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A Multicenter Phase II Rater-Blinded Randomized Controlled Trial to Compare the Effectiveness of Eye Movement Desensitization Reprocessing Therapy vs. Treatment as Usual in Patients With Substance Use Disorder and History of Psychological Trauma: A Study Design and Protocol

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Background: Psychological trauma has a strong negative impact on the onset, course and prognosis of substance use disorders (SUD). Few trauma-oriented treatment approaches have been trialed, but preliminary evidence exists of the efficacy of Eye Movement Desensitization and Reprocessing (EMDR) therapy in improving clinical symptoms in SUD patients.

Objective: To assess if EMDR therapy leads to: (1) reduced substance consumption; (2) an improvement in psychopathological and in trauma-related symptoms; and (3) an improvement in overall functioning. Our hypothesis is that the EMDR group will improve in all variables when compared to the treatment as usual (TAU) group at 6 and 12-months visits.

Method: In this multicenter phase II rater-blinded randomized controlled trial, 142 SUD patients with a history of psychological trauma will be randomly assigned to EMDR (n = 71) or to TAU (n = 71). Patients in the EMDR group will receive 20 psychotherapeutic sessions of 60 min over 6 months. Substance use will be measured using the Timeline Followback Questionnaire, the Dependence Severity Scale and the Visual Analog Scale.

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Traumatic events will be measured by The Holmes-Rahe Life Stress Inventory, the Childhood Trauma Questionnaire Scale, the Global Assessment of Posttraumatic Stress Questionnaire, the Impact of Event Scale-Revised and the Dissociative Experiences Scale. Clinical symptomatology will be evaluated using the Hamilton Depression Rating Scale, the Young Mania Rating Scale and the Brief Psychiatric Rating Scale. Functionality will be assessed with the Functioning Assessment Short Test. All variables will be measured at baseline, post-treatment and 12 months as follow-up. Primary outcome: to test the efficacy of EMDR therapy in reducing the severity of substance use. The secondary outcomes: to test the efficacy in reducing trauma-related psychological symptoms and psychopathological symptoms and in improving overall functioning in patients with comorbid SUD and a history of psychological trauma.

Conclusion: This study will provide evidence of whether EMDR therapy is effective in reducing addiction-related, trauma and clinical symptoms and in improving functionality in patients with SUD and a history of trauma.

Clinical Trial Registration: The trial is registered at ClinicalTrials.gov, identifier: NCT03517592.

Keywords: substance use disorder, addiction, psychological trauma, comorbidity, EMDR therapy, treatment as usual

INTRODUCTION

Substance use disorders (SUD) represent an important social and public health problem due to their negative consequences in terms of delinquency, family disintegration, academic and occupational disengagement, mental illness, transmission of infectious diseases, intoxication, and mortality rates (1). One significant risk factor for problematic alcohol and substance use is the presence of multiple adverse childhood events, as shown by a recent meta-analysis in the Lancet (2). Different studies have found that between 66 and 97.4% of SUD patients have experienced Criterion A traumatic events according to DSM IV criteria (3–7), and the prevalence of post-traumatic stress disorder (PTSD) in inpatients with SUD is estimated to range from 25–51%, two to four times more than general population rates ranging from 1.3 to 12.3% (8). Even adverse events not meeting PTSD Criterion A have an important impact in the course of the disorder because they have been shown to be associated with substance use outcomes (2).

In order to clarify the difference between psychological trauma, PTSD and subthreshold PTSD, we will provide a brief definition of them. Psychological trauma is a term that refers to any life event that causes discomfort to the subject and exceeds an individual's abilities to integrate the emotions involved with the experience (9). The term PTSD refers to, based on DSM-V criteria (10), exposure to actual or threatened death, serious injury, or sexual violence, accompanied by the presence of the following trauma-related symptoms: intrusion, persistent avoidance of stimuli, negative alterations in cognitions and mood and marked alterations in arousal and reactivity. Symptoms must have a duration of more than 1 month and cause clinically significant distress or impairment in the patient's overall functioning, and not be attributable to the physiological effects of a substance or another medical condition (10). Finally, the term subthreshold PTSD should be used when the clinical presentation does not meet all criteria for PTSD diagnosis.

A large study into populations addicted to alcohol and various illicit drugs found that PTSD and subsyndromal PTSD were correlated with addiction severity, a worse disease prognosis, more hospital admissions, poorer response to treatment, shorter periods of abstinence and greater craving (4). These characteristics make this specific population difficult to treat. In addition, trauma is highly prevalent in patients with severe mental disorders (SMDs) such as depression, bipolar disorder or psychosis, where PTSD and SUD are frequently comorbid and negatively influence the course of mental illness (11, 12). In some cases, disease course is worsened by a high prevalence of trauma-related dissociative symptoms (13). These findings suggest psychological trauma should be assessed in SUD and in dual pathology patients and be included as an objective of the treatment plan (12, 14).

Along these lines, even though pharmacological treatment such as selective serotonin reuptake inhibitors, atypical antipsychotics and benzodiazepines have demonstrated a limited efficacy in the treatment of PTSD and psychological trauma, some drugs such as prazosin could be a promising strategy to consider in adjuvant treatment with the psychological approach, given the positive results shown in specific PTSD symptoms as reported the meta-analysis of Berardis et al. (15).

TABLE 1 | SPIRIT flow diagram: schedule of enrolment, interventions, and assessments.

	Study period				
	Enrolment	Allocation	Post-allocation		Close-out
TIMEPOINT	$-t_1$ & t_0	0	t_1	t_2	T_3
ENROLMENT					
Eligibility screen	X				
PRISM	X				
MINI	X				
HDRS	X			X	X
YMRS	X			X	X
BPRS	X			X	X
TLFB	X		X	X	X
SDS	X		X	X	X
EVA	X		X	X	X
CTQ	X				
H-RLSI	X				
EGEP	X			X	X
IES-R	X			X	X
DES	X			X	X
Informed consent	X				
Allocation		X			
INTERVENTIONS					
EMDR					
TAU					
ASSESSMENTS					
FAST	X			X	X

PRISM, Psychiatric Research Interview for Substance and Mental Disorders; MINI, Mini-International Neuropsychiatric Interview; HDRS, Hamilton Depression Rating Scale; YMRS, Young's scale for the evaluation of the Mania; BPRS, Brief Scale of Psychiatric Evaluation; TLFB, Timeline Followback; SDS, Dependence severity scale; EVA, Analog visual scale; CTQ, Childhood Trauma Questionnaire; H-RLSI, The Holmes-Rahe Life Stress Inventory; EGEP, Global Assessment of Posttraumatic Stress Questionnaire; IES-R, Scale of the impact of events reviewed; DES, Scale of Dissociative Experiences; EMDR, Eye movement desensitization and reprocessing therapy; TAU, Treatment as usual; FAST, Functioning Assessment Short Test.

A recent Cochrane review into the efficacy of CBT-based therapies for comorbid SUD and PTSD found that preliminary evidence showed that trauma-focused therapy delivered alongside SUD therapy could improve PTSD symptoms at short- and long-term, and SUD symptoms at long-term, compared to treatment as usual. They concluded that more research is needed on trauma-focused therapies for this population, but that there is very little evidence to support individual therapies not focused on trauma (16).

One leading trauma-focused treatment is Eye Movement Desensitization and Reprocessing (EMDR) therapy, recommended as a first-line PTSD treatment by international bodies such as the American Psychiatric Association (APA) (17) and the World Health Organization (WHO) (18). Initial studies have shown the potential for EMDR to be applied to the SUD population. Until nowadays, there are three published trials in SUD and EMDR: two small randomized controlled trials (RCT) and one non-randomized controlled trial of EMDR vs. treatment as usual (TAU) in patients with SUD (19–21). They have suggested that EMDR, compared to the control group, significantly improves craving (19), depression, anxiety, self-esteem (19, 20), and dissociative symptoms (21), but results must be repeated with larger samples. A large scale RCT is currently underway (22) to determine the efficacy of EMDR in reducing PTSD symptoms in an inpatient sample with comorbid SUD and PTSD or sub-threshold PTSD.

In the current study, we aim to carry out the first large RCT into the impact of EMDR on SUD symptoms in outpatients (with or without comorbid SMDs) with a history of psychological trauma. This is groundbreaking in, firstly, focusing on addiction outcomes instead of PTSD symptoms as a primary outcome and, secondly, in including all patients showing trauma-associated symptoms, even if they do not fulfill PTSD or subsyndromal PTSD criteria.

Additionally, EMDR is an interesting psychotherapeutic tool for this population due to its potential to improve the course of comorbid SMDs, where strong preliminary evidence also shows EMDR to be a promising treatment beyond PTSD (23), such as in bipolar disorder (24), or psychosis (25), as well as in depression (26, 27) and anxiety (28–30). The evidence that EMDR is efficacious in these kind of patients will help facilitate its application in complex real-world settings.

METHODS

This is a multicenter phase II rater-blinded randomized controlled trial, phase II, with two parallel branches, EMDR and TAU, of patients diagnosed with SUD who have a comorbid history of psychological trauma, even if they do not currently meet DSM-V criteria for PTSD. The patients will be matched by site, age, sex, and diagnosis. One group will consist of TAU plus 20 individual 60-min EMDR sessions over a duration of 6 months, while the other group will receive TAU only. Patients will be evaluated at baseline (T0), 3 months (T1: only substance use-related symptoms), post-treatment at 6 months (T2), and at 12 months as follow-up (T3) (see **Table 1**). Clinical raters carrying out evaluations will be blind to the participants' research condition. Patients will not be blind to treatment as a sham alternative to EMDR therapy is impossible due to its use of bilateral stimulation.

The study has been approved by the Ethic Committees of the Hospital Benito Menni, Germanes Hospitalàries del Sagrat Cor de Jesús (PR-2018-04), and the IMIM, Parc de Salut Mar (2017/7615/I). All participants will sign informed consent prior to enrollment. Details of the trial design can be also gathered from **Supplementary Material** (Standard Protocol Items: Recommendations for Interventional Trials [SPIRIT] Checklist).

This is a multicenter phase II collaborative project will involve the participation of five different centers from the Barcelona catchment area, Spain: four outpatient addiction clinics pertaining to the Institute of Neuropsychiatry and Addictions (INAD), Parc de Salut Mar, and a fifth pertaining to the Hospital Benito Menni, in Sant Boi de Llobregat. Both institutions involved are centers of reference in mental

health treatment and research, facilitating the recruitment and development of the project. EMDR therapists have extensive experience in EMDR protocols and SUD. All participating raters will be trained in the blind-to-treatment application of all clinical assessments.

Study Outcomes

The primary outcome is to test the efficacy of EMDR therapy in reducing the severity of substance use in patients with comorbid SUD and a history of psychological trauma, irrespective of whether the patient meets DSM-V PTSD criteria. Changes from baseline in the severity of substance use are measured by the Timeline Follow Back (TLFB) (31), the Severity of Dependence Scale (SDS) (32), and the Visual Analog Scale (VAS).

The secondary outcome is to test the efficacy of EMDR in improving trauma-related psychological symptoms, psychopathological symptoms, and the overall functionality in SUD patients with a history of psychological trauma. Changes in psychological trauma and dissociative symptoms are measured using the Global Assessment of Posttraumatic Stress Questionnaire (EGEP-5) (33), the Impact of Event Scale-Revised (IES-R) (34), and the Dissociative Experiences Scale (DES) (35), respectively. The type and severity of traumatic experiences are measured using the Childhood Trauma Questionnaire (CTQ) (36) and The Holmes-Rahe Life Stress Inventory (37). Changes in psychopathological symptoms are measured by the Hamilton Depression Rating Scale (HDRS) (38), Young Mania Rating Scale (YMRS) (39), and the Brief Psychiatric Rating Scale (BPRS) (40). Changes in overall functioning will be measured using the Functioning Assessment Short Test (FAST) (41).

Hypotheses

1. Patients in the EMDR group will show a reduction in the level and severity of substance use-related symptoms as compared to the TAU group.
2. Patients in the EMDR group will show a reduction in the number of relapses as compared to the TAU group.
3. Patients in the EMDR group will show a reduction in the severity of trauma-related symptoms as compared to the TAU group.
4. There will be a reduction in depressive symptoms associated with a comorbid psychiatric disorder in the EMDR group as compared to the TAU group.
5. There will be a reduction in (hypo) manic symptoms associated with a comorbid psychiatric disorder in the EMDR group as compared to the TAU group.
6. There will be a reduction in general psychopathology symptoms associated with psychiatric comorbidity in the EMDR group as compared to the TAU group.
7. Patients in the EMDR group will show an improvement in functioning as compared to the TAU group.

Study Participants

The study sample will consist of 142 outpatients fulfilling the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), for SUD based on a clinical interview (Psychiatric Research Interview for Substance and Mental Disorders; PRISM) (42) and a review of case notes.

Inclusion criteria are: (1) aged 18–65, (2) outpatient, and (3) presence of one or more traumatic events currently causing trauma-associated symptoms (Impact of Events Scale-Revised, IES-R > 0) and Subjective Disturbance Unit (SUD) > 5, that assesses subjective disturbance in a scale between 0 and 10, but it is not necessary that traumatic events meet DSM-5 criteria for PTSD.

Exclusion criteria are: (1) presence of organic brain diseases, (2) presence of acute suicidal ideation, (3) having received a trauma-focused therapy or attended psychotherapeutic groups for survivors of violence within the last 2 years, or (4) acute episode of comorbid psychiatric disorder.

Randomization Procedure

Clinical trials use randomization to balance confounding factors (to an uncontrolled extent) and to conceal allocation. However, complete randomization in small to moderate studies may fail to balance groups, severely affecting inference. To overcome this issue Efron (43) introduced the biased coin methods, which randomize each patient to one or the other group with a probability or another with the aim of increasing the balance of known confounding factors. Importantly, these methods still randomize each of the patients, thus balancing the unknown confounding factors (to the uncontrolled extend that complete randomization does) and concealing allocation (44). Non-deterministic dynamic allocation designs, such as the biased coin methods, were included in international guidelines for drug clinical trials (45) adopted by the European Community, Japan, United States FDA, Canada and Switzerland (Implementation of E9 Statistical Principles for Clinical Trials. URL: https://www.ich.org/products/guidelines/efficacy/efficacy-single/article/statistical-principles-for-clinical-trials.html).

In this trial, all patients meeting the inclusion criteria will receive the baseline (T0) assessment. After T0, participants will be assigned to the EMDR or TAU group following a biased coin procedure (46): (1) the first two patients will be randomly allocated to EMDR with $p = 0.5$, (2) the next patient will be allocated as follows: (b1) if one group already includes at least two more patients than the other group, the patient will be randomly allocated to EMDR with $p = 0.8$ is this is the smallest group and with $p = 0.2$ if it is the largest group, (b2) otherwise, we will first simulate that the patient is allocated to EMDR and calculate the sum of the between-group square standardized differences in site, age, sex, diagnosis (dual vs. not dual) and number of substances consumed during the month before the randomization (none. one or more than one), we will then simulate that the patient is allocated to TAU and recalculate the sum, and finally randomly allocate the patient to EMDR with $p = 0.8$ if this was associated to the smallest sum and with $p = 0.2$ if not. For example, if we had already included 10 patients to the EMDR group and 8 patients to the TAU group, the 19th patient would be randomly allocated with $p = 0.2$ for EMDR and $p = 0.8$ for TAU. If he/she was allocated to TAU, for the 20th patient we would calculate the above sum of covariates after simulating that the he/she is allocated to EMDR and after simulating that he/she is

allocated to TAU, and if the sum of the EMDR simulation was larger than the sum of the TAU simulation, we would randomly allocate the 20th patient with $p = 0.2$ for EMDR and $p = 0.8$ for TAU. Following this procedure, the final groups should be balanced in size and matched in site, age, sex and diagnosis. All steps of the randomization process will be automatically carried out by an independent researcher in a central location using a computer program.

Computation of Sample Size

The study aims to assess the efficacy of EMDR therapy compared with TAU, in inpatients with SUD, in terms of a reduction in substance use, a reduction in symptoms associated with craving and associated symptoms of anxiety and depression, and an improvement in functioning.

We aim for the study to be able to detect medium-sized differences in the pre-post changes between groups with an 80% statistical power. Given that there are no previous studies that report the variability of these changes, we have defined medium-sized differences as those with a medium effect size ($d = 0.5$). With the function power.t.test from R (http: //www.r-project.org/), we have calculated that the number of patients required to detect medium-sized differences ($d = 0.5$) with a statistical power of 80% is $n = 64$ per intervention group (two groups, total $n = 128$). Assuming a loss percentage of approximately 10% of the patients in the study, it would be necessary to recruit approximately 142 patients, 71 for each intervention branch.

Statistical Analysis

The distribution of socio-demographic and clinical characteristics between groups in the baseline state will be summarized using descriptive statistics. The change in clinical and functional variables with regard to baseline evaluation at strategic points of the intervention will be analyzed using mixed-effects repeated-measures linear models, including as fixed factors time, treatment conditions and their interactions, and as a random factor the site. The differences between groups, for the categorical variables and main clinics, will be analyzed by adding covariates to the models. Those covariates that are statistically significant may be added in the same model to determine which covariates are best predictors of the response. The size of the effects will be estimated using the g of Hedges or the r of Pearson. It will be corrected for multiple comparisons. The statistical software used for the analysis will be the latest available version of R. We will conduct an intention to treat (ITT) analysis. The "Last Observation Carried Forward" (LOCF) method will be used for losses of follow-up.

STEPWISE PROCEDURES

Intervention

EMDR

Patients in the EMDR condition will receive 20 individual sessions of 60 min each, using the standard EMDR therapy protocol developed by Shapiro (47) and a further specific protocol for SUD, the CRAVEX protocol, developed by Hase (48) to treat both trauma-related symptoms and SUD symptoms, respectively.

The current standard protocol includes eight phases, briefly described below:

1. Patient history: The therapist assesses the patient's attachment history, medical history, physical problems and identifies traumatic events and their relationship to current symptoms. A treatment plan is developed.
2. Patient preparation: A safe therapeutic environment is established, the theory and processes of EMDR are explained, and the therapist may try out different modalities of bilateral stimulation, including eye movements, where the patient's eyes follow the therapist's fingers moving in horizontally or diagonally across their field of vision. While eye movements are generally recommended, if they are not well-tolerated, another modality, such as tapping the back of the patient's hands or auditory tones, may be used.
3. Patient assessment: The therapist helps the patient to bring the traumatic memory to mind and identify associated cognitions, emotions and physical sensations. The patient identifies the image which represents the worst part of the traumatic memory and an associated negative cognition, and is helped to identify a positive cognition to replace this. Finally, the patient identifies the distress level they experience upon bringing the traumatic experience and negative cognition to mind. Distress is measured using the Subjective Units of Disturbance Scale (SUD), scored from 0 (minimum disturbance) to 10 (maximum disturbance).
4. Memory desensitization: The patient brings to mind the traumatic image, negative cognition and associated emotion and notices any physical discomfort generated in the present moment. The patient focuses on this material and a 30–40 s set of bilateral stimulation is applied, during which the patient is instructed to observe what is happening without judgment, and afterwards express what occurred. The therapist asks the patient to focus on new material without comment, assessment, or interpretation. This is repeated until no new material arises and the traumatic memory generates no distress (SUD = 0 or 1).
5. Installing the positive cognition: The patient brings the positive cognition and original experience to mind. Further sets of bilateral stimulation are applied, causing the patient to link the positive cognition with the original memory, until the positive belief is fully installed.
6. Body scan: The therapist asks the patient to close their eyes and focus on the original experience and positive cognition, and to notice if any sensation arises. If a negative or uncomfortable sensation is reported, the therapist will resume bilateral stimulation until it disappears. If the sensation is positive, it will be reinforced with short sets (10–12 s) of bilateral stimulation.
7. Closure: The therapist explains possible effects following the session, such as new insights, thoughts, memories, and even dreams or nightmares, and offers recommendations about what to do in each case.

TABLE 2 | Measurements to evaluate consumption symptoms.

Clinical variable	Measurement interview/ Self-report	T0	T1	T2	T3
		Baseline	Mid-treatment	Post-treatment 6 months	Post-treatment 12 months
Timeline	TLFB	x	x	x	x
Dependence	SDS	x	x	x	x
Craving	EVA	x	x	x	x

TLFB, Timeline Followback Questionnaire; SDS, Severity of Dependence Scale; EVA, Visual Analog Scale.

8. Reevaluation: The therapist assesses the patient's experiences since the previous session and reevaluates the traumatic memory to confirm functional processing. If the memory has been desensitized, the therapist selects a new target of either another traumatic memory, a current trigger of distress, or a potentially threatening future event.

The CRAVEX protocol (48) will also be applied to process craving. This protocol focuses on the concept of addiction memory (AM), in which the biological effect of the drugs has a serious impact on the brain comparable to trauma, which leads to the formation of a maladaptive implicit memory which if reprocessed can decrease cravings or urges, and potentially promote access to the brain channels connected to the initial reasons the individual became addicted (49). Instead of SUD, the CRAVEX protocol uses Level of Urge (LOU), with a scale of 0 (no urge) to 10 (worst urge imaginable), referring to the urge to consume the substance. As in the standard protocol, positive and negative cognitions, emotions and physical sensations are identified but, in this case, they are associated with the last time that the subject consumed the drug. Bilateral stimulation is used until the AM is desensitized, and finally the positive cognition is installed.

TAU

All patients included in this study will participate in the TAU condition, comprising the standard care package offered by the Drug and Alcohol Outpatient Unit. This is a multidisciplinary unit with doctors, psychiatrists, clinical psychologists, nurses, and social workers on the staff. An individual care plan is drawn up depending on individual needs and may include follow-up psychiatric visits to evaluate clinical status and, if necessary, readjust pharmacological treatment, and psychological visits to assess and detect risk situations and prevent relapses using a non-trauma focused CBT. In no case will psychological treatment focus on PTSD. TAU also includes nurse visits for health and self-care habits and nurses may also carry out abstinence controls.

Dropouts and Follow-Up

If a participant requires an inpatient stay due to substance misuse or an acute episode of a comorbid disorder during the 6-month intervention period, the patient will be excluded from the trial and considered as dropout because the hospital admission will mean the patient cannot continue with the EMDR psychotherapy during the acute phase. In the case of relapse during follow-up, patients will be maintained in the trial to obtain maximum information on the course of the illness.

TABLE 3 | Measurements to evaluate psychological trauma symptoms.

Clinical variable	Measurement interview/ Self-report	T0	T1	T2	T3
		Baseline	Mid-treatment	Post-treatment 6 months	Post-treatment 12 months
Childhood T	CTQ	x			
PTSD	EGEP	x		x	x
Traumatic events	H-RLSI	x			
Trauma's impact	IES-R	x		x	x
Dissociation	DES	x		x	x

Childhood T, Childhood trauma; CTQ, Childhood Trauma Questionnaire; PTSD, post-traumatic stress disorder; EGEP, Global Assessment of Posttraumatic Stress Questionnaire; H-RLSI, The Holmes-Rahe Life Stress Inventory; IES-R, Impact Event Scale; DES, Scale of Dissociative Experiences.

MATERIALS AND EQUIPMENT

Instruments and Measures

The consumption of substances will be quantified using the following tools (see **Table 2**):

1. Timeline Followback Questionnaire (TLFB): The TLFB (31) is a retrospective calendar-based measure of daily substance use, initially developed to obtain self-reports of alcohol use but nowadays also used for other substances.
2. Severity of Dependence Scale (SDS): The SDS (32) is a 5-item questionnaire indicating the degree of dependence on different types of drugs. Each item is scored on a 4-point scale (0–3) and summed to create a total score. Higher scores indicate greater dependence.
3. Visual Analog Scale (VAS): A self-report scale to measure craving intensity, classically used to measure pain intensity. It ranges from 0 to 10: the higher the score, the greater the craving severity.

Trauma-related symptoms will be evaluated using the tools listed in **Table 3**:

1. Childhood Trauma Questionnaire (CTQ): The CTQ (36), Spanish validation (50), is a self-administered 28-item scale developed as a screening tool for histories of childhood abuse and neglect, with 5 subscales: emotional, physical or sexual abuse, and emotional or physical neglect. A 5-point Likert scale is used for the responses, ranging from "Never True" to "Very Often True."
2. Global Assessment of Posttraumatic Stress Questionnaire(EGEP-5): The EGEP-5 (51) is a clinical interview for the diagnosis of PTSD, both current and in the past, based on DSM-V criteria. This scale contains three sections: events, symptoms and functioning.

3. The Holmes-Rahe Life Stress Inventory (37); Spanish validation (52): this is a scale assessing the frequency of 43 common stressful life events over the past 12 months, providing a standardized measure of their impact (53). Scores below 150 reflect low levels of stress, scores between 150 and 299 represent a 50% risk of a stress-related illness in the near future and scores above 300 represent an 80% risk (37), although each individual's reactions to stress and coping ability must be considered.
4. Impact of Event Scale-Revised (IES-R): The IES-R (54), Spanish validation (55), is a 22-item self-report measure of subjective distress over the previous 7 days related to a specific stressful life event. Items correspond directly to 14 of the 17 DSM-IV symptoms of PTSD. Items are rated on a 5-point scale ranging from 0 and 4, yielding a total score ranging from 0 to 88, with subscale scores for Intrusion, Avoidance, and Hyperarousal.
5. Dissociative Experiences Scale (DES): The DES (36), Spanish validation (56), is a 28-item self-reported questionnaire measuring a wide range of dissociative experiences, from normal to pathological, with an overall mean score ranging from 0 to 100 (57).

Diagnosis, clinical symptoms, and functioning will be assessed using the following instruments (see **Table 4**):

1. The clinical diagnosis of SUD will be made according to DSM-5 criteria, using the Spanish version of the clinical interview Psychiatric Research Interview for Substance and Mental Disorders (PRISM) (42).
2. Mini-International Neuropsychiatric Interview (MINI): A Spanish-validated brief structured diagnostic interview to assess the 17 most common psychiatric disorders as per DSM-IV criteria (58).
3. Hamilton Depression Rating Scale (HDRS): The HDRS (38), Spanish validation (59), is a 17-item hetero-administered scale designed to be used in patients previously diagnosed with depression, to quantitatively assess the severity of and changes in depressive symptoms. Each item has three or five possible answers, scored 0–2 or 0–4, respectively. Total scores range from 0 to 52.
4. Young Mania Rating Scale (YMRS): The YMRS (39), Spanish validation (60), is an 11-item hetero-administered scale which quantifies the severity of manic and hypomanic episodes. Four items are given more weight to compensate for poor cooperation from severely ill patients and are graded on a 0–8 scale (irritability, speech, thought content and disruptive/aggressive behavior), while the remaining seven items are graded on a 0–4 scale.
5. Brief Psychiatric Rating Scale (BPRS): The BPRS (40), Spanish validation (61), is an 18-item hetero-administered scale measuring psychopathological changes. It includes anxious, affective and psychotic symptoms, with each rated on a severity scale of 1–7.
6. Functioning Assessment Short Test (FAST): The FAST (41) is a 24-item instrument to evaluate functioning in six areas: autonomy, occupational functioning, cognitive functioning, finances, relationships and leisure. Each item is rated on a 4-point scale and summed to obtain a global score ranging from 0 to 72. The higher scores indicate poorer functional status.

TABLE 4 | Measurements to evaluate clinical symptoms and functionality.

Clinical variable	Measurement interview/ Self-report	T0	T1	T2	T3
		Baseline	Mid-treatment	Post-treatment 6 months	Post-treatment 12 months
Diagnosis	PRISM	x			
Diagnosis	MINI	x			
Mania	YMRS	x		x	x
Depression	HDRS	x		x	x
Psychiatric S.	BPRS	x		x	x
Functionality	FAST	x		x	x

PRISM, Psychiatric Research Interview for Substance and Mental Disorders; MINI, Mini-International Neuropsychiatric Interview; YMRS, Young Mania Rating Scale; HDRS, Hamilton Depression Rating Scale; Psychiatric S, Psychiatric symptoms; BPRS, Brief Scale of Psychiatric Evaluation, FAST, Functioning Assessment Short Test; Psychiatric S, Psychiatric symptoms.

Anticipated Results

The expected results of the current study will provide evidence of whether EMDR therapy is effective in reducing symptoms related to substance use, trauma-related and clinical symptoms in outpatients with SUD and a comorbid history of psychological trauma.

DISCUSSION

In recent years, the third-generation psychotherapies such as EMDR, which emerged in the 90s within the tradition of behavioral therapy (62), have gained considerable interest in both social and scientific fields due to their ability to integrate cognitive, emotional and behavioral components within the same psychotherapeutic approach, processing adverse life events and therefore ameliorating associated psychiatric symptoms. To date, preliminary evidence exists suggesting EMDR therapy is efficacious in SUD patients, thanks to previous studies done in that population (20, 63). In a more recent publication (21), a quasi-experimental study of 40 SUD outpatients found that EMDR as an add-on treatment had a pronounced effect in reducing post-traumatic and dissociative symptoms and also caused a significant improvement in the global severity of psychiatric symptoms. The aim of our trial is to provide further evidence of a positive effect of EMDR in this difficult-to-treat population in a larger RCT. In our study, we aim to treat real-world dual patients, with a wide range of substances used and varied comorbid psychiatric and somatic illnesses (except neurological disorders). In contrast to prior studies, we also include a year follow-up to test whether possible improvements are maintained. With results from a large RCT, we aim to promote trauma-oriented therapies in patients with dual disorders. Although it has been shown that there is a

clear association between PTSD and addiction (64), most mental health care programs do not offer trauma-oriented therapies for patients with SUD. To understand better the relationship between the presence of traumatic events and the diagnosis of SUD, we will study several variables before, during and after treatment. We will assess variables of clinical severity, consumption and overall functioning with specific and validated instruments. In short, the potential of this study is to demonstrate the effectiveness and safety of EMDR in dual disorders. Along these lines, we could be closer to establishing an effective new psychological treatment for these patients in addition to the standard treatment. In this way, the impact of this trial is to improve the clinical evolution and prognosis and to reduce hospital admissions in SUD patients.

LIMITATIONS

A limitation of this study is the inclusion of heterogeneous patients with various psychiatric diagnoses, including SUD with somatic and other psychiatric comorbidities. This trial has been specifically designed as a pragmatic real-world study with few exclusion criteria. We believe this limitation can be sufficiently controlled by matching samples in both arms and by the fact that the main common clinical underlying variable of all patients is a comorbid psychological trauma. Furthermore, the lack of control regarding drug treatment is a potential source of bias. To partly overcome this limitation, the "pharmacological treatment" variable will be taken into account and the treatment regimen should not be changed as far as possible, once patients have been stabilized. Moreover, it should be noted that our center has extensive experience in the treatment of SUD and uses standardized treatment protocols, which will also help limit this potential issue.

AUTHOR CONTRIBUTIONS

BA and MT had the idea for the project. AV-G, AM-A, LB, MR-M, and BA contributed to the design of the study. AV-G wrote the first draft of the manuscript, with supervision from AM-A, BH, and BA (primary supervisor). JR will carry out the randomization of patients and the statistical analyses. JR, LB, BH, WL, MR-M, VP, and MT contributed to the revisions and modifications of the manuscript and all have approved the final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00108/full#supplementary-material

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EMDR as Add-On Treatment for Psychiatric and Traumatic Symptoms in Patients with Substance Use Disorder

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Background: Substance use disorders (SUD) are patterns of substance use leading to severe impairment on social, working and economic levels. *In vivo* and clinical findings have enhanced the role of the brain's stress-related system in maintaining SUD behaviors. Several studies have also revealed a high prevalence of post-traumatic symptoms among SUD patients, suggesting that a trauma-informed treatment approach could lead to better treatment outcomes. However, only few studies have evaluated the use of eye movement desensitization and reprocessing (EMDR) in SUD without consistent results. The aim of the present pilot study was to assess the efficacy of a combined trauma-focused (TF) and addiction-focused (AF) EMDR intervention in treating post-traumatic and stress-related symptoms of patients with SUD.

Methods: Forty patients with different SUD were enrolled in the study. Twenty patients underwent treatment as usual (TAU), the other 20 patients were treated with TAU plus 24 weekly sessions of EMDR. All patients were assessed before and after intervention for several psychological dimensions using specific tools (i.e., BDI-II, DES, IES-R, STAI, and SCL-90-GSI). A repeated measure MANOVA was performed to evaluate both between groups (TAU + EMDR vs. TAU) and within group (pre- vs. post-intervention) effects and interactions. A secondary outcome was the dichotomous variable yielded by the urine drug testing immunoassay (yes/no).

Results: The RM-MANOVA revealed both a significant pre–post main effect ($p < 0.001$), and a significant group-by-time main effect ($p < 0.001$). Significant improvements on IES-R, DES, and SCL-90-GSI scales were shown in both groups according to time effects ($p < 0.05$). However, significant greater effects were found for TAU + EMDR group than TAU group. No differences were found between TAU and TAU + EMDR groups in terms of urine drug immunoassay results before and after the interventions.

Conclusions: The TAU + EMDR group showed a significant improvement of post-traumatic and dissociative symptoms, accompanied by a reduction in anxiety and

overall psychopathology levels, whereas TAU group showed a significant reduction only in post-traumatic symptoms. Although our results can only be considered preliminary, this study suggests that a combined TF- and AF- EMDR protocol is an effective and well-accepted add-on treatment for patients with SUD.

Keywords: eye movement desensitization and reprocessing, substance use disorder, traumatic stress, dissociation, anxiety, depression, psychiatric symptoms, adverse childhood experiences

INTRODUCTION

Substance use disorders (SUD) are pathological patterns of behaviors related to substance use leading to severe impairment of familial, social and working relationships as well as of economic conditions (American Psychiatric Association, 2013).

Although the neurobiological circuitry that is associated with drug reward has been broadened in recent years, the meso-cortical-striatal dopamine system is still the most important pathway involved in the rewarding properties of almost all drugs (Koob and Volkow, 2016).

However, *in vivo* and clinical findings have also enhanced the role of brain's stress-related system in maintaining SUD behaviors: the chronic administration of all major drugs with dependence or abuse potential is associated with corticotropin-releasing factor variation leading to both hypothalamic-pituitary-adrenal axis and brain stress system dysregulation (Koob, 2013).

The increase of corticotropin-releasing factor, dynorphin, and norepinephrine recruited in the extended amygdala contributes to the development of negative emotional states during acute withdrawal (such as chronic irritability, dysphoria, and loss of motivation; Koob and Volkow, 2016).

From an epidemiologic point of view, patients having any lifetime SUD showed higher risk of also having a post-traumatic stress disorder (PTSD; OR = 1.6, 95% CI = 1.27–2.10, Grant et al., 2016) with a prevalence of current PTSD ranging from 15 to 42% (Mills et al., 2005; Reynolds et al., 2005, 2011; Driessen et al., 2008).

Moreover, some studies conducted on SUD showed that 67–92% of the patients report having experienced at least one traumatic event according to the DSM-IV PTSD criterion A (Dragan and Lis-Turlejska, 2007; Reynolds et al., 2011).

Furthermore, several studies have also reported a strong relationship between exposure to severe stress in childhood and substance abuse (Dube et al., 2003; Green et al., 2010). One of the most important studies, conducted by the Center for Disease Control along with the Kaiser Hospital in San Diego, released the landmark Adverse Childhood Experience (ACE) study, showing that individuals who experienced four or more types of ACEs were at a four to 12-fold increased risk of developing alcohol or drug abuse problems (Felitti et al., 1998).

Research has shown that substance abuse treatment using a trauma-informed approach could lead to better treatment outcomes, such as greater symptom reduction and increased retention in treatment (Amaro et al., 2007; LeTendre and Reed, 2017).

Such involvement of stress systems, trauma, and PTSD in SUD suggested a possible role of intervention possibly impacting on traumatic and stress disorders in the treatment of patients with SUD.

Among the different psychological approaches, eye movement desensitization and reprocessing (EMDR) has emerged as an evidence-based therapy for the treatment of psychological sequelae of traumatic events and other negative stressful experiences (Shapiro, 2014).

EMDR is a psychotherapeutic approach that focuses on trauma elaboration. It is guided by the adaptive information processing (AIP) model, that posits that stressful events not fully processed and integrated into the already existing memory networks are stored in a dysfunctional way. A distinct characteristic of EMDR therapy is the use of alternating bilateral stimulation (eye movements, tactile, or audio), which appears to produce a physiological effect promoting accelerated reprocessing of dysfunctionally stored information related to the traumatic event (Jeffries and Davis, 2013; Carletto et al., 2017; Pagani et al., 2017).

EMDR is considered one of the elective psychotherapeutic treatments for PTSD, according to several meta-analyses and clinical guidelines (Van Etten and Taylor, 1998; Davidson and Parker, 2001; Bradley et al., 2005; National Collaborating Centre for Mental Health, 2005; Bisson et al., 2013; WHO, 2013; Chen et al., 2014, 2015) and its neurobiological effects are also supported by neuroimaging findings (Pagani et al., 2012, 2015; Boukezzi et al., 2017).

Furthermore, in recent years the use of EMDR has expanded beyond PTSD and several studies have reported its efficacy for treatment of trauma-associated symptoms in patients with other psychiatric conditions (for a review see Valiente-Gómez et al., 2017). Among these, several protocols of treatment were developed in order to address traumatic experiences of SUD patients.

The clinical application of trauma-focused EMDR (TF-EMDR) in some studies resulted in EMDR being efficacious in the treatment of traumatic symptoms, but not in addiction behavior severity (see reviews by Roberts et al., 2015 and Markus and Hornsveld, 2017). Subsequently, some authors focused on the role of TF-EMDR in patients with SUD without PTSD, considering different types of outcomes even in relation to the addiction with fairly positive results but without conclusive findings.

Finally, as a third possible application of EMDR in SUD, there were some proposals of addiction-focused EMDR (AF-EMDR) protocols, such as the desensitization of triggers and urge reprocessing (DeTUR) protocol by Popky (2005), the feeling-state addiction protocol (FSAP) by Miller (2010) and the craving extinguished (CravEx) protocol by Hase et al. (2008). All these

protocols were specifically focused on the addiction rather on trauma but only the CravEx was clinically evaluated in a randomized clinical trial. Comparing treatment as usual (TAU) with CravEx plus TAU in a sample of patients with alcohol use disorder, Hase et al. (2008) have found a significant reduction in craving and depression severity up to 1 month after treatment.

To the best of our knowledge, no studies have yet evaluated the efficacy of both trauma and addiction-focused protocols on the relapse rate and stress-related symptoms of patients with SUD. Therefore, the aim of the present pilot study was to assess the efficacy of a combined trauma-focused and addiction-focused EMDR protocol in treating post-traumatic and stress-related symptoms of patients with SUD. We hypothesized that this combined adjunctive EMDR intervention would be more effective than a TAU intervention.

MATERIALS AND METHODS

Design

This was a quasi-experimental study investigating the efficacy of an additional EMDR treatment as compared with TAU alone in patients diagnosed with SUD.

Setting

The participants were recruited in two settings: an outpatient territorial service for drug addiction in northern Italy (Ser.T. of Limbiate, MI) and a residential facility in central Italy (Comunità di Capodarco di Fermo, FM) from March 2015 to May 2016.

The study was approved by the Medical Ethics Committee of Azienda Territoriale dei Servizi of Brianza (MB, Italy) and by the Board of Directors of Capodarco (FM, Italy). Informed written consent was obtained from all the participants.

Participants

The subjects of the study were patients with a diagnosis of SUD, who were referred to one of the two above-mentioned centers for drug addiction treatment.

Inclusion criteria were as follows: (1) a diagnosis of SUD, according to DSM-5; (2) age between 18 and 65 years; (3) fluent Italian language; (4) legal capacity to consent to the treatment; (5) maintenance of psychotropic medications throughout the study.

Exclusion criteria were as follows: (1) having a pathological gambling disorder without comorbidity with other SUDs; (2) presence of other severe psychiatric disorders such as psychosis or bipolar disorder; (3) cognitive disorders such as overt dementia; (4) suicide attempts; (5) current pregnancy.

Assessment

The recruitment of participants was carried out by a psychiatrist and psychologist who proposed participation in the research protocol to patients during a clinical visit in the outpatient setting and during the first visit after admission in the inpatient setting. The research protocol was proposed to consecutive patients who met the inclusion criteria, with an explanation of the aims of the study, and patients were asked whether they were willing to receive an additional psychotherapeutic intervention (EMDR) other than TAU. Patients could choose the group to which they wanted to be assigned (TAU or TAU + EMDR). On reaching the maximum number of patients in the TAU + EMDR group, the remaining patients were assigned to the TAU alone group.

The psychological assessment was performed by psychologists independent of the research protocol, using the same timing and tools, i.e., at baseline before the first session of treatment (T0), and after the end of treatment (T1).

The following psychological self-report questionnaires were administered:

Impact of Event Scale—Revised (IES-R). The IES-R (Weiss and Marmar, 1997) is a 22- item self-report questionnaire consisting of three subscales (eight items relate to intrusions, eight items evaluate avoidance, and six items assess hyperarousal). The scale assesses subjective distress caused by traumatic events. An IES-R score equal to or >33 represents the best cut-off for a probable diagnosis of PTSD. The IES-R was found to be highly internally consistent (Cronbach's alpha, $\alpha = 0.96$; Creamer et al., 2003).

State-Trait Anxiety Inventory (STAI-Y). The STAI-Y (Spielberger et al., 1983) is used to measure the presence and severity of current symptoms of anxiety (state anxiety; STAI-1) and a generalized propensity to be anxious (trait anxiety; STAI-2). Range of scores for each subtest is 20–80, the higher score indicating greater anxiety. A cutoff point of 39–40 has been suggested to detect clinically significant symptoms for the state anxiety scale. The STAI-Y has shown an adequate to excellent internal reliability ($\alpha = 0.86$–0.95).

Beck Depression Inventory-II (BDI-II). The BDI-II (Beck and Steer, 1993) is a 21-item self-report instrument that assesses the presence and severity of depression symptoms. A score above 13 indicates presence of depression symptoms. The internal consistency of the BDI-II is good to excellent ($\alpha = 0.83$–0.96; Wang and Gorenstein, 2013).

Symptom Checklist 90 Items revised version (SCL-90- R) (Derogatis et al., 1973; Derogatis, 1994) is a 90-items self-report questionnaire that evaluates a broad range of psychological problems and symptoms of psychopathology. For the purpose of this study we chose to utilize the Global Severity Index (GSI), as it represents the best global indicator of the intensity of psychic distress reported by the subject and it demonstrated a high Cronbach's alpha value ($\alpha = 0.97$; Prinz et al., 2013). This global index combines information about the number of reported symptoms and the intensity of perceived discomfort. A score between 55 and 65 indicates a distress level of moderate intensity, while a score above 65 reveals a severe intensity of discomfort, beyond the threshold of clinical attention.

Dissociative Experiences Scale (DES) (Bernstein and Putnam, 1986; Frischholz et al., 1990) is a brief, 28-item, self-report inventory of the frequency of dissociative experiences. It represents a reliable and valid measure for determining the contribution of dissociation to various psychiatric disorders and a screening instrument for dissociative disorders. High levels of dissociation are indicated by scores of 30 or more. The DES has an excellent internal consistency, with Cronbach's alpha ranging from 0.96 to 0.97 (Dubester and Braun, 1995).

The *Adverse Childhood Experience Questionnaire (ACE)* (Felitti et al., 1998) is a 10-item self-report measure developed

for the ACE study to identify childhood experiences of abuse and neglect. The internal consistency of the ACE questionnaire is adequate ($\alpha = 0.88$; Murphy et al., 2014). This questionnaire was administered only at baseline.

Treatments

Treatment as Usual

All patients received TAU, which consisted of standard treatment for recovery from SUD in the National Health Service in Italy. TAU included clinical interviews with the addiction specialist and administration of medications appropriate for each patient (e.g., alcohol craving, heroin substitute treatment). Comorbid psychiatric conditions such as depression or anxiety disorders were treated in accordance with the patient's needs, including appropriate medication.

Lastly, TAU included psychological treatment (both individual and group sessions) and participation in psycho-educational group sessions.

Eye Movement Desensitization and Reprocessing

Participants received 24 weekly EMDR sessions over a period of 6 months. The EMDR treatment used in this study incorporated both elements of the classic TF-EMDR protocol (Shapiro, 2001) and of the existing AF-EMDR protocols (Hase, 2010; Knipe, 2010; Miller, 2010; Popky, 2010), in accordance with the Palette of EMDR Interventions in Addiction (PEIA; Markus and Hornsveld, 2017).

The EMDR treatment steps were as follows:

1) Building a positive therapeutic relationship;
2) Information gathering (trauma history, addiction history);
3) Strengthening the motivation for treatment through positive and achievable therapeutic goals and enhancing personal resources;
4) Desensitization of traumatic events in chronological order;
5) Desensitization of the "first time" memory and the dependence of precipitating factors;
6) Desensitization of the level of urge;
7) Desensitization of the recall of the relapse;
8) Desensitizing triggers of triggering behavior;
9) Installing a positive state for each triggering factor.

EMDR treatment was provided by four clinical psychotherapists specialized in EMDR therapy (who at least had completed the Level II EMDR program). The EMDR therapists were supervised monthly by an EMDR consultant.

Statistical Analyses

Data were processed and analyzed using the Statistical Package for Social Sciences (SPSS version 22.0; Chicago, IL, USA).

Both parametric and nonparametric tests were used, in accordance with Shapiro–Wilk as a test for normality. Baseline group differences were assessed using Student's *t*-test or Mann–Whitney *U*-test to compare the two groups for continuous measures and Fisher's Exact Test for categorical measures.

GLM repeated measures multivariate ANOVA (RM-MANOVA) was used to analyze the main pre- and post-intervention effects and interactions both between and within TAU + EMDR and TAU groups. Pairwise comparison between groups were made by simple contrast and are reported as means difference with the Sidak correction 95% confidence interval (95%CI) for multiple comparisons.

A $p < 0.05$ was considered statistically significant throughout all of the analyses.

RESULTS

A total of 40 patients were enrolled in the study: 20 were assigned to the TAU + EMDR intervention and the other 20 patients were assigned to the TAU treatment. We did not register any dropout from the treatments.

Table 1 presents the sociodemographic characteristics of these patients at baseline. There were no significant differences in demographics between the two groups at baseline (T0), except for adverse childhood experiences, which were more frequent in the TAU + EMDR group (**Table 1**).

There were several differences between the two groups at baseline. Overall, patients in the TAU + EMDR group showed higher post-traumatic stress and anxiety symptoms and more psychiatric symptoms.

We evaluated whether the different psychotherapy treatments (TAU + EMDR or TAU) administered to the patients had a different impact on the psychological variables of interests. A repeated-measures MANOVA was performed on the pre- and post-intervention clinical scores (IES-R, DES, SCL-90-GSI,

TABLE 1 | Demographic data of participants at baseline.

	EMDR ($N = 20$) Mean (*SD*)/ Median (IQR)	TAU ($N = 20$) Mean (*SD*)/ Median (IQR)	*p*
Age (years)	32 (8)	32 (19)	0.820[a]
Years of substance use	19.40 (7.98)	21.10 (9.59)	0.546[b]
Adverse Childhood Experiences	4 (5)	2 (2)	0.004[a]
	***n* (%)**	***n* (%)**	
Gender			0.487[c]
Female	2 (10)	0 (0)	
Male	18 (90)	20 (100)	
Marital status			0.410[c]
Single	17 (85)	14 (70)	
Married	1 (5)	4 (20)	
Separated/divorced	2 (10)	2 (10)	
Level of education			0.198[c]
Primary school	0 (0)	3 (15)	
Low secondary school	9 (45)	10 (50)	
High secondary school	11 (55)	7 (35)	

EMDR, Eye Movement Desensitization and Reprocessing group; TAU, Therapy As Usual group.

[a] *Mann–Whitney U-test.*

[b] *Pearson's independent samples t-test.*

[c] *Fisher's exact test.*

STAI-1, STAI-2, BDI-II), comparing group and time effects and interactions between group and time.

The RM-MANOVA yielded a significant pre–post main effect [$F_{(6, 33)} = 10.102$, $p < 0.001$; $\eta^2_p = 0.647$], and a significant interaction between the pre–post measures and the treatment condition [$F_{(6, 33)} = 7.830$, $p < 0.001$; $\eta^2_p = 0.587$].

Significant time effects were found across both groups for all variables except for STAI-1 and STAI-2, indicating that the mean participant scores improved from time 0 (pre-intervention) to time 1 (post-intervention) on all variables except for anxiety symptoms (**Table 2**).

Group-by-time interaction effects were found for IES-R, DES, SCL-90-GSI, STAI-1, and STAI-2 total scores, indicating that clinical improvements regarding these variables were different in the two treatment groups. No group-by-time interaction was found for BDI-II, showing that change on this measure was similar for both treatment groups (**Table 2**).

Planned *post-hoc* analyses of simple effects of pre–post were conducted for all variables with a significant group-by-time effect (DES, IES-R, SCL-90-GSI, STAI-1, STAI-2,) by GLM pairwise comparisons using the Sidak adjustment for multiple comparisons.

The two groups significantly differ for IES-R scores at baseline, with participants in the TAU + EMDR group showing higher post-traumatic symptoms than those in the TAU group (**Table 2**). The analysis of simple effects over time indicated both groups had an improvement in post-traumatic symptoms (**Table 3**), but the TAU + EMDR group scored significantly lower compared to the TAU group at post-treatment (**Table 2**).

As regards the DES score, there was no significant difference between groups at baseline (**Table 2**). Results indicated that the group-by-time effect is explained by the significant difference between dissociative pre- and post-treatment scores for participants who underwent EMDR intervention (**Table 3**).

Moreover, there was also a difference between groups at baseline for the SCL-90-GSI score, with more severe psychiatric symptoms in the TAU + EMDR group (**Table 2**). The comparison between pre- and post-treatment indicated a significant improvement in the TAU + EMDR group between T0 and T1, while there was no difference in the TAU group (**Table 3**).

In the case of STAI-1, results indicated that there was a significant difference between the two groups at baseline, as the STAI-1 scores at baseline in TAU + EMDR group were significantly higher than those in TAU group (**Table 2**). Concurrently, there was a significant difference between STAI-1 pre- and post-treatment scores in the TAU group but not in the TAU + EMDR group. This indicates that the group-by-time effect was due to the significant difference between groups at baseline and to the significant worsening of state anxiety symptoms in patients in the TAU group (**Table 3**).

With regard to STAI-2, a significant difference between the two groups at baseline was found, as STAI-2 scores at baseline in TAU + EMDR group were significantly higher than those in TAU group (**Table 2**). Moreover, there was a significant reduction of STAI-2 scores in the TAU + EMDR group that was not present in the TAU group. This indicates that the improvements over time on trait anxiety were registered only in the TAU+ EMDR treatment group (**Table 3**).

No differences were found before and after treatment in the urine drug testing immunoassays, which showed a similar increase of negative results after the interventions (TAU group from 65% at baseline to 85% at T1; TAU + EMDR group from 70% at baseline to 80% at T1; $\chi^2 = 0.067$, $p = 0.795$).

DISCUSSION

Overall, all SUD patients included in the study improved their clinical condition with a significant reduction of post-traumatic, dissociative and psychiatric symptoms, regardless of the type of treatment.

Both TAU and TAU + EMDR interventions had a significant effect in reducing post-traumatic symptoms, but the add-on EMDR proved to have a significant greater effect, allowing a shift from baseline levels above the clinical cut-off to post-treatment normal levels. This finding is in line with those of previous studies (Perez-Dandieu and Tapia, 2014; Brown et al., 2015), which showed that adding EMDR to TAU has a significant effect on post-traumatic symptoms.

In the same way, according to the results of the present study, the add-on EMDR has an important effect in reducing

TABLE 2 | Comparison of clinical variables for the two groups (TAU and TAU + EMDR).

	Pre-treatment		*p*	Post-treatment		*p*	Effect Time			Effect Time × Group		
	TAU (*N* = 20)	TAU + EMDR (*N* = 20)		TAU (*N* = 20)	TAU + EMDR (*N* = 20)		*F*	*P*	η^2_p	*F*	*P*	η^2_p
BDI-II	11.60 (7.45)	18.35 (14.08)	0.066	10.10 (7.58)	11.65 (12.54)	0.639	8.646	0.006	0.185	3.477	0.070	0.084
STAI-1	41.95 (4.17)	46.35 (5.26)	0.006	46.25 (5.28)	43.50 (5.31)	0.109	0.459	0.502	0.012	11.160	0.002	0.227
STAI-2	42.05 (2.69)	45.65 (5.49)	0.012	43.20 (3.14)	42.60 (7.61)	0.746	1.476	0.232	0.037	7.212	0.011	0.160
DES	10.93 (8.07)	15.69 (14.05)	0.196	8.53 (6.67)	6.72 (7.13)	0.411	15.766	<0.001	0.293	5.279	0.027	0.122
IES-R	23.90 (15.35)	39.65 (23.12)	0.015	12.30 (11.76)	6.05 (5.88)	0.040	48.282	<0.001	0.560	11.438	0.002	0.231
SCL-90-GSI	62.65 (10.39)	73.90 (2.94)	<0.001	61.95 (11.55)	63.25 (12.37)	0.733	14.378	0.001	0.275	11.050	0.002	0.225

Data are mean (SD).

TAU, Therapy As Usual group;

TAU + EMDR, Eye Movement Desensitization and Reprocessing in addition to TAU group.

TABLE 3 | Comparison between T0 and T1 of clinical variables for the two groups (TAU and TAU + EMDR).

	TAU				TAU + EMDR			
	T0	T1	Mean difference (95%CI)	*p*	T0	T1	Mean difference (95%CI)	*p*
BDI-II	11.60 (7.45)	10.10 (7.58)	−1.500 (−5.492; 2.492)	0.452	18.35 (14.08)	11.65 (12.54)	−6.700 (−10.692; −2.708)	0.002
STAI-1	41.95 (4.17)	46.25 (5.28)	4.300 (1.236; 7.384)	0.007	46.35 (5.26)	43.50 (5.31)	−2.850 (−5.914; 0.214)	0.067
STAI-2	42.05 (2.69)	43.20 (3.14)	1.150 (−1.089; 3.389)	0.305	45.65 (5.49)	42.60 (7.61)	−3.050 (−5.289; −0.811)	0.009
DES	10.93 (8.07)	8.53 (6.67)	−2.395 (−6.493; 1.703)	0.244	15.69 (14.05)	6.72 (7.13)	−8.973 (−13.071; −4.874)	<0.001
IES-R-Total	23.90 (15.35)	12.30 (11.76)	−11.600 (−20.912; −2.288)	0.016	39.65 (23.12)	6.05 (5.88)	−33.600 (−42.912; −24.288)	<0.001
SCL-90 Total	62.65 (10.39)	61.95 (11.55)	−0.700 (−4.985; 3.585)	0.743	73.90 (2.94)	63.25 (12.37)	−10.650 (−14.935; −6.365)	<0.001

Data are mean (SD).
TAU, Therapy As Usual group;
TAU + EMDR, Eye Movement Desensitization and Reprocessing in addition to TAU group.

dissociative symptoms, probably due to the well-recognized effect of EMDR on the reintegration of previous dysfunctionally stored memories (Nardo et al., 2013; van der Hart et al., 2013).

As regards the effect of EMDR on stress-related psychiatric symptoms, a significant improvement in the global severity of psychiatric symptoms was observed in patients who received add-on EMDR as compared to TAU alone, suggesting that EMDR also has a beneficial impact on a wide range of symptoms of clinical relevance, beyond post-traumatic symptoms.

In terms of anxiety, our results show a significant effect of add-on EMDR in improving trait anxiety that is not shown in TAU alone. In spite of its tendency to be stable over time, a number of studies revealed that trait anxiety can improve as a result of a psychological intervention over time (Vøllestad et al., 2011; Lee et al., 2015). Our results suggest that EMDR intervention might also affect the trait-like tendency to experience anxiety over time and across situations. Another interesting finding of our study is that state anxiety worsened in the TAU alone group, whereas in the TAU + EMDR group it remained stable. An increase of anxiety levels, mediated by adrenocorticotropic hormone, corticosterone, and amygdala corticotrophin releasing factor (CRF), is commonly observed during acute withdrawal stages of substance treatment and recovery programs (Koob and Volkow, 2016). It would seem that the TAU alone does not impact on this increase in anxiety levels, whereas the add-on of an EMDR intervention seems to be able to counterbalance this physiological elevation of anxiety related to abstinence.

With regard to depressive symptoms, no significant change was observed in either group, although our findings suggest a trend toward improvement in the group that received add-on EMDR, partially confirming previous findings (Hase et al., 2008; Perez-Dandieu and Tapia, 2014).

This study presents a methodological limitation that may moderate the interpretation of the results outlined so far. The non-randomized design led to the significant differences between the two groups at baseline. In fact, participants who received EMDR treatment showed higher baseline levels of symptoms compared to the group receiving only TAU treatment. These differences at baseline could limit a conclusive interpretation of the results of the study, as the improvements obtained by the group that received EMDR in addition to TAU could also be due to a spontaneous reduction of symptoms linked to the fact that higher reductions are observed when there are higher starting levels.

At the same time, the findings of the present study suggest that EMDR may be more useful in subjects who experienced more adverse childhood experiences and higher levels of symptoms, in order to strengthen standard treatment that otherwise would only be partially effective, especially on withdrawal-related anxiety. Consistent with previous literature reporting that adverse childhood events have significant implications for substance abuse treatment and that a trauma-informed approach to SUD leads to better treatment outcomes (Felitti et al., 1998; LeTendre and Reed, 2017), our findings suggest that exposure to adverse childhood experiences should be routinely assessed in treatment settings, in order to provide specific interventions to reduce traumatic burden associated with SUD. Future randomized controlled studies with larger samples should better investigate these aspects.

Another limit of the present study is that aspects related to craving and abstinence were not specifically investigated. The results of our study are in line with previous studies, which show that EMDR has beneficial effects on symptoms related to the traumatic history and only limited effects on additional outcomes (Markus and Hornsveld, 2017). The present study aimed to focus on post-traumatic and associated aspects linked to the relationship between addiction and traumatic burden, but future studies on similar populations should also take into account addict-related aspects.

This study also has some strengths. The results of the study confirm that EMDR could be a viable and well-accepted add-on treatment for patients with SUD, with some evidence of both efficacy and good compliance. Moreover, to the best of our knowledge this is the first study evaluating the clinical impact of an add-on EMDR intervention focused on both traumatic and addiction-related memories, and it found the first promising evidence of the efficacy of this combined TF- and AF-EMDR protocol. Further studies could evaluate the usefulness of combining TF- and AF-EMDR protocols in different clinical samples.

Although our results can only be considered preliminary, this study suggests that add-on EMDR is more effective

than TAU alone in improving post-traumatic and dissociative symptoms, accompanied also by a reduction in anxiety and overall psychopathology levels.

The findings of this study underline the importance of assessing ACEs and other traumatic experiences in this population because they may contribute to the onset and maintenance of SUDs and lead to a worsening of psychopathological severity. As a clinical consequence, it could be useful to offer these patients specific add-on treatments addressing both ACEs and traumatic experiences related to addiction, in adjunction to standard treatments.

Future studies, such as that designed by Markus et al. (2015) on alcohol-dependent patients, would be better to investigate not only the effectiveness of an EMDR add-on treatment but also the mediators, moderators, and predictors of treatment outcome, in order to be able to delineate effective interventions for these disorders, which represent a major public health problem.

AUTHOR CONTRIBUTIONS

MB is the national coordinator of the research. MB, IF, and MP were responsible for the conception and the design of the study. MB, TA, AC, PM, CR, and IF were responsible for data collection and for clinical treatments. SC and FO were responsible for the data analysis. IF, MB, LO, and MP contributed to the interpretation of data. SC and FO wrote the article, which was critically revised by all the others authors. All authors have approved the final version of the manuscript.

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Conflict of Interest Statement: IF is the president of EMDR Europe Association and the president of EMDR Italy Association. SC, LO, and MP have been invited speakers in national and international EMDR conferences.

The other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling Editor declared a shared affiliation, though no other collaboration, with several of the authors, SC, FO, and LO, and states that the process nevertheless met the standards of a fair and objective review.