Treating PTSD in patients with co-occurring substance use disorders: a randomized controlled trial to compare the efficacy of different types and timing of treatment.

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Primary objectives:1). Compare efficacy of Prolonged Exposure therapy (PE), Eye Movement Desensitization and Reprocessing (EMDR), and Imagery Rescripting (ImRs) with a 3-month waitlist condition (WL) in reducing posttraumatic stress disorder (PTSD)…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Anxiety disorders and symptoms
Study type	Interventional

Summary

ID

NL-OMON54610

Source
ToetsingOnline

Brief title
Treatment Of PTSD and Addiction (TOP-A)

Condition

- Anxiety disorders and symptoms

Synonym
Post-traumatic stress disorder; trauma complaints

Research involving
Human

Sponsors and support

Primary sponsor: Arkin (Amsterdam)
Source(s) of monetary or material Support: Stichting tot Steun VCVGZ; Huidige amendement: Fonds Slachtofferhulp

Intervention

Keyword: Post-traumatic stress disorder, Randomized Controlled Trial, Revictimization, Substance use disorder

Outcome measures

Primary outcome

The main study parameter is severity of PTSD symptoms as measured with

Clinician Administered PTSD Scale for DSM 5 (CAPS-5) (Weathers et al., 2013).

The CAPS-5 is the gold standard in PTSD assessment. It is a 30-item structured

interview, corresponding to the DSM-5 diagnosis for PTSD, that provides a

current total severity score.

Current amendment:

The primary outcome of the study is violent revictimization as measured with

the safety monitor, which assesses the prevalence and context details of three

types of interpersonal violence, sexual abuse, threat, and physical abuse, over

the past three years. It is a structured interview which has been used in the

past in research on victimization and that is used annually by the central

bureau for statistics in the Netherlands (CBS).

Secondary outcome

Measured by therapist:

- Completion of PTSD treatment (yes/no);

- Completion of SUD treatment (yes/no);

Measured with self-report questionnaire during assessments:

- Psychological distress (Brief Symptom Inventory (BSI));

- Alcohol and drug use problems (Alcohol Use Disorder Identification Test (AUDIT) Drug Use Disorder Identification Test (DUDIT));

- Substance use past 30 days (MATE-Q-nl module 1)

- Interpersonal problems (Inventory of Interpersonal Problems (IIP-32));

- Emotion dysregulation (Difficulties in Emotion Regulation Scale (DERS));

- Trauma-related guilt (Trauma Related Guilt Inventory (TRGI));

- Trauma-related shame (Trauma Related Shame Inventory (TRSI));

- Internalised and externalised anger and anger control (Zelf Expressie en Controle Vragenlijst (ZECV));

- Recent victimization (Veiligheidsmonitor (VM));

- Care consumption/costs (Treatment Inventory of Costs in Patients with psychiatric disorders (TiC-P));

- Quality of Life (EuroQol 5D (EQ-5D-5L)).

- (Recent) victimization and (recent) perpetration (minor extension of LEC-5));

Measured with experimental tasks during assessments:

-Impulsivity (delay discounting task); and emotion regulation task.

Measured with self-report questionnaire at start of therapy sessions:

- PTSD symptoms (PTSD symptom scale -self report (PSS-SR) (every session);

- Substance use in past 7 days (every session);

- Working alliance (Working Alliance Inventory - short form (WAI-SF)

Other study parameters

- Demographic characteristics;

- Complex PTSD (ITQ part 2)

- Childhood trauma (Childhood Trauma Questionnaire (CTQ));

- Daily Emotional Support ((DES) subscale from Social Support Questionnaire (SSQ));

- Traumatic Life events (LEC-5);

- Patient preference of type and timing of PTSD treatment;

- Therapist working experience;

- Therapist preference of type and timing of PTSD treatment;

- Number of sessions of PTSD-treatment attended;

- Number of sessions of SUD-treatment attended.

Current amendment:

In addition to above-mentioned secundary outcome measures:

Extension of the safety monitor to assess perpetration of crime, fear of sexuality questionnaire (FSQ), emotional abuse assessed with the emotional abuse subscale of the NEMESIS questionnaire).

Study description

Background summary

Posttraumatic stress disorder (PTSD) and substance use disorder (SUD) often co-occur, with an estimated prevalence of current PTSD of 25% amongst individuals with an SUD (Driessen et al., 2008). SUDs are also prevalent amongst individuals with PTSD. In a large epidemiological study in the United States, 46% of a PTSD sample met criteria for a substance use disorder (Pietrzak et al., 2011). Individuals with both disorders have a more severe clinical profile than those with either disorder alone, with worse physical health, more interpersonal problems and greater severity of substance use (Schafer et al., 2007). Furthermore, these patients are more likely to meet criteria for additional psychiatric disorders, such as depression. Individuals with co-occurring PTSD and SUD are considered to be more difficult to treat than individuals with either condition alone, with poorer treatment outcomes, poorer treatment adherence and shorter periods of abstinence post-treatment (Roberts et al., 2016). Despite the high prevalence, patients in treatment for SUD are often not assessed for PTSD or offered PTSD-focused interventions. Prolonged Exposure therapy (PE) is considered a first line treatment for PTSD. A recent meta-analysis indicated that PE is an effective treatment for reducing symptoms of PTSD, achieving remission of PTSD diagnosis and improving depression symptoms for adults with PTSD (Cusack et al. 2016); 66% more subjects treated with PE than subjects in waitlist control groups achieved remission of PTSD diagnosis. PE involves confrontation with distressing stimuli related to the trauma until anxiety is reduced. It is a manualized intervention, including both imaginal and in vivo exposure components (Foa et al., 2007). The aim of both aspects is to extinguish the conditioned emotional response to traumatic stimuli. Another first line treatment for PTSD is Eye Movement Desensitization and Reprocessing (EMDR). Evidence supports the efficacy of EMDR for achieving remission of PTSD diagnosis and improving depression symptoms (Cusack et al., 2016); 64% more subjects treated with EMDR recovered from PTSD compared to subjects in waitlist control groups. Both PE and EMDR are extensively used in clinical practice to treat patients with PTSD. So far, head-to-head evidence is insufficient to determine the comparative effectiveness of these treatments (Cusack et al., 2016). Most randomized controlled trials evaluating PTSD treatments exclude individuals with substance related problems. In patients suffering from both PTSD and SUD, EMDR has been studied in only one randomized pilot study with a sample size of 12 patients (Perez-Dandieu et al., 2014). This pilot study indicated that adding EMDR to regular addiction treatment leads to a significant reduction of PTSD symptoms. Prolonged Exposure therapy has been studied more extensively in patients with co-occurring PTSD/SUD. Several studies and a recent review indicate that PE is effective in reducing PTSD symptoms in patients with SUDs, when it is added to regular addiction treatment (see Roberts et al., 2016 for a review). However, PE is less effective in individuals with PTSD/SUD compared to individuals with PTSD alone. This may be caused by the finding that, disturbingly, adding PE to regular addiction treatment leads to higher drop-out rates than regular

addiction treatment only (Roberts et al., 2016). Coffey et al. (2016) tried to increase treatment completion and effectiveness of PE in patients with PTSD/SUD by adding a 90-minute trauma-focused motivational enhancement session prior to PE. Unfortunately, adding this session was not effective in increasing treatment completion or effectiveness of PE. While valuable advances have been made towards the treatment of co-occurring PTSD and SUD, it is essential to conduct head-to-head comparisons of effective treatments to determine the comparative effectiveness. Furthermore, it is necessary to search for a more fitting treatment for patients with comorbid PTSD-SUD diagnoses, that leads to lower drop-out rates. A promising new approach for treating PTSD in patients with substance use disorders is Imagery Rescripting (ImRs). ImRs is a therapy that is becoming increasingly popular for treating PTSD and other disorders. It is a technique that changes the meaning of emotional memories and images (like intrusions and nightmares). With ImRs the patient is instructed to imagine the memory (or image) as vividly as possible, as if it is happening in the here and now, and to imagine that the sequence of events is changed in a direction that the person desires (Arntz, 2012). A meta-analysis of 19 studies showed that ImRs is effective in reducing aversive imagery and related psychological complaints, with large effects obtained in a small number of sessions (Morina et al., 2017). In chronic PTSD patients, the addition of ImRs to PE led to a significant reduction of treatment drop-outs and a better effect on anger, anger control, shame and guilt compared to PE alone (Arntz et al., 2007). Another study showed that ImRs was highly effective in patients that did not respond to PE (Grunert et al., 2007). The authors suggest that, when fear is not the predominant emotion related to the trauma, but emotions like anger, shame or guilt dominate, ImRs may be a better treatment (Grunert, et al. 2007). On the other hand, Langkaas et al. (2017) did not find a difference between PE and ImRs on non-fear emotions in an RCT among inpatients with PTSD. It should be noted however that the inpatient treatment packages had considerable overlap, which limits the power of the design. Two RCTs in (complex) PTSD patients compared ImRs to waitlist and found large effects in favour of ImRs (Jung & Steil, 2013; Raabe et al., in prep.). The last study also found ImRs to be much more effective than Cloitre*s stabilization program (Cloitre et al., 2010), and no evidence that preceding ImRs with the stabilization program increases effectiveness or reduces dropout (Raabe et al., in prep). The recent release of the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5; American Psychiatric Association, 2013) has expanded the scope of criteria of PTSD beyond a fear-based concept, considering that a traumatic event is also followed by shame, guilt and/or anger. Trauma-related shame and guilt seem to play a central role in the maintenance of PTSD symptoms, by contributing to emotional aversiveness of the trauma memory. PTSD patients with a higher degree of shame and guilt are more likely to suffer from depression (Aakvaag et al., 2016) and have higher levels of PTSD symptoms over the course of treatment (Oktedalen et al., 2015). Reducing the level of nonfear emotions such as shame and guilt may increase the effectiveness of treatment of PTSD symptoms (Saraiya & Lopez-Castro, 2016). Holl et al. (2017) found that individuals with a history of childhood trauma used substances to regulate intense posttraumatic

shame. The authors suggest that shame may have a crucial role in the development of substance use disorders following a traumatic event. Given its effectiveness in reducing drop-out and feelings of anger, shame and guilt in patients with PTSD, Imagery Rescripting is a promising approach for treating PTSD in patients with substance use disorders (SUDs). In the studies examining Prolonged Exposure in patients with co-occurring PTSD/SUD, PE and addiction treatment were delivered simultaneously (Roberts et al., 2016). The meta-analysisfound that adding PTSD treatment to Treatment As Usual (TAU) was more effective than TAU in reducing PTSD severity up to seven months follow up. A study conducted at Jellinek showed that simultaneous treatment can be safely implemented in inpatient as well as outpatient care without negative effects on SUD treatment (van Dam, 2013). However, treatment facilities often

Study objective

Primary objectives:
1). Compare efficacy of Prolonged Exposure therapy (PE), Eye Movement Desensitization and Reprocessing (EMDR), and Imagery Rescripting (ImRs) with a 3-month waitlist condition (WL) in reducing posttraumatic stress disorder (PTSD) symptoms in patients with co-occurring PTSD and substance use disorder (SUD).
Hypothesis: We expect that at 3-month follow-up, all trauma-focused therapies will have led to a stronger reduction of PTSD symptoms than the waitlist condition.

2). Compare effectiveness of simultaneous SUD/PTSD treatment with sequential SUD/PTSD treatment in reducing PTSD symptoms in patients with co-occurring PTSD/SUD.
Hypothesis: We expect a greater reduction of PTSD symptoms in the simultaneous treatment condition compared to the sequential treatment condition across the whole follow-up period.

3). Explore differential efficacy between active treatments (PE vs EMDR; PE vs ImRs; EMDR vs ImRs) in reducing PTSD symptoms in patients with co-occurring PTSD/SUD.

Secondary objectives:
- Compare PE, EMDR, ImRs and waitlist in terms of secondary outcome measures, e.g. treatment completion, patient satisfaction, intensity of trauma related emotions.
- Compare simultaneous and sequential treatment in terms of secondary outcome measures.
- Compare differential cost-effectiveness between the active treatment arms and between simultaneous versus sequential treatment.
- Determine which treatment is most effective for which patient, by examining whether specific predominant trauma-related emotions (fear, anger, shame or guilt) predict and moderate treatment effectiveness.

Current amendment:

Primary objective:

1) Identify risk and protective factors for revictimization in patients that received treatment for PTSD/SUD

Secondary objectives:

2) Compare effectiveness of simultaneous SUD/PTSD treatment with sequential SUD/PTSD treatment in reducing PTSD symptoms at 48-month follow-up in patients with co-occurring PTSD/SUD

3) Gain insight into context characteristics of revictimization incidents in patients who have been treated for PTSD/SUD.

4) Explore the role of fear of sexuality in characterizing differences between revictimized and non-rectivimized patients that were treated for PTSD/SUD

5) Compare treatment arms in terms of secondary outcome measures at 48-month follow-up, such as residual SUD symptoms, health care consumption, quality of life, and emotional abuse

6) Determine predictors of severity of PTSD symptoms at 48-month follow-up.

Study design

This study is a single blind 6-arm randomized controlled trial comparing simultaneous SUD/PTSD treatment to sequential SUD/PTSD treatment, whilst also comparing Prolonged Exposure, Eye Movement Desensitization and Reprocessing, Imagery Rescripting, to only SUD treatment in patients with SUD/PTSD. Study population: Study participants will be patients (18 years of age or older) who applied for treatment of a substance use disorder at Jellinek Amsterdam, Utrecht for whom treatment of co-occurring PTSD is indicated.

The flow chart of the study design is depicted in Figure 1. After a baseline assessment, patients will be randomly assigned to PE, EMDR, ImRs or waitlist (each 25% chance). All patients will receive SUD treatment directly after the baseline assessment. Patients allocated to PE, EMDR or ImRs will receive PTSD and SUD treatment simultaneously (75% of the sample), whereas patients in the 3-month waitlist condition will receive PTSD treatment after completing 3 months SUD treatment (25% of the sample). After the first follow-up measure, patients in the waitlist condition will be randomly allocated to either PE (33% chance), EMDR (33% chance) or ImRs (33% chance) and start with the PTSD treatment. The waitlist condition is necessary to enable a comparison between SUD treatment plus PTSD treatment vs. SUD treatment only; and additionally

enable a comparison between simultaneous and sequential treatment of PTSD and SUD. This is important, since currently it is unknown which timing of PTSD treatment is most effective. Follow-up assessments will take place at 3, 6 and 9 months after the baseline assessment.

The study will be conducted at Jellinek Amsterdam and Jellinek Utrecht. The duration of the study will be 3.5 years, from inclusion of the first participant until the last follow-up measure of the final participant. The trial will be registered in the Netherlands Trial Register (NTR).

Current amendment:

Alle deelnemers die geïncludeerd zijn in de TOPA studie en voldoen aan de inclusie criteria worden telefonisch benaderd voor de aanvullende vervolgmeting. Er is een minimale periode van zeven dagen tussen het benaderen van deelnemers en de vervolgmeting. De meting kan of online (via beeldbellen) of in persoon (bij een Arkin locatie) afgenomen worden.

Intervention

All treatments will be provided by trained therapists working at Jellinek and will consist of twelve 90-minute sessions conducted twice per week.

Intervention 1: Prolonged Exposure (PE): PE involves confrontation with distressing stimuli related to the trauma until anxiety is reduced. It is a manualized intervention including both imaginal and in vivo exposure components (Foa et al., 2007). Imaginal exposure uses confrontation to trauma memories through imagination, whereas in vivo exposure involves confronting real life situations that provoke anxiety and are avoided because of their association with the traumatic event. The aim of both is to extinguish the conditioned emotional response to traumatic stimuli.

Intervention 2: Eye Movement Desensitization and Reprocessing (EMDR): EMDR is a manualized intervention in which the patient is asked to hold the distressing image in mind, along with the associated negative cognitions and bodily sensations, while engaging in saccadic eye movements. After approximately 20 seconds, the therapist asks the patient to *blank it out*, take a deep breath and note any changes occurring in the image, sensations, thoughts or emotions. This process is repeated until desensitization has occurred.

Intervention 3: Imagery Rescripting (ImRs): With ImRs the individual is instructed to imagine the trauma memory as vividly as possible, as if it is happening in the here and now, and to imagine that the sequence of events is changed in a direction that the person desires (Arntz, 2012). The procedure aims to correct dysfunctional meanings attached to trauma memories and restore perceived control.

Current amendment:
not applicable

Study burden and risks

Patients suffering from a substance use disorder are at high risk of suffering from a co-occurring post-traumatic stress disorder. With this study, we can investigate the efficacy of interventions aimed at reducing PTSD symptoms. Participants are expected to benefit from the investigated interventions since it is hypothesized that all three interventions will lead to a reduction of PTSD symptoms. The PTSD treatment Prolonged Exposure is currently already offered to participants as part of regular treatment at Jellinek. In order to participate, participants will have to invest four times 60 to 90 minutes to complete the assessments. Apart from the investment of time, there is no additional burden for participants. Participants in all trial arms will be provided with the same amount of therapy and the same amount of assessments. We see no risks associated with participating in this study.

Current amendment
We expect that the burden voor participation is minimal. Participants will invest 90-120 minutes of their time for the assessment. There are no risks associated with the participation in the follow-up assessment.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- age 18 years or older;
- substance use disorder(s) according to the Diagnostic and Statistical Manual of Mental Disorders 5 criteria (DSM-5; American Psychiatric Association, 2013) with a primary diagnosis involving one of the following substances: alcohol, cannabis, cocaine (snorting) amphetamine, benzodiazepine, opioid.
- posttraumatic stress disorder according to the DSM-5 criteria;
- sufficient understanding of the Dutch language.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study: - acute psychotic disorder; - mental retardation or cognitive impairment (estimated IQ<70); - current physical or sexual abuse or death threats; - suicidal behavior; (A suicide attempt during the past 3 month or acute suicidal ideations according to the MINI) - life threatening self-mutilation; - homelessness. - involvement in a compensation case or legal procedures concerning admission or stay in the Netherlands - involvement in legal procedures regarding the index trauma - engagement in any other current PTSD treatment Current amendement: - Explicit indication at the baseline IC that they do not wish to be approached for future research

Study design

Design

Study type: Interventional

Masking:	Single blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-09-2019
Enrollment:	205
Type:	Actual

Ethics review

Approved WMO Date:	02-07-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-05-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-08-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389

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Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL68144.018.19