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A randomized controlled trial

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Effectiveness of treating post-traumatic stress disorder in patients with co-occurring substance use disorder with prolonged exposure, eye movement desensitization and reprocessing or imagery rescripting: A randomized controlled trial

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Abstract

Background and aims: Post-traumatic stress disorder (PTSD) and substance use disorder (SUD) are highly co-occurring and evidence for the optimal ways of treating PTSD in SUD patients is mixed. Our aim was to compare three different PTSD treatments, each added simultaneously to SUD treatment, with SUD treatment alone in patients with co-occurring SUD-PTSD. These PTSD treatments were: Prolonged Exposure (PE), Eye Movement Desensitization and Reprocessing (EMDR) and Imagery Rescripting (ImRs).

Design: A single-blind 4-arm randomized controlled trial with follow-up at 3 months.

Setting: Two addiction treatment centers in the Netherlands, providing intra- and extramural care.

Participants: 209 patients with SUD and co-morbid PTSD were included [mean age 37.5 (standard deviation, SD = 11.99), female sex = 46.4%, mean Clinically Administered PTSD Scale (CAPS) score = 37.35 (SD = 9.28)].

Interventions: Participants were randomized to either simultaneous SUD + PE ($n = 53$), SUD + EMDR ($n = 50$), SUD + ImRs ($n = 55$) or to SUD treatment only ($n = 51$), with the active PTSD treatments consisting of 12 sessions each within 3 months. Standard protocols were used.

Measurements: The primary outcome was clinician-administered PTSD symptom severity as measured by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (CAPS-5) at 3 month follow-up. Secondary outcomes included loss of PTSD diagnosis, full remission of PTSD and SUD-severity, also recorded at 3 months.

Findings: Compared with SUD only, the mean differences in CAPS-5 score were $B = -5.41$ [95% confidence interval (CI) = 10.88, 0.05, $P = 0.052$] for SUD + PE, $B = -7.97$ (95% CI = -13.57, -2.37, $P = 0.006$) for SUD + EMDR and $B = -10.03$ (95% CI = -15.29, -4.77, $P < 0.001$) for SUD + ImRs. When adjusted for baseline covariates, mean differences were $B = -5.81$ (95% CI = -11.48, -0.15, $P = 0.044$) for SUD + PE, $B = -8.85$ (95% CI = -14.60, -3.10, $P = 0.003$) for SUD + EMDR and $B = -10.75$ (95% CI = -15.94, -5.56, $P < 0.001$) for SUD + ImRs. No between-group differences in SUD outcomes were found.

Conclusions: Among people with co-occurring substance use disorder (SUD) and post-traumatic stress disorder (PTSD), trauma-focused PTSD treatment as add-on to SUD treatment appears to be effective in decreasing PTSD severity compared with manualized SUD only treatment and does not appear to increase SUD severity.

KEYWORDS

eye movement desensitization and reprocessing (EMDR), imagery rescripting (ImRs), post-traumatic stress disorder (PTSD), prolonged exposure (PE), substance use disorder (SUD), treatment effectiveness

INTRODUCTION

Post-traumatic stress disorder (PTSD) and substance use disorder (SUD) are highly co-occurring disorders [1], and individuals with both disorders are perceived as more complex to treat than those with either disorder alone [2]. The findings for treatment of PTSD in patients with SUD are somewhat ambiguous.

First, a recent meta-analysis reported that trauma-focused treatment alongside SUD is superior to the usual SUD treatment alone in patients with co-occurring SUD and PTSD, but the effects are modest and the treatment dropout rates are high [3]. Another meta-analysis found that solely trauma-focused treatment is not superior to solely manualized SUD treatment in reducing PTSD symptoms [4]. A previous Cochrane review on psychological therapies for PTSD and SUD found the quality of evidence to be low or very low for all comparisons that were made [5].

Prolonged exposure (PE) has been studied most thoroughly in patients with both SUD and PTSD and is found to be effective; however, the effect sizes are smaller compared with patients with PTSD without SUD and the treatment dropout rates are higher [6]. Previous attempts to lower dropout rates have not been successful [7]. Eye movement desensitization and reprocessing (EMDR) is a well-established treatment for PTSD [8, 9]; however, its application in individuals with co-occurring SUD has been the subject of only a handful of pilot studies [10, 11]. Imagery rescripting (ImRs) is another propitious treatment for PTSD with promising results regarding dropout [12], but has not yet been studied in patients with SUD.

More knowledge on the effectiveness of treatment of PTSD for patients with SUD and PTSD is critical to enhance treatment outcomes, promoting treatment completion and facilitating the development of more unequivocal guidelines on the treatment of these patients.

The aim of the present study is threefold, with the first aim being the subject of this article. First, to compare the effectiveness of PE, EMDR and ImRs as add-ons to regular manualized SUD treatment with manualized SUD treatment alone in patients with SUD and PTSD. Second, to compare effectiveness of simultaneous SUD and PTSD treatment with sequential SUD and PTSD treatment in patients with SUD and PTSD. Third, to explore differential effectiveness between three trauma-focused PTSD treatments (PE vs EMDR; PE vs ImRs; EMDR vs ImRs) in patients with SUD and PTSD

(see our protocol article [13]). In our trial design, the emphasis was placed on testing each PTSD treatment when given simultaneously with SUD treatment in the first phase of up to 3 months (aim 1), and only this phase is covered here. A further report will cover aims 2 and 3. The primary outcome was PTSD severity; the secondary outcomes were loss of PTSD diagnosis, full remission of PTSD diagnosis and SUD severity. We hypothesized that the addition of any trauma-focused therapy (i.e. PE, EMDR or ImRs) to manualized SUD treatment would lead to a significantly greater decrease in PTSD severity than manualized SUD treatment alone at the 3-month follow-up [13].

METHODS

Study design

The first phase of the Treatment of PTSD and Addiction (TOPA) study is a single blind four-arm randomized controlled trial (RCT) in patients with SUD and PTSD. Follow-up was after treatment completion at 3 months. For the second phase, participants in the control arm were randomized to receive PTSD treatment after completion of the first phase. Details and results of this second phase will be reported in a later article. Participants were recruited at two departments of Jellinek, a large Dutch addiction treatment facility center, providing intra- and extramural care. The research protocol was approved by the Medical Ethical Committee of the Amsterdam Academic Medical Centre (AMC) and the trial has been registered at the Netherlands Trial Register (NTR L7885). Full trial procedures and details have been published elsewhere [13].

Participants

A total of 209 participants who registered for SUD treatment and were also diagnosed with PTSD were included. Inclusion criteria were: (a) age 18 years or older; (b) substance use disorder(s) according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) [14], with a primary diagnosis involving one of the following substances: alcohol, cannabis, cocaine (snorting), amphetamine, benzodiazepine, opioids; (c) PTSD according to the DSM-5 criteria; and (d) sufficient understanding of the Dutch language to be able to

fill out Dutch questionnaires and follow therapy in Dutch [13]. Exclusion criteria were: (a) acute psychotic disorder; (b) intellectual disability or cognitive impairment (estimated IQ < 70); (c) current physical or sexual abuse or death threats; (d) high acute suicidal behavior (operationalized as current high suicidality score on the Mini-International Neuropsychiatric Interview as well as a serious suicide attempt within the past 3 months); (e) life-threatening self-mutilation; (f) homelessness; (g) involvement in a compensation case or legal procedures concerning admission or stay in the Netherlands; (h) involvement in legal procedures regarding the index trauma; (i) engagement in any other current PTSD treatment. Sample characteristics are provided in Table 1.

Procedures

All patients attending intake at the addiction treatment departments were screened with the Jellinek-PTSD questionnaire [15]. Those with a positive screen underwent PTSD assessment using the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), a routine procedure at Jellinek. Patients meeting PTSD criteria received study information, including a patient information letter. Potential participants were invited for an inclusion interview, screening SUD criteria with the Structured Clinical Interview for DSM-5 (SCID-5-S), and inclusion and exclusion criteria screening. All eligible patients were invited for the baseline assessment. Assessments consisted of a semi-structured interview and self-report questionnaires. Assessments incorporated in this article took place at baseline and again at the 3-month follow-up and were conducted by junior researchers (MSc in Psychology) masked to the treatment condition.

Randomization and masking

Randomization after baseline, using block randomization, was stratified for location (Amsterdam or Utrecht) and SUD treatment intensity (inpatient, day treatment or outpatient treatment). Participants were assigned randomly to simultaneous PE, EMDR or ImRs treatment or to SUD treatment alone (25% chance each), with block sizes of four and eight, as depicted in the trial flow chart (Figure 1). An independent researcher from Arkin conducted the randomization process using a computer-generated block randomization schedule. To avoid selection bias, researchers were masked for block size order and did not have access to the randomization schedule. Post-randomization, participants were informed only of treatment timing; the treatment type was disclosed by the therapist at the first PTSD treatment session. All participants provided written informed consent.

Intervention

All participants started standard care for SUD directly after baseline. SUD treatment was not modified for the purpose of the trial and consisted of empirically supported forms of SUD care, with standardized treatment protocols and with variability in care intensity and type. Outpatient treatment ($n = 112$) consisted of one session per week either individually (1 hour) or in a group (2 hours). Day treatment ($n = 58$) consisted of 3 days of treatment per week (5 hours per day in a group setting, supplemented with one individual session per week of 1 hour). Inpatient treatment ($n = 39$) consisted of two phases: first, a 6-week admission (4.5 hours of treatment per day, 5 days a week, all in group setting, supplemented with one individual session per

TABLE 1 Baseline characteristics of the study sample.

Characteristic	Total sample ($n = 209$)	PE + SUD ($n = 53$)	EMDR+SUD ($n = 50$)	ImRs+SUD ($n = 55$)	SUD only ($n = 51$)
Age, years, mean (SD)	37.5 (11.99)	37.85 (13.85)	36.34 (11.10)	37.36 (11.30)	38.24 (11.75)
Female sex, %	46.4	45.3	54.0	41.8	45.1
Education level, ^a %					
1	25.3	16.9	24.0	30.9	29.5
2	41.6	54.7	34.0	40.0	37.3
3	31.6	28.3	40.0	29.1	29.4
Other	1.4	0	2.0	0	3.90
CAPS sum score, mean (SD)	37.35 (9.28)	36.55 (8.85)	38.30 (11.35)	37.35 (8.30)	37.28 (8.66)
Main SUD disorder, %					
Alcohol	99	23	24	19	33
Cannabis	70	20	19	20	11
Cocaine	21	7	3	8	3
Sedating substances	7	2	3	2	0
Opiates	5	1	0	3	1
Other	7	0	1	3	3

Abbreviations: CAPS, clinician-administered PTSD scale; EMDR, eye movement desensitization and reprocessing; ImRs, imagery rescripting; PE, prolonged exposure; PTSD, post-traumatic stress disorder; SD, standard deviation; seq, sequential; sim, simultaneous; SUD, substance use disorder.

^a1, no degree, primary school or secondary school lower level; 2, secondary school higher level; 3, post-secondary.

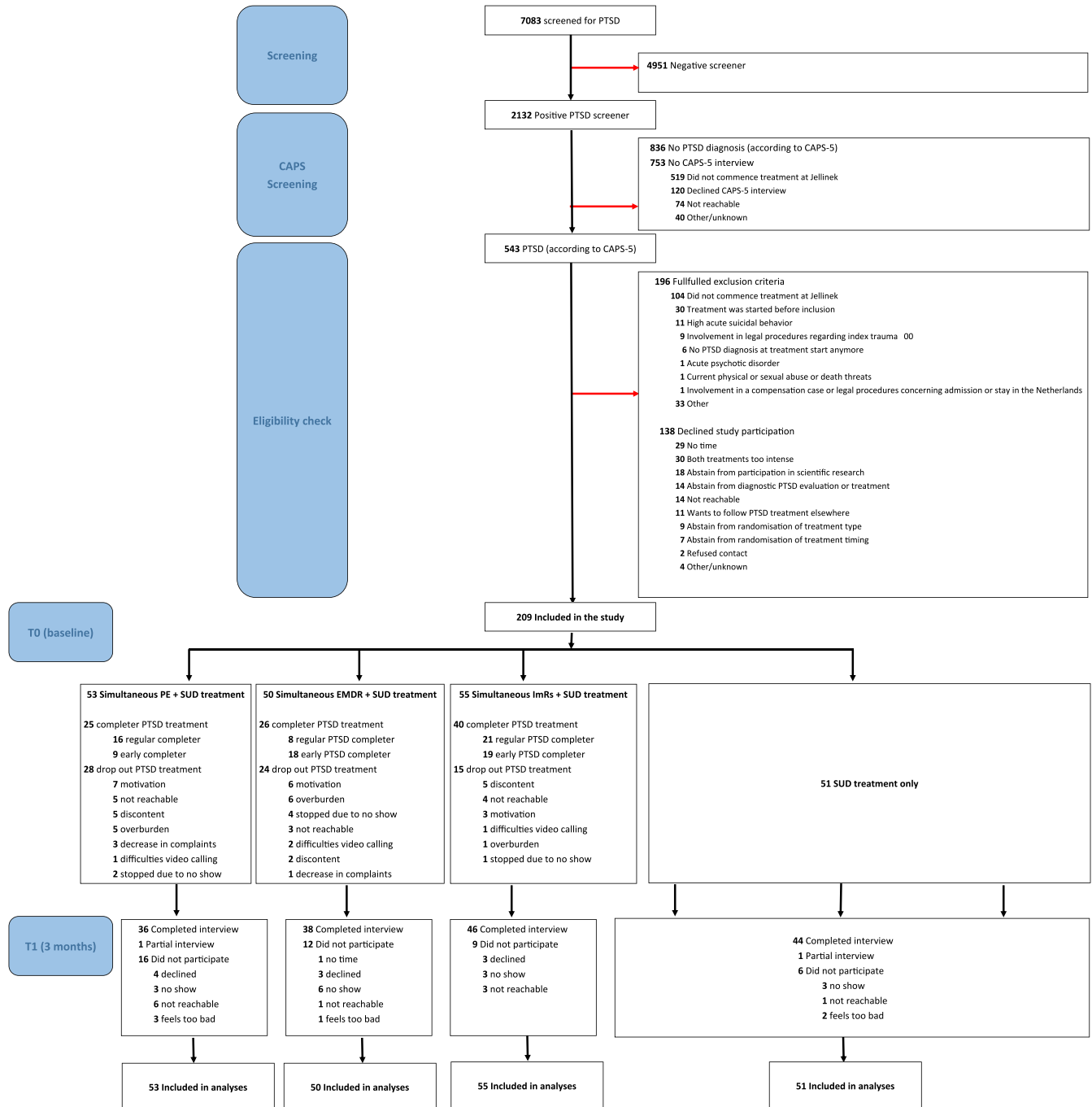


FIGURE 1 Flow chart of the study design. Abbreviations: CAPS-5, clinician-administered PTSD scale for DSM-5; EMDR, eye movement desensitization and reprocessing; ImRs, imagery rescripting; PE, prolonged exposure; PTSD, post-traumatic stress disorder; SUD, substance use disorder.

week of 1 hour), followed by a 6-week day treatment of 3 days per week (with the same intensity as the day treatment described above). The treatment was conducted according to acceptance and commitment therapy (ACT), cognitive behavioral therapy (CBT) or the Minnesota (12-step) model, possibly supplemented with medication-assisted support and detoxification. Participants across all four treatment arms received comparable SUD care, with similar timing and content. Abstinence was encouraged as much as possible during the PTSD

treatment but was not mandatory. If a client was significantly under the influence during a session to the extent that the therapist deemed their learning capacity insufficient, the session would be terminated. However, this situation did not occur during the trial.

For participants in the arms with PTSD treatment, this PTSD treatment started within 2 weeks of baseline and was completed before the scheduled assessment at 3 months after baseline. PTSD treatments involved 12 90-minute sessions, twice a week, by two

alternating PTSD therapists following the therapist rotation model [16]. In this model, each client is treated by multiple therapists. It was previously tested for trauma-focused PTSD treatment and was found to reduce negative concerns of therapists over starting trauma-focused treatment. Furthermore, possibly because the therapists had to hand over the content of each session to each other it countered therapist drift. Finally, it countered therapist avoidance behavior, possibly because therapists shared the responsibility for the PTSD treatment together, rather than individually [16]. Although several studies have applied this approach effectively [17, 18], evidence for this rotation model is still limited. Therapists ($n = 35$) were (mental healthcare) psychologists working at Jellinek and trained in all three therapy types for the purpose of this study by an expert for each therapy (2 days by A. Van Minnen for PE, 4 days by E. ten Broeke for EMDR and 2 days by A. Arntz for ImRs). From all therapists, at least two sessions of all three therapy types were recorded and checked for protocol adherence before start of the trial. In all PTSD treatments, the first sessions consisted of psychoeducation and identifying key traumatic experiences for therapy. From the second session onwards, each session involved a 60-minute intervention, with the remaining 30 minutes utilized for administering questionnaires, reviewing the treatment rationale and evaluating the session. While patients were encouraged to remain abstinent from substances, this was not mandatory. The PE therapy followed the Dutch translation [19] of the PE protocol established by Foa *et al.* [20]. PE involves confronting trauma-related stimuli to reduce anxiety through imaginal (recounting memories) and *in vivo* (real-life situations) exposure. The aim is to diminish emotional responses to trauma triggers [20]. Every session consisted of imaginal exposure and *in vivo* exposure was added every other session. Homework included daily listening to recorded sessions. Only trauma events meeting DSM-5A criteria are included. EMDR therapy adhered to the Dutch adaptation [21] of Shapiro's standard eight-phase protocol [22]. EMDR is a therapy that reduces traumatic memory intensity and changes negative beliefs by having the patient focus on distressing images while performing eye movements, repeating the process until desensitization occurs [22]. ImRs therapy followed the protocol by Arntz and Weertman [23]. ImRs is a technique that rescripts trauma memories to change their emotional impact. The patient imagines the trauma as if it is happening now, then alters the sequence. The process continues until the patient is satisfied [23]. The therapist actively participated in the rescripting for two to five sessions while the patient viewed their younger self. Henceforth, the patient entered the image as their current self, reshaping the scene to protect and fulfill the needs of their younger self. Both EMDR and ImRs can also address trauma events without DSM-5A criteria, and this was allowed within our trial as long as there was sufficient time after addressing DSM-5A criteria traumas and if they were related to the PTSD symptoms. Therapies other than the manualized SUD treatment as well as medication changes other than for SUD were discouraged and participants were explicitly instructed not to start any other PTSD treatment until the last follow-up.

All therapists received 1 hour of peer supervision weekly (group size, 6–8) as well as yearly supervision by the experts, who also

trained all therapists in the PTSD treatments (2 hours per treatment). Additional consultation by the trainers was provided upon request. All treatment sessions were audiotaped, of which 16 sessions per treatment type were randomly selected and rated for treatment fidelity by trained junior researchers who were masked to treatment allocation. Treatment fidelity was scored on scales where each item was rated as 'yes', 'no' or 'not applicable'. The interrater agreement on the three scales was very high, all with intraclass correlation coefficients (ICCs) of >0.99 (average ratings). Analysis of the rating scores indicated treatment conditions were statistically distinguishable from each other, with Cohen's $d > 5$ (Appendix S1).

Measurements

Primary outcome measures

The primary clinical study parameter, PTSD severity, was measured both at baseline and at the 3-month follow-up (primary outcome variable) using a Dutch translation of the CAPS-5. Scores on the CAPS-5 range from 0 to 80, with higher scores indicating higher severity of PTSD symptoms. Junior researchers underwent CAPS-5 training and received ongoing supervision.

Secondary outcome measures

Secondary outcomes included loss of PTSD diagnosis (no longer meeting criteria of ≥ 1 B criterion, ≥ 1 C criterion, ≥ 2 D criterion and ≥ 2 E criterion) and full remission (CAPS-5 score of <20) [24]. Based on the more recently proposed uniformity regarding the cut-off value for full remission, we have also added the cut-off value of <12 , as this better reflects the lower total score of the CAPS-5 compared with the CAPS-4 [25]. Substance use problems in the last 3 months were measured with the Alcohol Use Disorder Identification Test (AUDIT) [26] and Drug Use Disorders Identification Test (DUDIT) [27]. The total score of the AUDIT ranges from 0 to 40, and the DUDIT ranges from 0 to 44, with higher scores indicating more problems with alcohol consumption or drug use, respectively.

Other measures

Baseline characteristics of age, sex, education level, CAPS scores and main SUD disorder are presented in Table 1. PTSD treatment completion is presented in the flow chart (Figure 1). Non-completion of PTSD treatment occurred if PTSD treatment was not completed within the allocated time frame. Early completion was possible if: (1) both therapist and patient concluded that the patient no longer experienced PTSD symptoms; (2) this was discussed with colleagues in weekly peer supervision with at least one researcher included; and (3) a total score below 13 on the PTSD checklist for DSM-5 (PCL-5) was present

for two consecutive sessions, excluding four specific items (items 15, 16, 19 and 20). These conditions were the same for all three types of PTSD treatment.

Statistical analysis

The sample size calculation was published elsewhere [28]. The sample size calculation was primarily based on other aims, requesting more power, than that of the present article, resulting in a planned $n = 51$ participants per arm. For the present study, we aimed to demonstrate that each of the trauma-focused treatments combined with SUD treatment has, compared with SUD treatment alone, an additional average effect of at least 10 points on the CAPS-5, representing 1 SD of CAPS-5 scores in PTSD samples [29–33]. This would be a large and clinically meaningful effect. However, the post-treatment SD typically increases to approximately 15 [31]. Thus, the minimal effect we aim to detect is a standardized mean difference (SMD) between trauma-focused + SUD treatment and SUD treatment alone of $10/15 = 0.67$, which is still a relevant effect (approximately 75% of the combined treatment group would have CAPS scores below the mean of the SUD treatment group). With the planned $n = 51$ participants per arm, the study has >90% power to detect such an effect at a two-tailed significance level of 0.05. Note that including the baseline CAPS-5 as a covariate, with an estimated correlation of 0.6 with the 3-month CAPS-5 [13], will increase the power. Analyses were conducted in R 4.2.1. $P < 0.05$ was chosen as the threshold for statistical significance. All reported P -values are two-tailed.

Primary outcome

For the primary outcome (CAPS-5 at 3 months), we conducted three linear regression analyses to examine the effectiveness of adding, respectively, PE, EMDR or ImRs to SUD treatment at the 3-month follow-up, with the CAPS-5 baseline score included as a covariate. Assumptions for linear regression analysis were met. Our primary analysis was performed according to the intention-to-treat principle. Baseline data were complete. CAPS-5 3-month follow-up data were missing for 21.05% of the participants. As there was no clear evidence about the nature of missing outcomes, missing data were assumed to be missing at random (MAR) and, for our primary analysis, were imputed using multiple imputation by chained equations. We created 50 multiple imputed data sets with 100 iterations, using the R package mice 3.15.0. Predictor variables for the imputation model were selected because they were included in the regression analyses (e.g. baseline value, condition), and/or because they were related to missingness (e.g. CAPS-5 baseline score) and/or to the imputed variables (e.g. last PCL-5 score). The regression analyses were repeated in the 50 multiple imputed data sets and results were pooled using Rubin's rules. In addition, two sensitivity analyses were included. For the first sensitivity analysis, missing data were

assumed to be missing not at random (MNAR), based on the assumption that those with missing follow-up data were less likely to have responded to treatment. For this sensitivity analysis, missing follow-up data were replaced with baseline values (last observation carried forward). For the second sensitivity analysis, missing data were assumed to be missing completely at random (MCAR). For this sensitivity analysis, missing data were ignored and only patients with complete data were included in the analysis (complete case analysis). In addition to the unadjusted models (only adjusted for CAPS-5 baseline value), for each analysis, a comparison model is presented adjusted for the baseline variables: age, sex, clinical site, baseline CAPS-5 score, baseline AUDIT score and baseline DUDIT score.

Secondary outcomes

Analyses of the secondary outcome measures – loss of PTSD diagnosis (yes/no), full remission of PTSD (yes/no), and AUDIT and DUDIT scores – were similar to that for the primary variable, except that for the dichotomous variables (loss of PTSD diagnosis and full remission of PTSD) we conducted three logistic regression analyses.

RESULTS

Recruitment took place from 19 September 2019 to 4 May 2022. In total, 209 participants were randomized, with a mean age of 37.45 years (SD = 11.99 years). The mean baseline CAPS-5 score was 37.35 (SD = 9.28).

Further baseline participant characteristics are presented in Table 1. Figure 1 shows the participant flow, including PTSD treatment completion for the treatment arms including PTSD treatment. The average number of completed PTSD sessions was 7.30 (SD = 4.41) for PE, 7.16 (SD = 4.08) for EMDR and 8.95 (SD = 3.40) for ImRs. In total, 78.95% of the participants completed the T1 measure, with no significant differences in the follow-up rates among the groups ($\chi^2 = 7510$, $df = 3$, $P = 0.057$). No harms or adverse events were reported.

Primary outcome

As shown in Table 2, in the unadjusted version of our primary analysis (with multiple imputed data), only EMDR and ImRs significantly outperformed SUD treatment alone in the reduction of PTSD symptoms at the 3-month follow-up. In the adjusted model, the results of EMDR and ImRs remained significant. Moreover, in the adjusted model PE also significantly outperformed SUD treatment alone in the reduction of PTSD symptoms at the 3-month follow-up.

In the first sensitivity analysis (with the last observation carried forward), in both the adjusted as well as the unadjusted models adding

TABLE 2 Primary outcome results from regression analyses to compare the addition of three different PTSD treatments to SUD treatment with SUD treatment alone at the 3-month follow-up.

	SUD + PE (n = 53)	SUD + EMDR (n = 50)	SUD + ImRs (n = 55)	SUD only (n = 51)
Primary analysis (MI)				
CAPS-5 sum score, mean (SD)	22.1 (14.48)	20.74 (15.91)	18.02 (14.56)	28.00 (14.95)
Baseline score, mean (SD)	36.55 (8.85)	38.30 (11.34)	37.35 (8.30)	37.27 (8.66)
Unadjusted analysis ^a				
B (SE)	-5.41 (2.75)	-7.97 (2.82)	-10.03 (2.65)	NA
95% CI of B, upper, lower	-10.88, 0.05	-13.57, -2.37	-15.29, -4.77	NA
P	0.052	0.006	<0.001	NA
Adjusted analysis ^b				
B (SE)	-5.81 (2.85)	-8.85 (2.89)	-10.75 (2.61)	NA
95% CI of B, upper, lower	-11.48, -0.15	-14.60, -3.10	-15.94, -5.56	NA
P	0.044	0.003	<0.001	NA
Sensitivity analysis 1 (LOCF)				
CAPS-5 sum score, mean (SD)	23.89 (16.39)	22.60 (18.47)	18.49 (14.95)	28.31 (15.08)
Baseline score, mean (SD)	36.55 (8.85)	38.30 (11.34)	37.35 (8.30)	37.27 (8.66)
Unadjusted analysis ^a				
B (SE)	-3.79 (2.72)	-6.67 (2.79)	-9.88 (2.61)	NA
95% CI of B, upper, lower	-9.18, 1.60	-12.22, -1.13	-15.06, -4.70	NA
P	0.166	0.019	<0.001	NA
Adjusted analysis ^b				
B (SE)	-4.40 (2.83)	-7.78 (2.93)	-10.54 (2.60)	NA
95% CI of B, upper, lower	-10.02, 1.22	-13.59, -1.96	-15.70, -5.38	NA
P	0.124	0.009	<0.001	NA
Sensitivity analysis 2 (CCA) ^c				
CAPS-5 sum score, mean (SD)	16.28 (13.33)	16.39 (15.42)	14.91 (13.56)	27.16 (15.53)
Baseline score, mean (SD)	36.55 (8.85)	38.30 (11.34)	37.35 (8.30)	37.27 (8.66)
Unadjusted analysis ^a				
B (SE)	-9.30 (3.05)	-10.56 (2.97)	-12.36 (2.67)	NA
95% CI of B, upper, lower	-15.37, -3.23	-16.46, -4.65	-17.67, -7.05	NA
P	0.003	<0.001	<0.001	NA
Adjusted analysis ^b				
B (SE)	-9.33 (3.14)	-11.76 (2.94)	-12.31 (2.69)	NA
95% CI of B, upper, lower	-15.59, -3.09	-17.62, -5.91	-17.66, -6.95	NA
P	0.004	<0.001	<0.001	NA

Abbreviations: AUDIT, Alcohol Use Disorder Identification Test; CAPS, Clinician-Administered PTSD scale; CCA, complete case analysis; CI, confidence interval; DUDIT, Drug Use Disorder Identification Test; EMDR, eye movement desensitization and reprocessing; ImRs, imagery rescripting; LOCF, last observation carried forward; MI, multiple imputation; NA, not applicable; PE, prolonged exposure; PTSD, post-traumatic stress disorder; SD, standard deviation; SE, standard error; SUD, substance use disorder. Significant findings are shown in bold.

^aOnly adjusted for baseline score of outcome variable (CAPS-5).

^bModels adjusted for age, sex, site, CAPS-5 baseline, AUDIT baseline and DUDIT baseline.

^cIncluding only participants with complete data on follow-up: n = 36 for SUD + PE; n = 38 for SUD + EMDR; n = 46 for SUD + ImRs; n = 44 for SUD alone.

EMDR or ImRs to SUD treatment was effective in reducing PTSD severity at the 3-month follow-up, whereas adding PE was not. In the second sensitivity analysis (complete analysis), in both the adjusted as well as the unadjusted models, adding any of the PTSD treatments (PE, EMDR or ImRs) was effective in reducing PTSD severity at the 3-month follow-up.

Secondary outcomes

As shown in Table 3, in both the unadjusted as well as the adjusted models, participants in the PE, EMDR and ImRs groups were more likely to achieve a loss of diagnosis at the 3-month follow-up than participants in the group with SUD treatment alone. In the sensitivity

TABLE 3 Results on the secondary outcomes of loss of PTSD diagnosis and full remission of PTSD (for both CAPS-5 < 20 and CAPS-5 < 12) from logistic regression analyses to compare the addition of three different PTSD treatments to SUD treatment with SUD treatment alone at the 3-month follow-up.

	SUD + PE (n = 53)	SUD + EMDR (n = 50)	SUD + ImRs (n = 55)	SUD only (n = 51)
Primary analysis (MI)				
Loss of diagnosis, %	65.8	66.4	69.8	41.4
Still PTSD, %	34.2	33.6	30.2	58.6
NNT	4.1	4	3.52	NA
Unadjusted analysis				
OR [95% CI]	2.74 [1.14, 6.55]	2.81 [1.15, 6.88]	3.29 [1.40, 7.73]	NA
P	0.026	0.026	0.008	NA
Adjusted analysis ^a				
OR [95% CI]	3.26 [1.20, 8.81]	4.42 [1.51, 12.97]	4.39 [1.54, 12.47]	NA
P	0.023	0.008	0.007	NA
Sensitivity analysis (LOCF) ^b				
Loss of diagnosis, %	54.7	58	63.6	37.3
Still PTSD, %	13.2	18	20	51
Loss to follow-up, %	32.1	24	16.4	11.8
NNT	5.73	4.82	3.79	NA
Unadjusted analysis				
OR [95% CI]	2.04 [0.93, 4.49]	2.33 [1.05, 5.17]	2.95 [1.34, 6.49]	NA
P	0.076	0.038	0.007	NA
Adjusted analysis ^a				
OR [95% CI]	2.36 [0.96, 6.00]	3.66 [1.44, 9.98]	3.97 [1.54, 11.00]	NA
P	0.064	0.008	0.006	NA
Primary analysis (MI)				
Full remission, %	45.9	52.4	63.9	25.7
No full remission, %	54.1	47.6	36.1	74.3
NNT	4.95	3.75	2.62	NA
Unadjusted analysis CAPS < 20				
OR [95% CI]	2.45 [1.06, 5.64]	3.17 [1.37, 7.37]	5.12 [2.21, 11.85]	NA
P	0.039	0.008	<0.001	NA
Unadjusted analysis CAPS < 12				
OR [95% CI]	2.77 [1.08, 7.12]	3.30 [1.28, 8.50]	3.07 [1.21, 7.81]	NA
P	0.037	0.015	0.020	NA
Adjusted analysis CAPS < 20 ^a				
OR [95% CI]	2.90 [1.13, 7.48]	5.73 [2.02, 16.23]	9.57 [3.20, 28.62]	NA
P	0.030	0.001	<0.001	NA
Adjusted analysis CAPS < 12 ^a				
OR [95% CI]	3.36 [1.17, 9.64]	4.61 [1.58, 13.50]	6.23 [1.91, 20.32]	NA
P	0.026	0.006	0.003	NA
Sensitivity analysis (LOCF) ^b				
Full remission, %	45.3	52	63.6	25.5
No full remission, %	22.6	24	20	62.7
Loss to follow-up, %	32.1	24	16.4	6 (11.8)
NNT	5.05	3.77	2.62	NA

TABLE 3 (Continued)

	SUD + PE (n = 53)	SUD + EMDR (n = 50)	SUD + ImRs (n = 55)	SUD only (n = 51)
Unadjusted analysis CAPS < 20				
OR [95% CI]	2.42 [1.06, 5.55]	3.17 [1.37, 7.33]	5.12 [2.22, 11.80]	NA
<i>P</i>	0.037	0.007	<0.001	NA
Unadjusted analysis CAPS < 12				
OR [95% CI]	2.76 [1.07, 7.11]	3.29 [1.28, 8.49]	3.07 [1.21, 7.81]	NA
<i>P</i>	0.035	0.014	0.019	NA
Adjusted analysis CAPS < 20 ^a				
OR [95% CI]	2.87 [1.14, 7.58]	5.74 [2.12, 17.24]	9.66 [3.44, 31.31]	NA
<i>P</i>	0.028	<0.001	<0.001	NA
Adjusted analysis CAPS < 12 ^a				
OR [95% CI]	3.36 [1.17, 9.64]	4.60 [1.57, 13.46]	6.23 [1.91, 20.32]	NA
<i>P</i>	0.024	0.005	0.002	NA

Abbreviations: AUDIT, Alcohol Use Disorder Identification Test; CI, confidence interval; DUDIT, Drug Use Disorder Identification Test; EMDR, eye movement desensitization and reprocessing; ImRs, imagery rescripting; LOCF, last observation carried forward; MI, multiple imputation; NA, not applicable; NNT, numbers needed to treat; OR, odds ratio; PE, prolonged exposure; PTSD, post-traumatic stress disorder; SUD, substance use disorder. Significant findings are shown in bold.

^aModels adjusted for age, sex, site, CAPS-5 baseline, AUDIT baseline and DUDIT baseline.

^bIn the sensitivity analysis, loss to follow-up was counted as still PTSD/no full remission.

analyses (with the last observation carried forward), in both the adjusted as well as the unadjusted models, only EMDR and ImRs significantly outperformed SUD treatment alone, whereas PE did not.

As shown in Table 3, in both the unadjusted as well as the adjusted model of the primary analysis (with multiple imputed data), participants in the PE, EMDR and ImRs groups were more likely to achieve full remission at the 3-month follow-up than participants in the group with SUD treatment alone. Similar results were found in the sensitivity analyses (with the last observation carried forward). We found no significant effects of adding PE, EMDR or ImRs to SUD treatment on reducing alcohol and drug use problems in the primary analyses, nor in any of the sensitivity analyses (see Table 4).

DISCUSSION

This is the first study that examined three trauma-focused PTSD treatments in a population with SUD and co-occurring PTSD seeking treatment for SUD. Additionally, this is the first study in which both EMDR and ImRs were evaluated for effectiveness in this population in an adequately powered RCT.

First and foremost, in line with our hypothesis, we found that adding trauma-focused PTSD treatment to SUD treatment is more effective than offering SUD treatment alone in reducing PTSD symptoms at the 3-month follow-up. For PE, however, findings were somewhat inconsistent, with mixed findings across unadjusted and adjusted models and sensitivity analyses. This aligns with earlier research on PE, where different studies report varying results, with small effect sizes and high dropout rates [3–5]. One explanation for

the mixed results for PE may be that this group has the highest drop-out rate. Our study was the first large RCT to test the effectiveness of EMDR and ImRs to treat PTSD in patients with PTSD and SUD. For both treatments, we found robust evidence that adding EMDR or ImRs to SUD treatment was superior to SUD treatment alone in reducing PTSD symptoms, with significant results across all sensitivity analyses. In addition, both EMDR and ImRs were superior to SUD treatment alone on the secondary outcomes of loss of PTSD diagnosis and full remission. For EMDR, these findings are in line with previous pilot studies [10, 11]. For ImRs, these are new findings, but the results are in line with previous research where ImRs proved to be an effective treatment method for patients without SUD [12]. Based on these findings, EMDR and ImRs seem particularly suitable to treat PTSD in this patient group.

Although in a prior meta-analysis solely trauma-focused PTSD treatment did not outperform solely manualized SUD treatment [4], we hypothesize that the combined working mechanisms of both therapies together might potentially enhance the effect of the individual treatments, making it more effective than either treatment alone. This is also in line with the systematic review and meta-analysis of Roberts *et al.* (2022), in which trauma-focused PTSD treatment was offered alongside SUD treatment [3].

Additionally, following the therapist rotation model [16], with sessions held twice a week, might also contributed to the positive results of this study. Moreover, the attendance of sessions twice a week might be easier for inpatient SUD treatment than for outpatient SUD treatment. As most other studies focus only on outpatient SUD treatment, the inclusion in our study of outpatient, day treatment and inpatient SUD treatment might also have contributed to the more

TABLE 4 Results on the secondary outcomes of AUDIT and DUDIT scores from regression analyses to compare the addition of three different PTSD treatments to SUD treatment with SUD treatment alone at the 3-month follow-up.

	SUD + PE (n = 53)	SUD + EMDR (n = 50)	SUD + ImRs (n = 55)	SUD only (n = 51)
Primary analysis (MI)				
AUDIT sum score, mean (SD)	10.01 (11.59)	9.73 (10.81)	7.59 (10.14)	11.87 (11.98)
Baseline score, mean (SD)	15.51 (12.19)	14.14 (11.24)	12.98 (12.36)	20.25 (12.84)
Unadjusted analysis ^a				
B (SE)	-0.70 (2.83)	0.01 (2.48)	-1.95 (2.33)	NA
95% CI of B, upper, lower	[-6.37, 4.98]	[-4.93, 4.95]	[-6.59, 2.69]	NA
P	0.807	0.997	0.406	NA
Adjusted analysis ^b				
B (SE)	-0.13 (2.81)	0.29 (2.50)	-2.04 (2.34)	NA
95% CI of B, upper, lower	[-5.77, 5.50]	[-4.70, 5.28]	[-6.70, 2.62]	NA
P	0.962	0.908	0.386	NA
Sensitivity analysis 1 (LOCF)				
AUDIT sum score, mean (SD)	8.98 (9.79)	8.06 (7.70)	7.0 (8.62)	12.43 (11.80)
Baseline score, mean (SD)	15.51 (12.19)	14.14 (11.24)	12.98 (12.36)	20.25 (12.84)
Unadjusted analysis ^a				
B (SE)	-1.45 (1.90)	-1.55 (1.71)	-2.31 (1.78)	NA
95% CI of B, upper, lower	[-5.21, 2.31]	[-4.94, 1.85]	[-5.83, 1.22]	NA
P	0.446	0.368	0.197	NA
Adjusted analysis ^b				
B (SE)	-0.80 (1.91)	-1.24 (1.76)	-2.19 (1.83)	NA
95% CI of B, upper, lower	[-4.59, 2.99]	[-4.73, 2.24]	[-5.83, 1.44]	NA
P	0.675	0.480	0.233	NA
Sensitivity analysis 2 (CCA) ^c				
AUDIT sum score, mean (SD)	6.94 (7.51)	7.76 (7.92)	5.67 (7.33)	11.09 (11.26)
Baseline score, mean (SD)	15.51 (12.19)	14.14 (11.24)	12.98 (12.36)	20.25 (12.84)
Unadjusted analysis ^a				
B (SE)	-3.17 (2.06)	-1.57 (1.88)	-2.95 (1.83)	NA
95% CI of B, upper, lower	[-7.28, 0.94]	[-5.32, 2.17]	[-6.59, 0.70]	NA
P	0.128	0.406	0.112	NA
Adjusted analysis ^b				
B (SE)	-2.06 (2.06)	-1.34 (1.92)	-2.74 (1.86)	NA
95% CI of B, upper, lower	[-6.17, 2.04]	[-5.16, 2.48]	[-6.44, 0.95]	NA
P	0.320	0.487	0.144	NA
Primary analysis (MI)				
DUDIT sum score, mean (SD)	9.52 (10.75)	9.07 (10.05)	8.67 (10.57)	8.03 (9.79)
Baseline score, mean (SD)	19.57 (13.45)	18.08 (13.61)	20.31 (13.83)	14.04 (12.35)
Unadjusted analysis ^a				
B (SE)	0.00 (2.36)	-0.20 (2.23)	-1.38 (2.05)	NA
95% CI of B, upper, lower	[-4.72, 4.72]	[-4.66, 4.26]	[-5.47, 2.71]	NA
P	1.000	0.929	0.503	NA
Adjusted analysis ^b				
B (SE)	0.34 (2.38)	-0.47 (2.23)	-1.39 (2.09)	NA
95% CI of B, upper, lower	[-4.43, 5.10]	[-4.92, 3.99]	[-5.54, 2.77]	NA
P	0.887	0.835	0.508	NA

TABLE 4 (Continued)

	SUD + PE (n = 53)	SUD + EMDR (n = 50)	SUD + ImRs (n = 55)	SUD only (n = 51)
Sensitivity analysis 1 (LOCF)				
DUDIT sum score, mean (SD)	12.40 (13.40)	10.58 (12.29)	10.87 (12.77)	7.94 (9.77)
Baseline score, mean (SD)	19.57 (13.45)	18.08 (13.61)	20.31 (13.83)	14.04 (12.35)
Unadjusted analysis ^a				
B (SE)	1.32 (1.86)	0.37 (1.69)	-0.12 (1.90)	NA
95% CI of B, upper, lower	[-2.36, 5.00]	[-2.99, 3.72]	[-3.89, 3.66]	NA
P	0.478	0.828	0.952	NA
Adjusted analysis ^b				
B (SE)	1.71 (1.85)	0.36 (1.75)	-0.20 (1.97)	NA
95% CI of B, upper, lower	[-1.97, 5.39]	[-3.22, 3.73]	[-4.11, 3.70]	NA
P	0.359	0.883	0.918	NA
Sensitivity analysis 2 (CCA) ^c				
DUDIT sum score, mean (SD)	6.97 (8.30)	7.74 (8.53)	7.28 (9.38)	7.42 (9.13)
Baseline score, mean (SD)	19.57 (13.45)	18.08 (13.61)	20.31 (13.83)	14.04 (12.35)
Unadjusted analysis ^a				
B (SE)	-1.48 (1.78)	-0.97 (1.66)	-1.51 (1.77)	NA
95% CI of B, upper, lower	[-5.02, 2.05]	[-4.28, 2.34]	[-5.02, 2.00]	NA
P	0.407	0.561	0.396	NA
Adjusted analysis ^b				
B (SE)	-0.88 (1.73)	-1.17 (1.70)	-1.76 (1.80)	NA
95% CI of B, upper, lower	[-4.34, 2.57]	[-4.55, 2.21]	[-5.30, 1.78]	NA
P	0.612	0.492	0.325	NA

Abbreviations: AUDIT, Alcohol Use Disorder Identification Test; CAPS, clinician-administered PTSD scale; CCA, complete case analysis; CI, confidence interval; DUDIT, Drug Use Disorder Identification Test; EMDR, eye movement desensitization and reprocessing; ImRs, imagery rescripting; LOCF, last observation carried forward; MI, multiple imputation; NA, not applicable; PE, prolonged exposure; PTSD, post-traumatic stress disorder; SD, standard deviation; SE, standard error; SUD, substance use disorder.

^aOnly adjusted for baseline score of outcome variable (AUDIT/DUDIT).

^bModels adjusted for age, sex, site, CAPS-5 baseline, AUDIT baseline and DUDIT baseline.

^cIncluding only participants with complete data on follow-up: $n = 36$ for SUD + PE; $n = 38$ for SUD + EMDR; $n = 46$ for SUD + ImRs; $n = 44$ for SUD alone.

favorable results. This aligns with Coffey's study, which also included inpatient SUD treatment and found higher-than-usual treatment completion rates for PE and medium effect sizes [7]. However, our study especially demonstrates the effectiveness of EMDR and ImRs as therapies for PTSD in patients with PTSD and SUD. Possibly, the less challenging nature of these two therapy forms may have contributed to this finding [16, 34]. Nevertheless, in line with the findings of Simpson [4], the PTSD symptoms also decreased in the manualized SUD-only group. An explanation for this result could be that SUD treatment also addresses negative emotions, cognitions and behaviors that at least partially overlap with PTSD symptoms (such as revoking the avoidance of negative emotions by drinking/using drugs). Besides, SUD treatment also consists of non-specific therapy factors that potentially contribute to this result [35]. Finally, participation in the study with repeated assessments could have served as concealed forms of exposure.

With regards to our secondary outcome of SUD severity, we found no significant differences between adding PTSD treatment to SUD treatment. Compared with manualized SUD treatment alone,

these findings largely overlap with previous research, which generally found no effect of PTSD treatment on SUD symptoms, with only the exception favoring PTSD treatment over SUD treatment at 6–12 months [3]. It is, nevertheless, imperative to highlight that, in this aforementioned meta-analysis, this advantage was coupled with a reduction in PTSD severity. Therefore, they argued that this outcome could potentially be elucidated by a 'reduced need to self-medicate' [3].

Strengths and limitations

This study has several strengths. First, this is the first study to compare the addition of three trauma-focused PTSD treatments as an add-on to SUD treatment with SUD treatment alone. As this study used a large sample size, minimal exclusion criteria, the inclusion of a socio-economically diverse sample with limited loss to follow-up and implemented established protocols for PTSD treatment, the results are generalizable to daily clinical practice. Furthermore, our

results can challenge the preconceptions about excluding patients with SUD in research into PTSD, as our findings show that PTSD treatment is indeed effective in this group of patients.

There are also some limitations. Owing to the COVID-19 pandemic, temporary changes were required for treatment and assessments. Face-to-face interventions were temporarily prohibited at the treatment facility and replaced by video calls. Although no alterations were made to the established treatment protocol and internet-delivered PTSD treatment appears to be promising [36], possible effects of the pandemic on treatment results cannot be ruled out. Another limitation is the fact that the SUD-only group received less therapy and attention compared with the groups that also received PE, EMDR or ImRs treatment. It therefore cannot be ruled out that the positive effect of adding PTSD treatment may be partly explained by the additional attention these groups received, rather than being solely attributable to the PTSD session itself. Moreover, our SUD-only group is not entirely comparable with SUD-only groups from other studies, as our group had the expectation of receiving PTSD treatment later. Also, for the analyses in this article we only looked at the 3-month follow-up, and so we cannot comment on the long-term effects. Furthermore, this study selected a few effective trauma-focused PTSD treatment forms. Other trauma-focused PTSD treatments, such as cognitive processing therapy [37], were not included in the current study. Therefore, we cannot rule out the possibility that other trauma-focused PTSD treatments may be more effective for addiction than the therapies examined in this study. Neither did we examine pharmacological treatments, as they were beyond the scope of our study. However, a recent meta-analysis shows that combining trauma-focused therapy with alcohol-targeted medication outperforms standard treatment [38]. Finally, our study included a variety of SUD treatment intensities, making our results more difficult to compare with studies that have focused solely on manualized 12-week CBT for SUD. On the other hand, this can also be seen as a strength of the study: it reflects real-world practice and demonstrates that PTSD treatment can also be beneficial for individuals who require the most intensive SUD care.

CONCLUSIONS AND CLINICAL IMPLICATIONS

In conclusion, this study indicates that trauma-focused PTSD treatment as an add-on to SUD treatment is significantly more effective in decreasing PTSD severity compared with manualized SUD treatment alone. It is the first study to demonstrate the effectiveness of EMDR and ImRs as PTSD treatment for patients with SUD and PTSD. Furthermore, PTSD treatment does not enhance SUD outcomes. This pioneering study underscores the importance of investigating not only PE but also EMDR and ImRs, suggesting that future research should focus on these treatments rather than solely on PE. Moreover, all three treatment types should be considered as first line treatment options for PTSD in patients with SUD and PTSD. We advocate offering PTSD treatment alongside SUD treatment and recommend shared

decision-making for treatment type. Patients' preferences, prior drop-out experiences and therapist or institutional treatment options should be taken into account.

AUTHOR CONTRIBUTIONS

Sera Lortye: involved in the development of the study protocol; responsible for data collection, access and verification of the data; involved in statistical analyses; drafting the main body of the article; revising the article following feedback. **Joanne P. Will:** involved in the development of the study protocol; responsible for data collection; provided critical revision of the article. **Loes A. Marquenie:** involved in the development of the study protocol; involved in funding acquisition; responsible for management of the Amsterdam location; provided critical revision of the article. **Nick M. Lommerse:** involved in the curation, access and verification of the data; provided critical revision of the article. **Nathalie Faber:** involved in data collection; provided critical revision of the article. **Anna E. Goudriaan:** involved in the development of the study protocol; involved in funding acquisition; provided critical revision of the article. **Arnoud Arntz:** involved in the initial conceptualization and design of the study; involved in funding acquisition; provided critical revision of the article. **Marleen M. de Waal:** involved in the initial conceptualization and design of the study; involved in funding acquisition; involved in the development of the study protocol; access and verification of the data; involved in statistical analyses; involved in writing the article; provided critical revision of the article. All authors have read and approved the final version for publication.

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DECLARATION OF INTERESTS

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are not publicly available because they contain information that could compromise the privacy of research participants but are available from the corresponding author (M.M. de Waal, m.m.dewaal@amsterdamumc.nl), upon reasonable request, after the completion of this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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