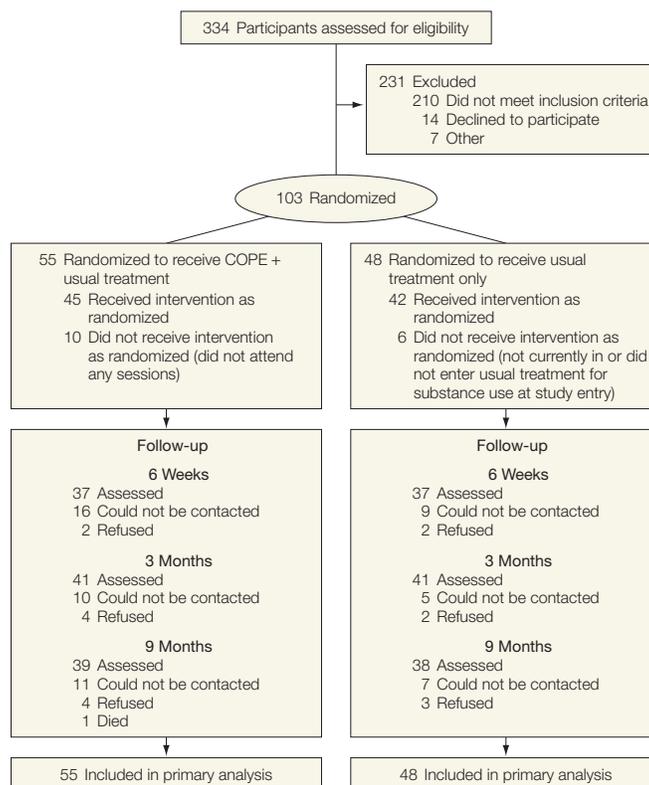
Of the 334 individuals assessed, more than one-third (103 [37.1%]) were eligible to participate (FIGURE). The primary reasons for exclusion were not meeting criteria for a diagnosis of PTSD (111 [52.9%]) or no substance use in the preceding month (82 [39.0%]); 14 individuals (6.7%) were currently suicidal or self-harming, 2 (1.0%) exhibited cognitive impairment severe enough to impede treatment, and 1 (0.5%) was younger than 18 years. The majority of eligible individuals agreed to participate (103 [83.1%]).

A total of 74, 82, and 77 participants were reinterviewed at 6 weeks, 3 months, and 9 months postbaseline, respectively, representing 71.8%, 79.6%, and 74.8% of participants enrolled in the study at baseline (Figure). Ninety-three participants (90.3%) completed at least 1 of the 3 follow-up interviews; 57 (55.3%) completed all 3 follow-up interviews. Detail regarding the pattern of follow-up data collected is provided in the eFigure available at <http://www.jama.com>.

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 (37 [67.3%] vs 37 [77.1%], respectively; OR, 0.61 [95% CI, 0.25 to 1.47]), 3 months (41 [74.5%] vs 41 [85.4%]; OR, 0.50 [95% CI, 0.18 to 1.37]), or 9 months (39 [70.9%] vs 38 [79.2%]; OR, 0.64 [95% CI, 0.26 to 1.59]) or in the number of follow-up interviews completed (median, 3.0 vs 3.0; $U=1142.5$; $P=.19$).

Patterns of study retention were largely unrelated to current substance use, severity of substance dependence, types of trauma exposure, age of first trauma exposure, or severity of PTSD (eTable 1). However, participants who completed the 6-week follow-up, compared with those who did not, were more likely to have experienced sexual molestation (54 [73.0%] vs 14 [48.3%], respectively; OR, 2.89 [95% CI, 1.19 to 7.05]). Participants who completed the 3-month follow-up, compared with those who did not, were more likely to have experi-

Figure. Study Flow



COPE indicates Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure.

enced rape (60 [73.2%] vs 10 [47.6%]; OR, 3.00 [95% CI, 1.12 to 8.04]) and less likely to have used inhalants in the month prior to baseline (3 [3.7%] vs 4 [19.0%]; OR, 0.16 [95% CI, 0.03 to 0.79]). Participants who completed the 9-month follow-up, compared with those who did not, were also more likely to have experienced rape (57 [74.0%] vs 13 [50.0%]; OR, 2.85 [95% CI, 1.13 to 7.17]). 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 substance dependence, or history of treatment for substance use (TABLE 1 and TABLE 2). Polysubstance 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 (22 [21.4%]), followed by cannabis (20 [19.4%]), amphetamines (18 [17.5%]), benzodiazepines (16 [15.5%]), alcohol (12 [11.7%]), cocaine (7 [6.8%]), other opiates (5 [4.9%]), and hallucinogens (1 [1.0%]). The distribution of main drug of concern did not differ according to group ($\chi^2=8.03$, $P=.43$).

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 with participants randomized to the treatment group. All participants had experienced multiple traumas and met crite-

ria for current PTSD. There were no significant differences between groups in PTSD, depression, or anxiety symptomatology (Table 2).

Treatment Exposure

COPE Treatment. Forty-five participants (81.8%) randomized to the treatment group attended at least 1 ses-

sion. Among 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 (22 [40.0%] imaginal, 28 [50.9%] in vivo). Participants attended a median of 0 sessions covering imaginal exposure (range, 0-7)

and 1 covering in vivo exposure (range, 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 associated with substance dependence and comorbidity. There was,

Table 1. Baseline Characteristics According to Group

Characteristic	No. (%)			OR (95% CI)
	Treatment (n = 55)	Control (n = 48)	Total (n = 103)	
Demographic				
Age, mean (SD), y ^a	33.4 (7.4)	33.5 (8.6)	33.7 (7.9)	
Women	33 (60.0)	31 (64.6)	64 (62.1)	0.82 (0.37 to 1.83)
Australian born	47 (85.5)	40 (83.3)	87 (84.5)	1.18 (0.40 to 3.42)
Aboriginal or Torres Strait Islander	2 (3.6)	4 (8.3)	6 (5.8)	0.42 (0.07 to 2.37)
School completed, median (range), y ^b	10 (7-12)	10 (7-12)	10 (7-12)	
Completed tertiary education	40 (72.7)	36 (75.0)	76 (73.8)	0.89 (0.37 to 2.15)
Unemployed	42 (76.4)	39 (81.3)	81 (78.6)	0.75 (0.29 to 1.94)
Prison history	17 (30.9)	19 (39.6)	36 (35.0)	0.68 (0.30 to 1.54)
Substance use				
Age of first intoxication, median (range) ^c	13 (7-29)	13 (6-27)	13 (6-29)	
History of injection drug use	43 (78.2)	39 (81.2)	82 (79.6)	0.83 (0.31 to 2.18)
Prior substance use treatment	50 (90.9)	46 (95.8)	96 (93.2)	0.44 (0.08 to 2.35)
Trauma exposure				
Type				
Physical assault	52 (94.5)	44 (91.7)	96 (93.2)	1.58 (0.34 to 7.42)
Threatened or held captive	50 (90.9)	42 (87.5)	92 (89.3)	1.43 (0.41 to 5.02)
Witnessed injury or death	46 (83.6)	35 (72.9)	81 (78.6)	1.90 (0.73 to 4.94)
Sexual assault ^d	42 (76.4)	38 (79.2)	80 (77.7)	0.85 (0.33 to 2.16)
Accident or disaster	40 (72.7)	28 (58.3)	68 (66.0)	1.90 (0.83 to 4.35)
Torture	15 (27.3)	10 (20.8)	25 (24.3)	1.43 (0.57 to 3.56)
Combat experience	1 (1.8)	1 (2.1)	2 (1.9)	0.87 (0.05 to 14.30)
Other	39 (70.9)	31 (64.6)	70 (68.0)	1.34 (0.58 to 3.06)
No. of trauma types experienced, median (range) ^e	6.0 (2-9)	5.5 (2-10)	6.0 (2-10)	
Age at first trauma, median (range) ^f	10 (1-44)	7 (2-28)	8 (1-44)	
Experienced trauma during childhood	38 (69.1)	41 (85.4)	79 (76.7)	0.38 (0.14 to 1.02)
Experienced sexual abuse during childhood	25 (45.5)	32 (66.7)	57 (55.3)	0.42 (0.19 to 0.93) ^g
PTSD				
Delayed onset ^h	14 (25.5)	11 (22.9)	25 (24.3)	1.15 (0.46 to 2.84)
Duration of trauma symptoms, median (range), y ⁱ	9 (0.25-36)	12 (0.08-40)	10 (0.08-40)	
Prior PTSD treatment	17 (30.9)	19 (39.6)	36 (35.0)	0.68 (0.30 to 1.54)
Other mental health history				
Screened positive for BPD	38 (69.1)	37 (77.1)	75 (72.8)	0.67 (0.28 to 1.61)
Attempted suicide				
Lifetime	32 (58.2)	22 (45.8)	54 (52.4)	1.64 (0.75 to 3.59)
Past year	6 (10.9)	4 (8.3)	10 (9.7)	1.35 (0.36 to 5.09)

Abbreviations: BPD, borderline personality disorder; OR, odd ratio; PTSD, posttraumatic stress disorder.

^at = 0.17 (df = 101), P = .87 for between-group comparisons.

^bU = 1316.0, P = .98 for between-group comparisons.

^cU = 1286.0, P = .82 for between-group comparisons.

^dIncludes rape and sexual molestation.

^eU = 1100.5, P = .14 for between-group comparisons.

^fU = 1087.0, P = .12 for between-group comparisons.

^gP = .03.

^hSymptoms had their onset more than 6 months following trauma exposure.

ⁱU = 1085.5, P = .12 for between-group comparisons.

therefore, considerable variability in the time taken to deliver the COPE treatment, ranging from 0 to 271 days (median, 71 days). Twenty-two participants (40.0%) randomized to receive COPE treatment were still receiving COPE after 3 months.

Usual Treatment. The majority of both the treatment and the control group were enrolled in usual treatment for substance dependence at study entry (44 [80.0%] vs 42 [87.5%], respectively; OR, 0.57 [95% CI, 0.19 to 1.68]). The type of usual treatment enrolled in at baseline did not differ significantly between the 2 groups ($\chi^2_1=7.00, P=.14$). The most

common treatment enrolled in for the treatment group was detoxification (28 [50.0%]), followed by maintenance therapies (12 [21.8%]) and residential rehabilitation (4 [7.3%]). The most common treatment enrolled in for the control group was detoxification (29 [60.4%]), followed by maintenance therapies (7 [14.6%]), residential rehabilitation (3 [6.5%]), and outpatient counseling (3 [6.3%]).

Percentage of time spent in treatment over the follow-up period was analyzed instead of days in treatment to control for differences in time to follow-up. As shown in TABLE 3, the treatment

group spent significantly less time in usual treatment compared with the control group over the entire 9-month follow-up period; however, there were no differences between groups in the percentage of time spent in treatment between follow-up points.

Primary Treatment Outcome Analysis

PTSD. There was a significant group \times time interaction in relation to PTSD symptom severity ($\chi^2_1=5.38, P=.02$). From baseline to 9-month follow-up, significant reductions in PTSD symptom severity were found for both the treatment group (mean difference,

Table 2. Unadjusted Comparisons Between the Treatment and Control Groups on Continuous Measures of Outcome

Outcome Measure	Mean (95% CI) ^a				IRR (95% CI)	
	Baseline	6 wk	3 mo	9 mo	Within-Group Difference Between Baseline and 9-mo Follow-up	Between-Group Difference Between Baseline and 9-mo Follow-up
No. of drug classes used						
COPE + usual care (n = 55)	3.71 (3.32 to 4.10)	2.04 (1.57 to 2.51)	2.07 (1.62 to 2.52)	2.13 (1.68 to 2.58)	0.57 (0.46 to 0.72) ^b	0.96 (0.69 to 1.34)
Usual care only (n = 48)	3.81 (3.40 to 4.22)	2.26 (1.67 to 2.85)	2.31 (1.80 to 2.82)	2.28 (1.71 to 2.85)	0.60 (0.47 to 0.76) ^b	1 [Reference]
Between-group difference at each interview, IRR (95% CI) ^c	0.97 (0.84 to 1.13)	0.90 (0.65 to 1.26)	0.89 (0.65 to 1.22)	0.94 (0.67 to 1.30)		
No. of dependence criteria met						
COPE + usual care (n = 55)	5.33 (5.09 to 5.57)	2.62 (1.68 to 3.56)	2.49 (1.75 to 3.23)	2.27 (1.58 to 2.96)	0.43 (0.31 to 0.58) ^b	0.85 (0.60 to 1.21)
Usual care only (n = 48)	5.58 (5.36 to 5.80)	2.96 (2.22 to 3.70)	3.41 (2.70 to 4.12)	2.98 (2.27 to 3.69)	0.52 (0.41 to 0.66) ^b	1 [Reference]
Between-group difference at each interview, IRR (95% CI) ^c	0.95 (0.90 to 1.01)	0.88 (0.57 to 1.37)	0.73 (0.50 to 1.05)	0.76 (0.51 to 1.14)		
CAPS						
COPE + usual care (n = 55)	91.13 (87.03 to 95.23)	68.93 (60.15 to 77.71)	67.85 (59.93 to 75.77)	52.89 (43.72 to 62.06)	-38.24 (-47.93 to -28.54) ^b	-16.09 (-29.00 to -3.19) ^d
Usual care only (n = 48)	89.38 (84.70 to 94.06)	75.93 (69.03 to 82.83)	73.38 (66.79 to 79.97)	67.23 (59.21 to 75.25)	-22.14 (-30.33 to -13.95) ^b	1 [Reference]
Mean between-group difference at each interview (95% CI) ^c	1.75 (-4.41 to 7.92)	-7.00 (-18.96 to 4.96)	-5.53 (-15.12 to 4.05)	-14.34 (-26.94 to -1.75) ^d		
BDI-II						
COPE + usual care (n = 55)	36.07 (33.17 to 38.97)	27.70 (22.55 to 32.85)	29.74 (25.74 to 33.74)	24.44 (19.29 to 29.59)	-11.64 (-17.08 to -6.19) ^b	-4.73 (-11.76 to 2.29)
Usual care only (n = 48)	31.69 (28.08 to 35.30)	25.39 (21.82 to 28.96)	25.94 (21.71 to 30.17)	24.78 (20.15 to 29.41)	-6.90 (-10.84 to -2.97) ^b	1 [Reference]
Mean between-group difference at each interview (95% CI) ^c	4.38 (-0.20 to 8.97)	2.31 (-3.86 to 8.48)	3.80 (-1.81 to 9.40)	-0.35 (-7.72 to 7.03)		
STAI						
COPE + usual care (n = 55)	54.69 (51.16 to 58.22)	49.24 (43.85 to 54.63)	49.89 (45.83 to 53.95)	46.44 (42.09 to 50.79)	-8.25 (-13.64 to -2.86) ^b	-5.34 (-12.47 to 1.80)
Usual care only (n = 48)	50.42 (46.89 to 53.95)	47.35 (43.29 to 51.41)	48.64 (44.19 to 53.09)	47.50 (43.15 to 51.85)	-2.91 (-7.16 to 1.34)	1 [Reference]
Mean between-group difference at each interview (95% CI) ^c	4.27 (-0.66 to 9.21)	1.89 (-4.03 to 7.81)	1.25 (-4.65 to 7.15)	-1.06 (-7.55 to 5.43)		

Abbreviations: BDI-II, Beck Depression Inventory II; CAPS, Clinician-Administered PTSD Scale; COPE, Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure; IRR, incidence rate ratio; STAI, State-Trait Anxiety Inventory.

^aGroup \times time interaction effect not significant at $P < .05$, except for CAPS, for which group \times time interaction effect was significant at $P = .02$.

^b $P < .001$.

^cReference category is the control group.

^d $P = .02$.

Table 3. Comparisons Between the Treatment and Control Groups of Percentage of Time Spent in Usual Treatment for Substance Dependence Over the Follow-up Period

Time in Treatment	Mean % (95% CI)			Difference Between Treatment and Control Groups, Mean % (95% CI)
	Treatment (n = 55)	Control (n = 48)	Total (n = 103)	
Cumulative (since baseline)				
6 wk	50.48 (40.50 to 60.46)	59.93 (49.54 to 70.32)	54.88 (47.69 to 62.07)	-9.45 (-23.91 to 5.01)
3 mo	57.01 (46.64 to 67.38)	66.51 (56.47 to 76.55)	61.44 (54.19 to 68.69)	-9.49 (-24.05 to 5.07)
9 mo	54.67 (43.85 to 65.49)	69.42 (59.50 to 79.34)	61.54 (53.84 to 69.24)	-14.74 (-29.15 to 0.33) ^a
Since last interview				
6 wk	50.48 (40.50 to 60.46)	59.93 (49.54 to 70.32)	54.88 (47.69 to 62.07)	-9.45 (-23.91 to 5.01)
3 mo	50.69 (39.54 to 61.84)	61.37 (49.83 to 72.91)	55.67 (47.63 to 63.71)	-10.67 (-26.82 to 5.48)
9 mo	52.91 (41.29 to 64.53)	67.71 (56.36 to 79.06)	59.81 (51.42 to 68.20)	-14.80 (-30.85 to 1.25)

^a*P* = .045.

-38.24; [95% CI, -47.93 to -28.54]) and the control group (mean difference, -22.14 [95% CI, -30.33 to -13.95]); however, the treatment group demonstrated a significantly greater reduction in PTSD symptom severity compared with the control group (mean difference, -16.09 [95% CI, -29.00 to -3.19]) (Table 3). At 9-month follow-up, PTSD symptom severity was significantly lower in the treatment group compared with the control group (52.89 vs 67.23; mean difference, -14.34 [95% CI, -26.94 to -1.75]). Although the prevalence of PTSD diagnosis at 9-month follow-up appears to be significantly lower in the treatment group compared with the control group (31 [56.4%] vs 38 [79.2%]; OR, 0.32 [95% CI, 0.13-0.81]) (Table 4), the group × time interaction in relation to PTSD diagnosis was not significant ($\chi^2=0.30$, *P* = .58).

Substance Use and Dependence. The group × time interactions in relation to rates of substance use ($\chi^2=0.00$, *P* > .99) and the number of drug classes used ($\chi^2=0.10$, *P* = .76) 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 the control group continued to use substances at 9-month follow-up (45 [81.8%] vs 35 [72.9%]) (Table 4), both the treatment and the control group demonstrated significant reductions in the number of drug classes used from baseline to 9-month follow-up

(Table 2). The degree of improvement in number of drug classes used did not differ significantly between groups (0.57 vs 0.60; IRR, 0.96 [95% CI, 0.69-1.34]).

The group × time interactions in relation to rates of substance dependence ($\chi^2=0.00$, *P* > .99) and severity of substance dependence ($\chi^2=2.09$, *P* = .15) were not significant, indicating that the prevalence of substance dependence and degree of change in severity of substance dependence over the follow-up period did not differ between the treatment and control groups. By the 9-month follow-up, rates of substance dependence had decreased 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 to 1.48]) (Table 4). Both the treatment and the control group also demonstrated significant reductions in severity of dependence from baseline to 9-month follow-up (Table 2); however, the degree of change did not differ significantly between groups (0.43 vs 0.52; IRR, 0.85 [95% CI, 0.60 to 1.21]).

Depression and Anxiety. The group × time interactions in relation to severity of depression ($\chi^2=1.31$, *P* = .26) and anxiety ($\chi^2=2.69$, *P* = .10) 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 the control group demonstrated significant reductions in severity of depression from baseline to 9-month follow-up (Table 2); however, the degree of change did not differ sig-

nificantly between groups (-11.64 vs -6.90; mean difference, -4.73 [95% CI, -11.76 to 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 vs -2.91; mean difference, -5.34 [95% CI, -12.47 to 1.80]) (Table 2).

Secondary Treatment Outcome Analysis

Secondary analyses were undertaken adjusting for covariates found to be unbalanced between groups (ie, history of childhood trauma, history of childhood sexual abuse, percentage of time spent in usual treatment during the study). The results of these analyses (eTable 2 and eTable 3) were consistent with those of the unadjusted analyses.

Serious Adverse Events

Two participants from the treatment group (3.6%) and 5 participants from the control group (10.4%) attempted suicide during the study (OR, 0.32 [95% CI, 0.06-1.76]). Although it is possible that these attempts were related to participation in the study, all 7 individuals reported that this was not the case and elected to remain involved with the study. Additionally, 1 participant from the treatment group (1.8%) died as a result of a preexisting medical condition.

COMMENT

Findings from the present study provide support for the efficacy of integrated exposure-based therapies for the treatment

Table 4. Unadjusted Comparisons Between the Treatment and Control Groups on Categorical Measures of Outcome

Outcome Measure	No. (%)			
	Baseline	6 wk	3 mo	9 mo
Abstinent, % ^a				
COPE + usual treatment (n = 55)	0	12 (21.8)	10 (18.2)	10 (18.2)
Usual treatment only (n = 48)	0	15 (31.3)	12 (25.0)	13 (27.1)
Between-group difference at each interview, OR (95% CI) ^b	NA	0.59 (0.24 to 1.46)	0.70 (0.24 to 1.99)	0.59 (0.21 to 1.65)
Diagnosis of substance dependence, % ^a				
COPE + usual treatment (n = 55)	55 (100)	26 (47.3)	26 (47.3)	25 (45.4)
Usual treatment only (n = 48)	48 (100)	28 (58.3)	28 (58.3)	27 (56.2)
Between-group difference at each interview, OR (95% CI) ^b	NA	0.64 (0.25 to 1.63)	0.62 (0.25 to 1.54)	0.64 (0.28 to 1.48)
Diagnosis of PTSD, % ^a				
COPE + usual treatment (n = 55)	55 (100)	48 (87.3)	47 (85.4)	31 (56.4)
Usual treatment only (n = 48)	48 (100)	45 (93.8)	43 (89.6)	38 (79.2)
Between-group difference at each interview, OR (95% CI) ^b	NA	0.41 (0.06 to 2.63)	0.68 (0.19 to 2.44)	0.32 (0.13 to 0.81) ^c

Abbreviations: COPE, Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure; NA, not applicable; OR, odds ratio; PTSD, posttraumatic stress disorder.

^aGroup × time interaction effect not significant at $P < .05$.

^bReference category is the control group.

^c $P = .02$.

of PTSD among patients with substance dependence. Consistent with our hypothesis, participants randomized to receive COPE plus usual treatment demonstrated significantly greater reductions in PTSD symptom severity compared with participants randomized to receive usual treatment alone (mean difference, -16.09). This also represents a clinically significant difference.²⁶ It is important to note that most participants randomized to receive COPE plus usual treatment 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 prolonged exposure therapy, is commenced.¹⁰ Although we agree that patients need to show some improvement in their substance use and an ability to use alternative coping strategies before prolonged exposure therapy is initiated, findings from the present study demonstrate that abstinence is not required.

Our second hypothesis, that individuals randomized to receive COPE plus usual care would demonstrate significantly greater reductions in severity of substance dependence, was not confirmed. Both groups demonstrated significant reductions in severity of substance dependence, but the difference between groups was not significant. This may be attributable to a lack of statistical power, because 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 period. Comparable reductions in severity of depression and anxiety were also observed between groups. Further research with larger samples 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 substance dependence symptoms have shown that improvements in PTSD symptoms are associated with subsequent improvements in substance dependence, but the reciprocal relationship is not observed.^{31,32} These findings highlight the importance of treating PTSD to improve substance dependence outcomes for individuals with this comorbidity.

The improvements in PTSD, substance dependence, and depression observed in the present study are consistent with the findings of a pilot study by Brady et al¹³ of an earlier version of the COPE treatment. Brady et al did not use a control group; however, similar within-group pretreatment to posttreatment effects were observed in both studies. These similarities are encouraging, given that Brady et al examined outcomes for treatment completers only (ie, patients who completed 10 of 16 sessions), and the baseline severity of PTSD symp-

toms in their study was considerably lower than that of participants randomized to receive COPE plus usual treatment in the present study (mean CAPS scores, 45.2 vs 91.1, respectively). The present findings add to those of Brady et al by demonstrating the efficacy of COPE using a more conservative ITT approach in a sample of substantially more disabled individuals. It should be noted however, that although those randomized to receive COPE plus usual treatment demonstrated significantly greater improvements in PTSD, at the end of the study 56.4% continued to meet diagnostic criteria for PTSD. Further analysis of these 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 a study by Triffleman et al¹² of Substance Dependence–Post-Traumatic Stress Disorder Therapy, an integrated 40-session therapy for PTSD and substance dependence that includes in vivo (but not imaginal) exposure. Substance Dependence–Post-Traumatic Stress Disorder Therapy was compared with Twelve-Step Facilitation Therapy, an evidence-based treatment for substance dependence that does not address trauma, in a sample of 19

methadone-maintained patients. As in the present study, both groups demonstrated significant improvements in PTSD and substance dependence symptoms; however, no between-group differences were found in relation to PTSD or substance dependence outcomes. Like the findings of the present study, the lack of differences observed by Triffleman et al¹² may also be attributable 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 et al,¹³ the present study demonstrated high treatment dropout rates, with participants attending a median of 5 of the 13 sessions offered. Although 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 in which 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 with that in studies of integrated PTSD treatments for patients with substance dependence that are not trauma-focused, studies of treatments for substance dependence alone, and studies of treatments for other mental health disorders.^{32,35} For example, in a study by Hien et al³² of Seeking Safety (a non-trauma-focused integrated treatment for substance dependence and PTSD), 82% of participants attended at least 1 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 values 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 2 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 experienced significant comorbidity, including likely borderline personality disorder—features typical of patients with PTSD and substance dependence.^{5,36} However, the findings cannot be generalized to individuals younger than 18 years; those not fluent in English; those currently suicidal, self-harming, or psychotic; or those with severe cognitive impairment, because these individuals were excluded from study participation.

A number of other limitations should also be noted. First, the study relied on measures of self-report alone. There is much controversy regarding the reliability and validity of self-reported drug use; however, an extensive literature documents its reliability and validity.³⁷ Overall, agreement between self-report and biomarkers is high; indeed, when there are discrepancies, this tends to be when respondents report drug use that has failed to be detected by the biological measures.³⁷ Sherman and Bigelow³⁸ suggested that drug use information reported by persons 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 patients with PTSD found participants' responses to be highly valid, with less than 10% of participants not reporting substance use detected by urine screens.^{39,40}

Second, although the effects observed remained after controlling for between-group differences in exposure to usual treatment and in 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 (ie, 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 with other treatments. Further research examining the efficacy of COPE relative to other active treatments of equivalent duration is necessary.

With regard to the analyses, it should also be noted that 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 α level of $P < .05$, and adjustments were not made to take into account multiple comparisons.

The present study provides evidence in support of integrated treatment for PTSD and substance dependence using prolonged exposure. The COPE treatment was found to be efficacious in reducing PTSD symptom severity when combined with usual treatment; however, no other between-group differences were observed in relation to severity of substance dependence, 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 those randomized to receive usual treatment only. The complex trauma, substance use, and psychiatric presentations commonly found among individuals with PTSD and substance dependence should not be a deterrent to providing trauma-focused treatment.

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Author Contributions: Dr Mills had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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