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Prolonged exposure therapy for PTSD in individuals with opioid use disorder: A randomized pilot study

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ABSTRACT

Objective: Nearly all individuals with opioid use disorder (OUD) report lifetime trauma exposure and one-third meet diagnostic criteria for posttraumatic stress disorder (PTSD). Although prolonged exposure (PE) therapy is a first-line treatment for PTSD, little is known about the effects of PE in individuals with co-occurring OUD. Furthermore, its efficacy is commonly undermined by poor therapy attendance. This pilot study evaluated the feasibility and initial efficacy of a novel PE protocol for improving PE attendance and PTSD symptoms among buprenorphine- or methadone-maintained adults with PTSD.

Method: Thirty participants with co-occurring PTSD and OUD were randomized to receive either: (a) continued medications for OUD (MOUD) treatment as usual (TAU), (b) Prolonged Exposure therapy (PE), or (c) PE with financial incentives delivered contingent upon PE session attendance (PE+). Primary outcomes included PE session attendance, PTSD symptom severity, and use of opioids other than prescribed MOUD.

Results: PE+ participants attended significantly more therapy sessions vs. PE (87% vs. 35%; $p < .0001$). PTSD symptom reductions were also significantly greater in the PE+ vs. TAU group ($p = .046$). Participants in the two PE conditions submitted significantly fewer urine samples that tested positive for opioids than TAU participants (0% vs. 22%; $p = .007$).

Conclusions: These findings provide preliminary support for the efficacy of PE+ for improving PE attendance and PTSD symptoms without prompting opioid relapse in individuals with co-occurring PTSD and OUD. These promising results justify a larger scale randomized clinical trial to more rigorously evaluate this novel treatment approach.

1. Introduction

In 2020, 9.3 million Americans reported prescription opioid misuse and 902,000 reported heroin use (Substance Abuse & Mental Health Services Administration, 2021). Opioid use disorder (OUD) is associated with adverse consequences, including opioid-related overdoses, emergency department visits, and deaths, as well as economic costs estimated at over $78 billion annually (Florence et al., 2016; Geller et al., 2019; Rudd et al., 2016).

Posttraumatic stress disorder (PTSD) is a chronic and debilitating condition that is highly prevalent among individuals with OUD. Nearly 90% of individuals with OUD report lifetime trauma exposure and 33% meet DSM diagnostic criteria for PTSD (Mills et al., 2005, 2006; Peirce et al., 2009). Although medications for opioid use disorder (MOUD; e.g., methadone, buprenorphine) are the most efficacious treatment for OUD (Mattick et al., 2014), MOUD patients with co-occurring PTSD are more likely to drop out of treatment and at greater risk of relapse to opioid use (Peirce et al., 2016; Schiff et al., 2010).

Prolonged exposure (PE) therapy is an empirically supported first-line treatment for PTSD (Jonas et al., 2013; Powers et al., 2010). PE disrupts the cycle of anxiety and avoidance that characterizes PTSD by deconditioning fear responses to trauma-related stimuli via sustained imaginal and in-vivo exposure exercises (Foa et al., 2019). Promising initial examinations of PE among individuals with OUD suggest that PE is safe and associated with significant reductions in PTSD symptoms (Peck et al., 2018; Schacht et al., 2017; Schiff et al., 2015). However, as

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with other cognitive behavioral interventions for trauma, PE completion rates are often low and present a challenge to PE efficacy, especially among patients with co-occurring PTSD and substance use disorder (SUD; Belleau et al., 2017). A quarter of participants with SUD do not attend a single therapy session (Coffey et al., 2006; Foa et al., 2013; Mills et al., 2012), and up to 62% drop out before completing treatment (Belleau et al., 2017). As a result, fewer than half of patients remain in treatment until the third session when exposure, the active component of treatment, begins (Brady et al., 2001; Mills et al., 2012; Sannibale et al., 2013).

Schacht et al. (2017) evaluated the efficacy of attendance-contingent financial incentives for improving PE attendance among 58 methadone-maintained patients with PTSD. In that study, participants were randomized to receive standard PE alone or PE plus monetary incentives delivered contingent upon attending PE sessions. Participants randomized to the PE+ incentives condition attended significantly more therapy sessions and demonstrated greater decreases in PTSD severity compared to those randomized to standard PE. However, because prior studies of PE in individuals with OUD have not included a condition in which patients received MOUD without PTSD-focused therapy, it is unclear to what extent improvements in PTSD symptoms were a function of PE versus the effects of MOUD more generally. This is important as prior studies suggest that MOUD alone, without counseling, is associated with significant improvements in psychiatric symptoms (Streck et al., 2018).

In this 12-week pilot study, we examined the feasibility of PE with financial incentives delivered contingent upon PE session attendance (PE+) for improving therapy attendance and PTSD symptoms among individuals with co-occurring PTSD and OUD as well as the initial efficacy of PE+ compared to standard PE without incentives (PE) and continued MOUD treatment as usual (TAU) without PTSD treatment. We hypothesized that participants randomly assigned to receive PE+ would attend more PE sessions than those randomized to PE and experience greater improvements in PTSD symptoms compared to those randomized to receive either PE or TAU.

2. Method

2.1. Participants

Adults with co-occurring PTSD and OUD were recruited via advertisements posted throughout the community and in local opioid treatment programs between November 2019 and March 2021. Participants were required to be $\geq$ 18 years old and maintained on a stable methadone or buprenorphine dose for $\geq$ 1 month preceding intake. They also had to meet current DSM-5 PTSD criteria (American Psychiatric Association, 2013) based on the Clinician Administered PTSD Scale for DSM-5 (CAPS-5; Weathers et al., 2013b) and score $\geq$ 33 on the PTSD Checklist (PCL-5; Weathers et al., 2013c). Participants with current delusions, hallucinations, or mania, imminent risk for suicide, or medical conditions likely interfere with consent or participation were excluded.

2.2. Procedure

Participants provided written informed consent, signed a release allowing study staff to confirm medication dose and clinical stability with the participant's MOUD provider, and completed an initial intake assessment. Thirty eligible individuals were enrolled with 10 participants randomly assigned to either: (a) continued MOUD treatment as usual (TAU), (b) Prolonged Exposure therapy (PE), or (c) PE with financial incentives delivered contingent upon PE session attendance (PE+). A minimum allocation procedure was used to achieve balance between conditions on characteristics likely to influence treatment outcomes (Altman & Bland, 2005). Stratification variables included sex, trauma type, PTSD symptom severity, MOUD medication type, MOUD medication dose and time in MOUD treatment. Participants also completed assessments at 4-, 8-, and 12-weeks post-randomization. Individuals received $50 for completion of the intake and each monthly assessment. The study was approved by the University of Vermont Institutional Review Board. Fig. 1 summarizes study design and participant flow.

2.3. Treatment conditions

2.3.1. Continued MOUD treatment as usual (TAU)

Participants randomized to the TAU condition continued to receive standard MOUD treatment from their current treatment provider and completed assessments at intake and study weeks 4, 8, and 12, but did not receive PTSD treatment as part of study participation.

2.3.2. Prolonged exposure therapy (PE)

In addition to receiving continued MOUD treatment and completing monthly assessments as above, PE participants also received 12 weekly individual PE sessions. During Sessions 1–2, participants received education about PTSD, the rationale for PE, and breathing retraining techniques as a method for managing PTSD-associated distress. In-vivo (Sessions 3–11) and imaginal exposures (Sessions 4–12) are active components of PE that provided patients with opportunities to confront trauma-related memories and real-life reminders that were previously avoided, yet not inherently harmful (Foa et al., 2019). Abstinence from non-prescribed substances was strongly encouraged but not required to participate in PE. However, study visits were rescheduled for participants who appeared to be experiencing the acute effects of opioids or other drugs or under the influence of alcohol.

Although the PE protocol was largely informed by conventional PE (Foa et al., 2019), the following modifications were made to support effective delivery of PE in a clinical population with co-occurring PTSD and OUD and facilitate future dissemination efforts: (a) sessions were 60 minutes in duration, as 60-minute PE sessions promote similar reductions in PTSD symptoms as more traditional 90-minute sessions (Nacasch et al., 2015) and (b) participants received psychoeducation regarding the association between PTSD and OUD. As the COVID-19 pandemic struck in the initial months of participant recruitment, we revised our protocol to permit therapy sessions and monthly assessments to be completed in person or remotely via a secure telemedicine platform.

Participants who missed two consecutive appointments were reminded of their option to withdraw from PE while continuing to complete monthly assessments. Those who missed four consecutive therapy sessions were withdrawn from PE but remained eligible to complete monthly assessments.

PE therapy sessions were conducted by one of five masters- or doctoral-level therapists with previous experience treating individuals with SUD. Therapists were trained in PE by the first author. Similar to PE trainings described by Foa et al. (2005, 2019), study therapists received intensive training in PE prior to delivering treatment to study participants and study therapists received ongoing supervision from the first author. All PE sessions were audio-recorded and recordings were monitored throughout the study.

2.3.3. PE with financial incentives delivered contingent upon PE session attendance (PE+)

Participants assigned to the PE+ condition received the procedures noted above for the PE condition plus attendance-contingent financial incentives delivered immediately following completion of PE sessions. The incentive schedule followed the general parameters of prior interventions developed to promote and sustain behavior change across a variety of clinical populations (Higgins et al., 1991; Roll & Higgins, 2000; Sigmon et al., 2016). The initial session was worth $20, and each consecutive attended session increased the amount by $5. Missed sessions earned no incentive and reset values for the next attended session back to the initial $20 value. However, to support continued attendance, two consecutive attended PE sessions following a reset returned the

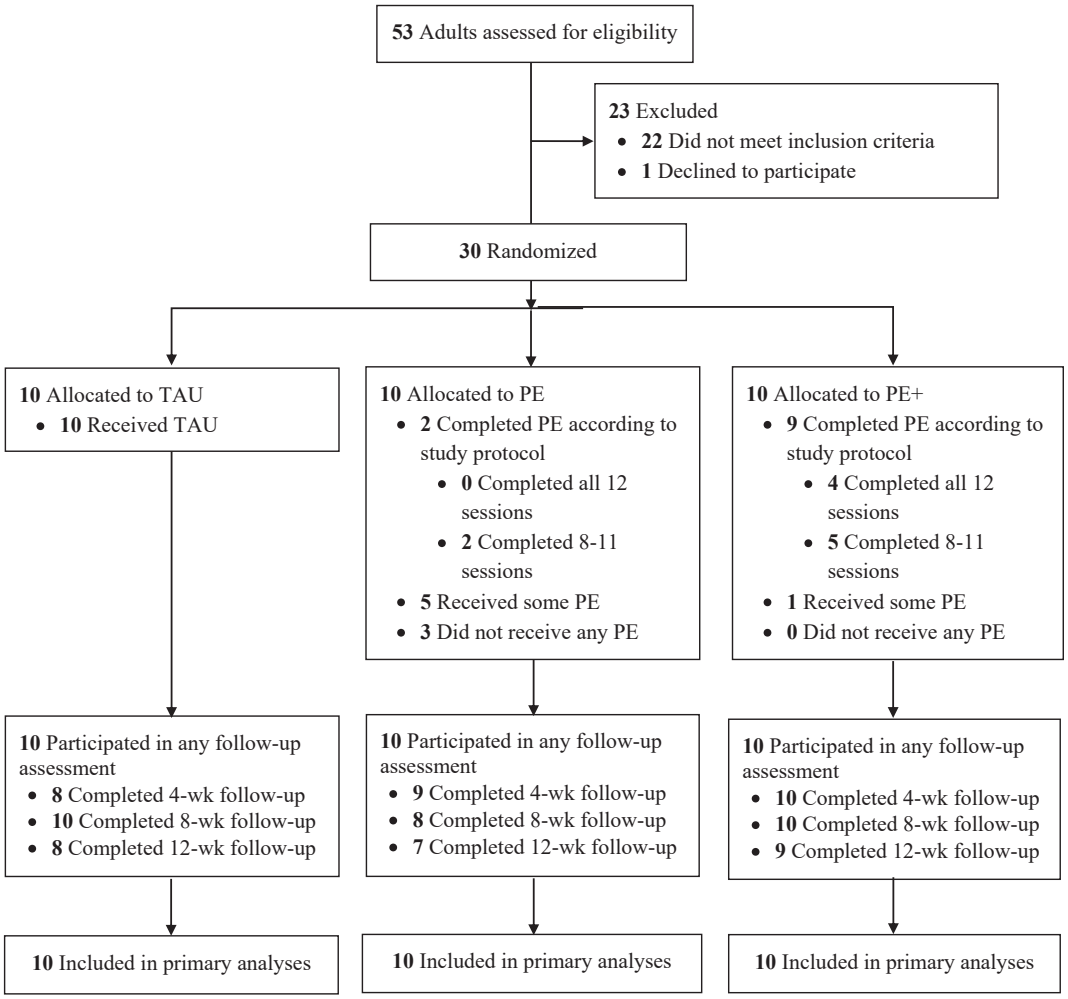

Fig. 1. CONSORT diagram depicting participant flow through the 12-week study.

dollar value back to the value immediately prior to the missed appointment. To further support consistent (vs. sporadic) attendance, participants received a $50 bonus for every two consecutive sessions attended. Additionally, to support completion of the full PE protocol, participants received a $100 bonus upon completion of Session 12. Overall, PE+ participants who attended every session could earn a maximum of $920 for continuous attendance throughout the 12-week study.

2.4. Assessments

2.4.1. Intake assessment

Participants completed staff- and self-administered assessment measures at intake, including a Demographic and Drug History Questionnaire and Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). PTSD symptoms were assessed using the Life Events Checklist for DSM-5 (LEC-5; Weathers et al., 2013a), CAPS-5 (Weathers et al., 2013b), and PCL-5 (Weathers et al., 2013c). The CAPS-5 is a 30-item structured diagnostic interview that is considered the gold standard for PTSD assessment. A randomly selected portion of the CAPS-5 (20%) were reviewed by KRP and NMK for consistency of diagnostic status and agreement was 100%. Other psychiatric symptoms were assessed via the Beck Anxiety Inventory (BAI; Beck & Steer, 1993), Beck Depression Inventory-II (BDI-II; Beck et al., 1996), and Addiction Severity Index (ASI; McLellan et al., 1992). Participants also provided urine samples for testing for opioids (e.g., heroin, methadone, buprenorphine, oxycodone, fentanyl) as well as other, non-opioid drugs (cocaine, amphetamines, benzodiazepines). Furthermore, the Timeline Follow-Back (TLFB; Sobell & Sobell, 1992), was administered to measure instances of non-prescribed drug use.

2.4.2. Outcome measures

PE therapy session attendance was recorded throughout the study. At study weeks 4, 8 and 12, participants in each of the three experimental conditions completed assessments consisting of the CAPS-5, PCL-5, BAI, BDI-II, ASI, and TLFB and provided urine samples for testing for opioids as well as other non-opioid drugs.

2.5. Statistical methods

Primary analyses included all randomized subjects independent of early dropout. PE and PE+ groups were compared on the percent of PE sessions attended using a Wald Chi square test derived from generalized estimated equations (GEE) for repeated measures for dichotomous outcomes (SAS, PROC GENMOD). The model was based on a binomial distribution and utilized a logit link function. PE and PE+ groups were also compared on the percent of subjects who completed treatment (attending $\geq$ 8 PE sessions; Foa et al., 2005) using Fisher's exact test. For the continuous primary outcome of PTSD severity (CAPS-5) and secondary outcomes of (PCL-5, BDI, BAI), mixed models repeated measures analyses (SAS, PROC MIXED) were used to compare the three treatment conditions across study assessments. The model including one across-subject fixed factor, condition (TAU, PE, and PE+), and one within-subject repeated fixed factor, time (intake, 4-, 8-, and 12-weeks).

Subject represented a random factor nested within condition. Compound symmetry was assumed for the variance–covariance structure and the Kenward-Roger approximation was used to estimate denominator degrees of freedom. Means presented for outcome measures are least square means which are computed based on linear combinations of the parameter estimates derived from the mixed model and account for missing data. Bonferroni adjusted Fisher's LSD procedure was used to evaluate the significance of changes from baseline to each of the three post treatment assessments within each treatment condition. Confidence intervals and significance levels for these comparisons are based on controlling experimentwise error at $\alpha = 0.05$ within each condition (comparisonwise error = 0.0167). Linear contrasts were used to compare the changes from baseline to the 12-week assessment across conditions. GEE repeated measures models were used to compare experimental conditions on biochemically verified and self-reported opioid and other drug abstinence across study weeks 4, 8, 12. Analyses of urine data are based only on the samples collected at monthly assessments conducted 4-, 8-, and 12-weeks post-randomization, meaning no assumptions were made with respect to missing urines being negative or positive. For the 30 participants in this study, 59 urine samples were provided out of 90 scheduled. Missing urine data ($n = 31$) represent a combination of attrition and participant enrollment during the peak of the COVID-19 pandemic (March 16th – June 15th, 2020) when institutional protocols precluded the collection of urine samples. For primary and secondary outcome measures, Cohen's d was used as a measure of effect size. For repeated measures designs, computations were based on the method described by Dunlap et al. (1996). Statistical analyses were performed using SAS Statistical Software, V9.4 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Baseline demographic and clinical characteristics

All participants were receiving buprenorphine or methadone treatment for OUD and submitted urine samples that were positive for their prescribed MOUD medication at intake. Most participants were female with an average age of 38.1 years (Table 1). Participants had been receiving MOUD treatment for an average of 4.5 years. Seventeen (57%) participants were maintained on buprenorphine and 13 (43%) were maintained on methadone. The average baseline CAPS-5 score was 41.5. The average number of trauma types experienced was 11.4, with the most commonly reported index trauma being sexual assault (33%). At intake, 90% of participants submitted urine samples that were negative for opioids other than prescribed MOUD and 70% submitted urine samples that were negative for other substances (cocaine, amphetamines, or benzodiazepines). TAU participants were older than those randomized to the two PE conditions.

3.2. Treatment attendance and completion

PE+ participants attended significantly more therapy sessions compared to PE participants (87% vs. 35%; difference = 52%, 95% CI [33%, 71%], $d = 2.26$, $p < .0001$; Fig. 2). Furthermore, a significantly greater percentage of PE+ participants completed treatment compared to PE participants (90% vs. 20%; difference = 70%, 95% CI [24%, 93%], $d = 1.98$, $p = .006$). No serious adverse events occurred during the study.

Across the two PE conditions, attendance rates were similar between telemedicine and in-person modalities (64% vs. 57%; difference = 7%, 95% CI [-20%, 34%], $d = 0.19$, $p = .56$). However, PE+ participants were significantly more likely than those in the PE condition to attend both telemedicine-delivered (84% vs. 45%; difference = 39%, 95% CI [14%, 64%], $d = 1.21$, $p = .02$) and in-person therapy sessions (90% vs. 26%; difference = 64%, 95% CI [40%, 88%], $d = 2.10$, $p < .0001$).

Table 1
Baseline demographic and clinical characteristics

Measure	Total ($n = 30$)	TAU ($n = 10$)	PE ($n = 10$)	PE+ ($n = 10$)
Age, years	38.1 (7.9)	44.7 (8.9)	33.8 (4.6)	35.9 (5.2)
Female, *N* (%)	19 (63.3)	7 (70.0)	6 (60.0)	6 (60.0)
White, *N* (%)	29 (96.7)	10 (100)	9 (90.0)	10 (100)
Education, years	13.3 (1.5)	13.6 (2.0)	13.6 (1.3)	12.8 (1.1)
Employed full-time, *N* (%)	6 (20.0)	2 (20.0)	2 (20.0)	2 (20.0)
Duration of illicit opioid use, years	7.4 (7.3)	9.1 (8.9)	4.6 (4.6)	8.2 (7.4)
Ever overdosed, *N* (%)	10 (33.3%)	3 (30.0%)	4 (40.0%)	3 (30.0%)
MOUD medication				
Buprenorphine, *N* (%)	17 (56.7%)	6 (60.0%)	6 (60.0%)	5 (50.0%)
Daily dose, mg	15.6 (5.6)	17.0 (6.2)	16.3 (5.7)	13.2 (5.0)
Methadone, *N* (%)	13 (43.3%)	4 (40.0%)	4 (40.0%)	5 (50.0%)
Daily dose, mg	92.2 (42.3)	103.8 (44.2)	55.8 (17.3)	112.0 (44.4)
Duration of MOUD, years	4.5 (4.1)	5.2 (5.2)	5.3 (4.4)	3.0 (2.2)
Index trauma				
Sexual assault, *N* (%)	10 (33.3%)	4 (40.0%)	2 (20.0%)	4 (40.0%)
Physical assault, *N* (%)	8 (26.7%)	4 (40.0%)	3 (30.0%)	1 (10.0%)
Witnessed injury or death, *N* (%)	4 (13.3%)	1 (10.0%)	1 (10.0%)	2 (20.0%)
Learned about injury or death, *N* (%)	3 (10.0%)	1 (10.0%)	0 (0%)	2 (20.0%)
Accident, *N* (%)	2 (6.7%)	0 (0%)	1 (10.0%)	1 (10.0%)
Combat, *N* (%)	1 (3.3%)	0 (0%)	1 (10.0%)	0 (0%)
Other, *N* (%)	2 (6.7%)	0 (0%)	2 (20.0%)	0 (0%)
History of PTSD treatment, *N* (%)	18 (60.0%)	5 (50.0%)	5 (50.0%)	8 (80.0%)
SUD other than OUD	21 (70.0%)	6 (60.0%)	8 (80.0%)	7 (70.0%)
Cigarette smoker, *N* (%)	23 (76.7%)	6 (60.0%)	9 (90.0%)	8 (80.0%)
Lifetime Suicide Attempt	17 (56.7%)	6 (60.0%)	5 (50.0%)	6 (60.0%)
Lifetime Panic Disorder	18 (60.0%)	6 (60.0%)	4 (40.0%)	8 (80.0%)
Lifetime Bipolar Disorder	16 (53.3%)	6 (60.0%)	4 (40.0%)	6 (60.0%)
Lifetime Generalized Anxiety Disorder	15 (50.0%)	6 (60.0%)	3 (30.0%)	6 (60.0%)
Lifetime Major Depressive Disorder	13 (43.3%)	4 (40.0%)	5 (50.0%)	4 (40.0%)
CAPS-5	41.5 (8.1)	38.9 (8.7)	41.4 (8.6)	44.1 (6.9)
PCL-5	56.0 (10.9)	57.1 (11.4)	51.4 (12.4)	59.5 (7.7)
BAI	26.2 (11.8)	31.7 (11.3)	21.5 (9.6)	25.3 (13.1)
BDI-II	32.3 (9.9)	34.4 (8.8)	29.7 (6.5)	32.8 (13.4)

Note. TAU = continued MOUD treatment as usual; PE = Prolonged Exposure therapy; PE+ = PE with financial incentives delivered contingent upon PE session attendance; MOUD = medications for opioid use disorder; PTSD = post-traumatic stress disorder; SUD = substance use disorder; OUD = opioid use disorder; CAPS-5 = Clinician Administered PTSD Scale for DSM-5; PCL-5 = PTSD Checklist for DSM-5; BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory. Values represent mean (SD) unless otherwise indicated.

3.3. PTSD severity and diagnostic remission

Participants in the PE+ and PE conditions experienced significant reductions in PTSD symptoms between intake and week 12 as measured

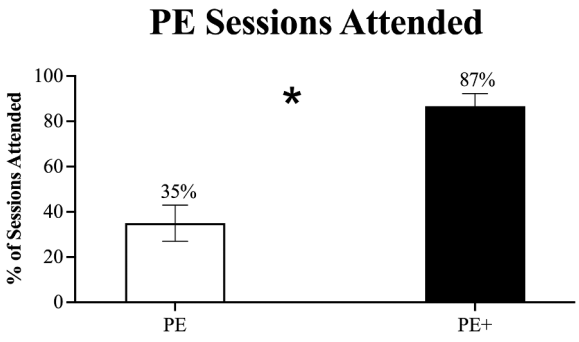

Fig. 2. Percentage of prolonged exposure (PE) therapy sessions attended by group. Error bars represent standard error of the mean. Asterisk indicates a significant (p <.05) difference in the percentage of PE sessions attended between those randomized to prolonged exposure therapy (PE), or PE with financial incentives delivered contingent upon PE session attendance (PE+).

by the CAPS-5 (PE+: mean decrease = 18.3, 95% CI [9.2, 27.4], $d = 2.2$; PE: mean decrease = 16.3, 95% CI [6.3, 26.3], $d = 2.0$, p's < 0.001; Table 2), whereas participants in the TAU condition did not report a significant change in symptoms (mean decrease = 7.4, 95% CI [-2.1, 16.8], $d = 0.91$, $p = .18$). In terms of markers of clinically significant change, 60% of PE+ participants achieved diagnostic remission at week 12 and no longer met criteria for PTSD compared to 40% of TAU and PE participants. Furthermore, improvements in PTSD symptoms were significantly greater for those who received PE+ compared to TAU (mean difference = 10.9, 95% CI [0.20, 21.6], $d = 1.34$, $p = .046$) while changes in PTSD symptoms for the PE condition did not differ significantly from the TAU condition (mean difference = 8.9, 95% CI:-2.2 to 20.1, Cohen's $d = 1.10$, $p = .12$; Fig. 3). A different pattern was observed on the PCL-5, with all three conditions reporting significant reductions in PTSD symptoms at week 12 compared to intake (TAU: mean decrease = 20.5, 95% CI [7.5, 33.6], $d = 1.93$; PE: mean decrease = 20.0, 95% CI [5.5, 34.5], $d = 1.89$; PE+: mean decrease = 24.8, 95% CI [12.1, 37.2], $d = 2.33$, p's < 0.01), with no significant between-group differences.

3.4. Other psychiatric symptoms

Anxiety symptoms as measured by the BAI significantly improved for those receiving TAU (mean decrease = 10.0, 95% CI [0.6, 19.5], $d = 0.88$, $p = .03$). Similar improvements were observed for subjects in the PE and PE+ conditions, but these changes were not significant (PE: mean decrease = 9.7, 95% CI [-0.2, 19.6], $d = 0.85$, $p = .057$; PE+: mean decrease = 8.5, 95% CI [-0.6, 17.6], $d = 0.75$, $p = .072$). There were no significant between group differences in changes over time. Depression symptoms as measured by the BDI-II significantly improved in all three conditions (TAU: mean decrease = 11.6, 95% CI [3.5, 19.8], $d = 1.32$; PE: mean decrease = 14.6, 95% CI [6.0, 23.2], $d = 1.67$; PE+: mean decrease = 9.6, 95% CI [1.8, 17.4], $d = 1.10$, p's < 0.01). There were no significant between-group differences.

Participants in both PE conditions also experienced significant reductions in psychiatric symptoms, as measured by the ASI Psychiatric Composite, between intake and week 12 (PE: mean decrease = 0.22, 95% CI [0.01, 0.43], $d = 1.51$; PE+: mean decrease = 0.18, 95% CI [0.02, 0.35], $d = 1.24$, p's < 0.05) whereas participants in the TAU condition did not report significant changes (mean decrease = 0.05, 95% CI [-0,12, 0.23], $d = 0.34$, $p = 0.99$). There were no significant differences in changes over time across groups.

3.5. Substance use outcomes

Over the entire 12-week treatment period, TAU participants provided significantly more urine samples that were positive for opioids other than prescribed MOUD (22%) than PE (0%) and PE+ (0%)

Table 2
Primary and secondary outcomes by group.

Measure	TAU		PE		PE+	
	n	Mean (*SE*)	*n*	Mean (*SE*)	*n*	Mean (*SE*)
CAPS-5						
Intake	10	38.9 (4.0)	10	41.4 (4.0)	10	44.1 (4.0)
Week 4	8	36.9 (4.2)	9	33.0 (4.1)	10	39.0 (4.0)
Week 8	10	30.3 (4.0)	8	**30.8 (4.2)**	10	**34.6 (4.0)**
Week 12	8	31.5 (4.2)[a]	7	**25.1 (4.4)[a,b]**	9	**25.8 (4.1)[b]**
PCL-5						
Intake	10	57.1 (5.0)	10	51.4 (15.0)	10	59.5 (5.0)
Week 4	8	47.2 (5.4)	9	**33.0 (5.2)**	10	49.8 (5.0)
Week 8	10	**37.5 (5.0)**	8	**26.1 (5.4)**	10	**36.9 (5.0)**
Week 12	8	**36.6 (5.4)**	6	**31.4 (6.0)**	9	**34.8 (5.2)**
BAI						
Intake	10	31.7 (3.4)	10	21.5 (3.4)	10	25.3 (3.4)
Week 4	8	25.2 (3.7)	9	17.8 (3.6)	9	24.6 (3.6)
Week 8	10	**17.7 (3.4)**	8	16.4 (3.7)	10	18.9 (3.4)
Week 12	8	**21.7 (3.7)**	7	11.8 (3.9)	9	16.8 (3.6)
BDI-II						
Intake	10	34.4 (3.9)	10	29.7 (3.9)	10	32.8 (3.9)
Week 4	8	32.0 (4.1)	9	26.2 (4.0)	10	**24.9 (3.9)**
Week 8	10	**25.9 (3.9)**	8	22.9 (4.1)	10	**23.8 (3.9)**
Week 12	8	**22.8 (4.1)**	7	**15.0 (4.2)**	9	**23.2 (4.0)**
ASI – Psychiatric Composite						
Intake	10	0.49 (0.05)	10	0.48 (0.05)	10	0.51 (0.05)
Week 12	7	0.43 (0.06)	5	**0.28 (0.07)**	8	**0.34 (0.05)**
Urine samples positive for opioids other than prescribed MOUD (%)[#]						
Intake	10	3 (30.0%)	10	0 (0%)	10	0 (0%)
Week 4	7	1 (14.3%)	8	0 (0%)	8	0 (0%)
Week 8	6	1 (16.7%)	7	0 (0%)	7	0 (0%)
Week 12	5	2 (40.0%)	6	0 (0%)	5	0 (0%)
Urine samples positive for non-opioid substances (%)[#]						
Intake	10	5 (50.0%)	10	2 (20.0%)	10	2 (20.0%)
Week 4	7	4 (57.1%)	8	1 (12.5%)	8	1 (12.5%)
Week 8	6	2 (33.3%)	7	1 (14.3%)	7	1 (14.3%)
Week 12	5	2 (40.0%)	6	3 (50.0%)	5	1 (20.0%)
Self-reported past-month opioid use other than prescribed MOUD (%)						
Intake	10	3 (30%)	10	2 (20%)	10	2 (20%)
Week 4	10	2 (20%)	10	1 (10%)	10	0 (0%)
Week 8	10	2 (20%)	8	1 (12.5%)	10	1 (10%)
Week 12	8	2 (25%)	7	0 (0%)	9	0 (0%)

(*continued on next page*)

Table 2 (*continued*)

Measure	TAU		PE		PE+	
	n	Mean (*SE*)	*n*	Mean (*SE*)	*n*	Mean (*SE*)
Self-reported past-month non-opioid substance use (%)						
Intake	10	5 (50%)	10	2 (20%)	10	3 (30%)
Week 4	10	3 (30%)	10	3 (30%)	10	2 (20%)
Week 8	10	4 (40%)	8	2 (25%)	10	1 (10%)
Week 12	8	2 (25%)	7	2 (28.6%)	9	2 (22.2%)

Note. TAU = continued MOUD treatment as usual; PE = Prolonged Exposure therapy; PE+ = PE with financial incentives delivered contingent upon PE session attendance; CAPS-5 = Clinician Administered PTSD Scale for DSM-5; PCL-5 = PTSD Checklist for DSM-5; BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory. Values represent mean (SE) unless otherwise indicated. Bold type indicates a significant difference between intake and the assessment time point within the experimental condition. Groups means that do not share a common superscript indicate that the change from intake to week 12 differed between experimental conditions ($p < .05$).

[#] Urine samples missing for follow-up assessments conducted between March – June of 2020 due to institution-wide restrictions on face-to-face research activity.

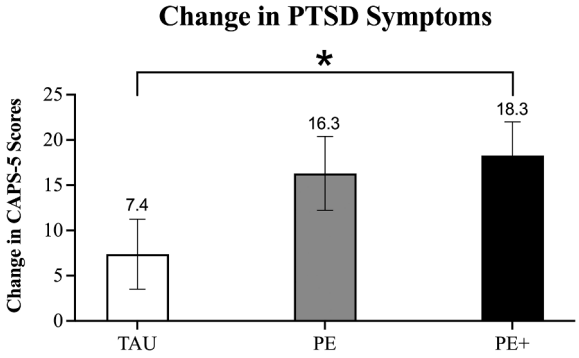

Fig. 3. Change in PTSD symptom severity for those randomized to continued MOUD treatment as usual (TAU), prolonged exposure therapy (PE), or PE with financial incentives delivered contingent upon PE session attendance (PE+) as measured by the Clinician Administered PTSD Scale for DSM-5. Asterisk indicates a significant ($p < .05$) difference in the reduction in CAPS-5 scores between intake and week 12 for those randomized to continued MOUD treatment as usual (TAU) versus PE with financial incentives delivered contingent upon PE session attendance (PE+). Error bars represent standard error of the mean.

participants (differences = 22%, 95% CI [5%, 39%], $d = 0.78$, $p = .007$). The trend was similar for other substances (e.g., cocaine, amphetamines, benzodiazepines), with 44% of TAU, 24% of PE, and 15% of PE+ participants submitting urine samples that were positive for one or more of these substances. However, there were no significant group differences in non-opioid drug use during the study. The percentage of participants who self-reported past-month opioid and non-opioid drug use on the TLFB did not differ significantly between treatment conditions at any assessment time point. Urine sample test results were generally consistent with past month self-reported opioid use. When urine sample and TLFB data were both available, there were only five instances in which they were discordant (2 in the TAU group, 2 in the PE group, and 1 in the PE+ group). In each instance, the participant self-reported past-month opioid use, but the urine sample was negative for opioids.

3.6. Treatment adherence and competence

All PE sessions were audio-recorded and 15% (n = 22) were randomly selected and evaluated for treatment fidelity. These therapy sessions contained a total of 150 essential intervention elements. A total of 131 (87%) essential elements were provided during therapy sessions. Competence providing the essential elements was rated separately using an adaptation of the Yale Adherence and Competence Scale (Carroll et al., 2000). Competency ratings (1 = not at all, 2 = a little, 3 = somewhat, 4 = considerable, 5 = extensive) were in the "considerable" range (M = 3.8, SD = 1.3), which is comparable to prior studies (Back et al., 2019).

4. Discussion

This study is among the first to evaluate PE for PTSD in individuals receiving MOUD treatment. Although preliminary studies suggest that PE is associated with reductions in PTSD symptom severity in patients receiving treatment for co-occurring OUD, poor attendance often limits the efficacy of PE. The present study provides preliminary support for a novel PE protocol for improving therapy attendance and suggests that the combination of PE plus MOUD may be associated with better clinical outcomes than MOUD alone.

As hypothesized, PE+ participants attended more therapy sessions compared to PE participants, providing preliminary support for the efficacy of attendance-based financial incentives for increasing PE attendance. Therapy attendance in the PE+ condition was higher than reported in prior studies of individuals with co-occurring PTSD and SUD (Coffey et al., 2016; Foa et al., 2013; Mills et al., 2012) as well as a prior study examining the efficacy of financial incentives for improving PE attendance in individuals receiving methadone treatment for OUD (Schacht et al., 2017). The well-established incentive schedule used in the present study differed from the schedule used by Schacht et al. (2017) and included important design features that may have increased PE attendance. First, although the present study and the Schacht et al. (2017) study implemented reinforcement schedules that incorporated an increasing magnitude of reinforcement for consecutively attended therapy sessions, the maximum possible total incentive amount in the present study ($920) was nearly double the amount ($480) in the Schacht et al. (2017) study. Second, participants in the present study were incentivized for attendance to every PE session (vs. the first nine). Third, bonuses were built into the schedule used in the present study to support consistent (vs. sporadic) attendance as well as completion of the 12-week PE protocol. These and other design features are associated with superior results (Roll & Shoptaw, 2006).

This pilot study also offers promising evidence for the feasibility of telemedicine for delivering PE to individuals with co-occurring PTSD and OUD. The efficacy of telemedicine-delivered PE has been demonstrated previously (Acierno et al., 2017; Morland et al., 2020). However, prior studies excluded individuals with SUDs. Thus, the efficacy of telemedicine-delivered PE for individuals with OUD and other SUDs remains unexamined. Furthermore, because approximately one-third of patients receiving telemedicine-delivered PE drop out of treatment prematurely (Acierno et al., 2017; Morland et al., 2020), efforts to increase attendance to telemedicine-delivered PE are critical.

This study is the first to our knowledge to evaluate the effects of PE above and beyond MOUD in individuals with co-occurring PTSD and OUD. Similar to prior studies (Peck et al., 2018; Schacht et al., 2017; Schiff et al., 2015), PE was associated with significant reductions in PTSD symptoms. Our findings also suggest that PE may be efficacious above and beyond MOUD for improving PTSD symptoms in adults with co-occurring OUD. Indeed, PE+ participants achieved significantly greater improvements in PTSD symptoms as measured by the CAPS-5 compared to TAU participants. These findings indicate the PE can improve PTSD symptoms among individuals who are maintained on a stable methadone or buprenorphine dose. However, additional research is needed to evaluate the feasibility and efficacy of PE in individuals who have recently initiated MOUD treatment. Notably, no significant group differences were observed on changes in self-reported PTSD, anxiety, or depression symptoms as measured by the PCL5. BAI, and BDI-II,

respectively. Although the CAPS-5 and PCL-5 are generally concordant in quantifying PTSD symptom change, recent research (Lee et al., 2022) indicates that, relative to the CAPS-5, change in PCL-5 scores may not provide the same level of precision in quantifying symptom change.

Most participants were abstinent from opioids other than prescribed MOUD, with 93% of all urine samples collected during the 12-week treatment period negative for non-prescribed opioids. Despite anecdotal concerns that PE will undermine participants' stability with drug use, participants who received PE did not provide any urine samples that were positive for opioids other than prescribed MOUD. This aligns with prior studies indicating that PE can improve PTSD symptoms without prompting opioid relapse among patients with OUD when PE and MOUD are delivered concurrently (Schacht et al., 2017; Schiff et al., 2015). Similar to prior studies (Saloner et al., 2021; Winkelman et al., 2018), our results indicate that individuals with OUD often engage in polysubstance use and continue to engage in use of other non-opioid substances even after initiating MOUD treatment. Taken together, more research is needed to determine whether PE is associated with greater improvements in substance use outcomes compared to MOUD alone.

Despite these promising findings, several limitations are worth bearing in mind. First, the small and racially homogenous sample limited the generalizability of our findings as well as our ability to examine differences in PTSD symptoms between experimental conditions. Second, the absence of a post-treatment follow-up assessment period precluded our ability to evaluate whether improvements in PTSD symptoms were sustained following completion of PE. Third, adherence to in-vivo and imaginal exposure homework assignments was not systematically assessed. A larger scale randomized clinical trial employing a nationwide recruitment strategy, post-treatment follow-up assessments and assessments of treatment adherence is planned to address the above limitations. The planned study will permit us to examine the generalizability of these findings in a more geographically and ethnically diverse sample, sustainability of improvements in PTSD and SUD symptoms, and mechanisms of change. Fourth, participants were not randomized to receive in-person or telemedicine-delivered therapy sessions but rather were permitted to choose between platforms and platforms could also vary within participants throughout the study. Thus, randomized trials examining the efficacy of telemedicine-delivered PE for individuals with OUD and other SUDs are needed. Fifth, although medication type (methadone versus buprenorphine) was included as a stratification variable and unlikely to be a confounding factor in the present study, the type and quantity of therapeutic services may vary across treatment programs, time, and patients. Additional research is needed to evaluate whether engagement in these services affects PTSD and SUD outcomes in individuals with co-occurring PTSD and OUD. Sixth, the cost of financial incentives may be a barrier to implementation in clinical settings. However, there is growing recognition by the White House Office of National Drug Control Policy (ONDCP) of the importance of financial incentives for effective SUD treatment and efforts by the Department of Health and Human Services' Centers for Medicare and Medicaid Services exploring reimbursement for motivational incentives (California Department of Health Care Services, 2021; ONDCP, 2021).

In summary, these results provide preliminary support for the efficacy of PE+ for improving PE attendance and PTSD symptoms in individuals with co-occurring PTSD and OUD. They also suggest that PE does not undermine patients' stability with drug use and may be associated with less substance use than MOUD alone. Our study also offers preliminary evidence for the feasibility of telemedicine-based PE for individuals with co-occurring PTSD and OUD that has the potential to extend access to evidence-based PTSD treatment to MOUD patients in vulnerable and underserved communities.

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CRediT authorship contribution statement

Kelly R. Peck: Conceptualization, Methodology, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Gary J. Badger:** Methodology, Software, Formal analysis, Resources, Data curation, Writing – original draft, Writing – review & editing. **Rebecca Cole:** Investigation, Data curation, Writing – review & editing, Visualization, Project administration. **Stephen T. Higgins:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition. **Nathaniel Moxley-Kelly:** Investigation, Data curation, Writing – review & editing, Project administration. **Stacey C. Sigmon:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [This work was supported in part by the National Institute of General Medical Sciences (P20GM103644) and the National Institute on Drug Abuse (5T32DA007242). The authors of this report were entirely responsible for the design of the study, the collection, analysis, and interpretation of data, the preparation of the manuscript, and the decision to submit the work for publication. KRP, GJB, RC, STH, NMK and SCS have no interests that may be perceived as conflicting with the research.]

Data availability

Data will be made available on request.

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