Faculty of Pharmacy
كلـــــــية الصـــيدلـــــة

Study Number & Rev.: IRB Protocol CL-006

Identifiers: NCT03469128

Study Title: Cognitive Processing Therapy Versus Sertraline for the Treatment of Comorbid Substance Use Disorder and Post-Traumatic Stress Disorder in Egyptian patients

Study Design: Randomized clinical trial

Sponsor Name: The British University in Egypt

Sponsor Address: El-Sherouk City, Cairo, Egypt

Data Analysis: 01-01-2020

Expected Completion Date: December 2020

Principal Investigator: Dr. Amani Elbarazi, Clinical Practice Department, Faculty of Pharmacy, The British University in Egypt, P.O. Box 43, El-Sherouk City, Cairo 11837, Egypt

STATEMENT OF CONFIDENTIALITY

Protocol signature page

The undersigned has read and understood the trial protocol detailed above and agrees to conduct the trial in compliance with the protocol.

Dr. Amani Elbarazi	Amani	BUE3570	01-01-2016
Principal Investigator (Please print name)	**Signature**	**Site name or ID number**	**Date**

Study Title: Cognitive Processing Therapy Versus Sertraline for the Treatment of Comorbid Substance Use Disorder and Post-Traumatic Stress Disorder in Egyptian patients

Internal Reference Number / Short title: CPT for patients with PTSD and SUD

Ethics Ref: 2016-2017PTBUE

IRAS Project ID: IRB Protocol CL-006

Date and Version No: 01-01-2016

Principal Investigator:	Dr. Amani Elbarazi, Clinical Practice Department, Faculty of Pharmacy, The British University in Egypt, P.O. Box 43, El-Sherouk City, Cairo 11837, Egypt
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Sponsor:	The British University in Egypt, P.O. Box 43, El-Sherouk City, Cairo 11837, Egypt.
Funder:	N/A
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Statistician Signature:	Prof. Mohamed M. Elmazar

Declaration there is no potential conflicts of interest.

Trial Title: Cognitive Processing Therapy Versus Sertraline for the Treatment of Comorbid Substance Use Disorder and Post-Traumatic Stress Disorder in Egyptian patients

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Dr. Amani Elbarazi	Amani	BUE3570	01-01-2016
Principal Investigator (Please print name)	**Signature**	**Site name or ID number**	**Date**

TABLE OF CONTENTS

1. KEY CONTACTS

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LAY SUMMARY

Background: Substance Use Disorder (SUD) often comorbid with Post-Traumatic Stress Disorder (PTSD). Aims: the primary objective of the present study was to investigate the effectiveness of Cognitive Processing Therapy (CPT) in comparison to Sertraline, and placebo in treating patients with comorbid Substance Use Disorder (SUD) and Posttraumatic Stress Disorder (PTSD) using a randomized controlled trial. The secondary objective was to determine the prevalence of PTSD among SUD patients. Methods: Data will be obtained through interviewing patients diagnosed with SUD. Patients will be interviewed by a clinician and asked to complete Mini-International Neuropsychiatric Interview (MINI), Clinician-Administered PTSD Scale (CAPS), Posttraumatic Stress Disorder Checklist (PCL-5), Beck Depression Inventory (BDI-II), Timeline Follow Back Interview (TLFB), and Brief Addiction Monitor (BAM). Patients with comorbid SUD and PTSD who will be randomized to one of the following groups: CPT, Sertraline, or Placebo. Assessments will be conducted at baseline, 3-, 6- and 12-months posttreatment. The primary outcomes will be the scores of CAPS, TLFB and BAM, while the secondary outcomes will be the scores of PCL, and BDI-II. Results: we predict that CPT will result in greater reductions in CAPS scores in CPT, as compared to Sertraline and control groups.

2. SYNOPSIS

Study Title	Cognitive Processing Therapy Versus Sertraline for the Treatment of Comorbid Substance Use Disorder and Post-Traumatic Stress Disorder in Egyptian patients.
Internal ref. no. / short title	CPT for patients with PTSD and SUD
Study registration	Study was registered at clinicaltrial.gov with Identifiers: NCT03469128 on 03/12/2018 and Initial Release: 01/31/2018
Sponsor	The British University in Egypt, El-Sherouk City, Suez Road, Postal No. 11837, P.O. 43 Tel: 19283 (Hot Line), +20226890000- Fax: +20226300010/20 www.bue.edu.eg
Funder	N/A
Study Design	Randomized Clinical Trial
Study Participants	500
Sample Size	150 participants, all of them were patients with SUD and PTSD 50 in the Cognitive Processing Therapy (CPT) group 50 in the Sertraline group 50 in the Placebo control group
Planned Study Period	the total length of the project: 2-3 years the duration of an individual participant's involvement: 3 months
Planned Recruitment period	6-12 months of recruiting

	Objectives	Outcome Measures	Timepoint(s)
Primary	To examine the efficacy of cognitive processing therapy (CPT) in treating comorbid SUD and PTSD compared to Sertraline and controls using a randomized controlled trial.	Interview by clinician Complete: Mini International Neuropsychiatric Interview (M.I.N.I), The Brief Addiction Monitor (BAM), PTSD Checklist–Civilian (PCL-5), Clinician-Administered PTSD Scale (CAPS).	Assessments will be conducted at baseline, 3-, 6- and 12-months posttreatment.
Secondary	To investigate the prevalence of PTSD among patients with SUD	Interview by clinician Complete: Mini International Neuropsychiatric Interview (M.I.N.I), The Brief Addiction Monitor (BAM), PTSD Checklist–Civilian (PCL-5), Clinician-Administered PTSD Scale (CAPS).	Patients diagnosed with SUD will be scanned for PTSD
Intervention(s)	Cognitive Processing Therapy (CPT)		
Comparator	Sertraline		
Comparator	Placebo control		

3. BACKGROUND AND RATIONALE

Substance-use disorders (SUD) are patterns of symptoms resulting from the use of a substance that a person continues using, despite experiencing problems because of that substance (American Psychiatric Association, 2013). Substance use disorder is a disease that affects a person's brain and behavior that caused by different factors including genetics (Goldman, Oroszi & Ducci, 2005), environmental (e.g., family's beliefs and attitudes) emotional, cognitive, social causes (peers who encourage drug use) and/or exposure to trauma (Hawkins, Catalano & Miller, 1992, Mayberry, Espelage & Koenig, 2009). Exposure to trauma and stress throughout a lifetime may result in increasing the probability of extensive alcohol consumption or using drugs as a maladaptive coping technique (Chilcoat & Breslau, 1998, McLellan, 2017). Substance Use Disorder (SUD) often comorbid with Post-Traumatic Stress Disorder (PTSD) (Grant et al., 2015, Gulliver & Steffen, 2010, Seal et al., 2011). Posttraumatic Stress Disorder (PTSD) is characterized by intrusive, avoidance, hyperarousal, symptoms, and negative alterations in cognitions and mood (American Psychiatric Association, 2013). Psychological consequences of trauma could be in the form of the body's aches and pains, emotional suffering, destructive thoughts, and/or destructive behaviors

(Fernandez et al., 1999, Fernandez & Kerns, 2012). Suffering caused by trauma may negatively impact a person's quality of life which can be manifested as a deterioration in his/her activities, feeling guilty, ashamed, and unworthy, and having destructive thoughts and behaviors about self, others, and the world (Kilpatrick, et al., 2013).

Avoidance and escaping are very common maladaptive strategies among PTSD patients. One example of escaping maladaptive strategies of PTSD patients is using alcohol and/or drugs to avoid thinking of trauma/s they experienced. Therefore, several studies have shown high rates of (PTSD) among patients with (SUD) (Flanagan et al., 2016, Debell et al., 2014, Breslau, Davis, & Schultz, 2003). Unfortunately, patients with comorbid SUD and PTSD have worse results on medication, are less compliant with treatment, are more likely to drop out of therapy, have higher rates of self-destructive behaviors, and are less likely to seek pharmacotherapy and psychological help and support (Smith & Randall, 2012, Brady et al., 1994). These findings highlight the demanding need for the development of treatments that address both disorders. Meta-analysis research showed that medicine is considered one of the options to treat comorbid PTSD and SUD patients (Lee et al., 2016). Sertraline and paroxetine are the drugs that were approved by the Food and Drug Administration to treat PTSD symptoms (PTSD: National Center for PTSD) (Brady et al., 2005). Sertraline is considered a front-line medication for PTSD shown to also impact SUD outcomes (Huang et al., 2020). Sertraline would be expected to treat SUD based on prior literature (Petrakis & Simpson, 2017). A study conducted by Hien et al. (2015) compared psychotherapy treatment called Seeking Safety (SS) combined with either medication (Sertraline), or placebo in a sample of patients with comorbid PTSD and alcohol use disorder (AUD). Seeking Safety is a non-exposure-based psychosocial treatment that addresses both PTSD and substance/Alcohol use disorder (Najavits et al., 1998). The results of Hien et al. (2015) showed that patients who received SS combined with sertraline had a significantly greater reduction in PTSD symptoms severity at the end of treatment than those who received SS combined with placebo.

Studies suggest that treatments that address PTSD and SUD simultaneously can be cost-effective, and have more effective therapeutic consequences (Mills et al., 2012). The study of Foa, Hembree, & Rothbaum, 2007) suggested the Prolonged Exposure (COPE) with cognitive behavioral therapy as an effective treatment for PTSD and SUD. Cognitive Behavioral Therapy (CBT) helps PTSD & SUD patients to learn how to detect their maladaptive and destructive thoughts and debate them with logic and delete them (Sannibale et al., 2013). CBT also helps patients to gain useful behavioral skills, increase pleasant activities, and develop effective healthy relationships with other people (Lydecker et al., 2010, Roberts et al., 2015). Also, Stress Inoculation Training (SIT) can help patients with PTSD to relax and be more attentive. SIT involves teaching patients coping skills to manage stress and anxiety caused by trauma (Meichenbaum, 2007).

The International Society for Traumatic Stress Studies recommends Cognitive Processing Therapy (CPT) and Prolonged Exposure Therapy (PE) as effective treatments for patients with comorbid PTSD & SUD (Bisson et al., 2019). CPT is a well-described therapeutic protocol written by Resick and Schnicke (1993) and later updated by Resick (2001, 2008, 2014, 2017).

CPT is a 12-session evidence-based manualized treatment consists of trauma-focused therapy and cognitive therapy (Resick, Monson, Chard, 2014). CPT includes pretreatment assessment, educating patients about PTSD's symptoms, types, causes, and how trauma can affect their daily life and functioning, identifying the "stuck points" which mean destructive thoughts related to the trauma, recognizing how trauma affects patient's self-esteem, trust, power, safety and intimacy, personal growth and setting future life goals to have the valuable meaning of life (Resick, Monson, Chard, 2014).

Randomized clinical trials reported that the (CPT) is successful in the management of PTSD with long-lasting 5 to 10-year outcomes and the highest impact and effect size of any PTSD therapy (e.g., Forbes, et al., 2012, Haagen, et al., 2015). Examining the impact of CPT among veterans who were diagnosed with PTSD and SUD and were participating in a six-week residential treatment program, showed that veterans with or without SUDs benefited from CPT equally (McDowell & Rodriguez, 2013). Kaysen et al., (2014) also investigated the effectiveness of CPT with patients with PTSD and AUD who attended at least 1 CPT session. Results have shown that CPT resulted in significant decreases in PTSD and depression over time. Further, Peck, et al., (2018) examined the effectiveness of 6-week day CPT-based treatment with patients diagnosed with PTSD and SUD. Their results showed that CPT significantly decreases maladaptive trauma-related cognitions. Bryan et al., (2018) examined the effectiveness of an intensive, 2-week CPT treatment program with veterans diagnosed with PTSD. They found that CPT significantly reduced PTSD symptom severity, rates of PTSD diagnosis, and suicide ideation.

Studies suggested that effective treatment approaches of PTSD in Egypt include CBT (e.g., Jalal et al., 2017), trauma-focused therapy (e.g., Lambert & Alhassoon, 2015), and interpersonal psychotherapy (Meffert et al., 2014). Yet, our study is the first trial that compare CPT with Sertraline among an Egyptian population.

However, despite the significant distress, impairment, and complicated clinical course facing patients with co-occurring SUD and PTSD, substantial gaps remain in the literature regarding effective treatment approaches. Recent encouraging advances include the psychosocial treatments and the examination of either psychosocial or pharmacological approaches to treating the complex presentation of SUD and PTSD. Therefore, the primary objective of the present study was to investigate the effectiveness of Cognitive Processing Therapy (CPT) in comparison to Sertraline in treating patients with comorbid SUD and PTSD. The secondary objective was to determine the prevalence of PTSD among SUD patients. We hypothesized that treating PTSD will echo in improvements in SUD. The current study marks the first randomized controlled trial to test the benefit of CPT for cooccurring (PTSD) and (SUD), with Sertraline, a front-line medication for PTSD shown to also impact (SUD) outcomes in the Arabic population.

4. OBJECTIVES AND OUTCOME MEASURES

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objectives To examine the efficacy of cognitive processing therapy (CPT) in treating comorbid SUD and PTSD compared to Sertraline and controls using a randomized controlled trial.	Mini-International Neuropsychiatric Interview (MINI), Clinician-Administered PTSD Scale (CAPS), Posttraumatic Stress Disorder Checklist (PCL-5), Beck Depression Inventory (BDI-II), Timeline Follow Back Interview (TLFB), and Brief Addiction Monitor (BAM).	Assessments were conducted at baseline, 3-, 6- and 12-months posttreatment
Secondary Objectives To investigate the prevalence of PTSD among patients with SUD	Interview by clinician Complete: Mini International Neuropsychiatric Interview (M.I.N.I), Clinician-Administered PTSD Scale (CAPS).	Patients diagnosed with SUD will be scanned for PTSD

5. STUDY DESIGN

This study is “Randomized clinical trial”

We are going to interview SUD patients in this study. Participants are going to be asked to complete an eligibility and baseline assessments, including structured interviews and self-report measures to be classified as comorbid PTSD & SUD patients. If we found patients who are diagnosed with both PTSD & SUD, we are going to divide them into three groups: 1) CPT group, 2) Sertraline group. The third group will be placebo control group.
All participants in all groups will complete standardized tests and checklists of PTSD and SUD symptoms as pre-treatment assessment, 3-, 6- and 12-months posttreatment

5.1. Study Participants

Comorbid PTSD & SUD patients

5.2. Inclusion Criteria

1) age older than 18 years, 2) patients meeting current diagnostic criteria for both PTSD and SUD as defined in DSM-5 3) have a good knowledge of English-language (reading, writing, and comprehension) because all assessments and therapy materials were in English

5.3. Exclusion Criteria

having 1) mental retardation, 2) having schizophrenia (or any other psychotic disorders) and/or 3) being pregnant.

6. PROTOCOL PROCEDURES

The intervention will be either psychotherapy or Sertraline. The psychotherapy chosen to this study is the Cognitive Behavioural Therapy (CPT).

Part I: each patient will attend 12 individual sessions with the therapist. The standard manual of CPT (Resick et al., 2014) is going to be employed but we will add some points related to substance use disorder treatment. We will add brief check-ins regarding any recent substance use or cravings at the beginning of sessions. We will teach patients to effectively process cognitions related to substance use by utilizing Challenging Belief Worksheets. The outlines of the therapy during the sessions will be as follows.

Sessions 1-4: education and Impact Statement

- Explain to the patients the PTSD and SUD symptoms, causes, and types. Patients are going to be asked to write Impact Statement. Patients are going to be learned connections between events, thoughts, and feelings. Patients are going to write detailed accounts of the trauma including sensory details, thoughts, and feelings. CPT +A.

Sessions 5-7 cognitive therapy:

-Patients are going to be asked to write everything they recall about the traumatic event, their emotions, feelings, thoughts, sensory details related to traumatic event. Describe how the trauma affect their perceptions and emotions in different domains such safety, trust, power and control, esteem, and intimacy. The patients are going to be asked to read their writings about the trauma every day for a week. They are going to be taught to accept the emotions that come up while reading the trauma's writings.

- we will use Socratic questioning regarding stuck points. Stuck points are thoughts that keep repeating again and again like a record inside the patient's brain.

-learning about patterns of faulty thinking (problematic thinking patterns). For example, assimilation, which means when patients alter incoming information to match their previous beliefs. If a patient thinks bad things only happen to bad people, they will then believe that because they were assaulted, they were a bad person and deserved the trauma. Another example, I feel guilty because I have done something wrong otherwise why would I feel guilty.

- we will employ challenging beliefs worksheets.

Sessions 8-10 over accommodation

-Modules and worksheets regarding: Safety, trust, power/control, esteem, intimacy.

-patients are going to be asked to rewrite impact statements.

- Patients are going to be asked to describe their emotions and thoughts about traumas but with more insight to identify the cognitive distortions and destructive thoughts by using worksheets. Patients are going to be taught to differentiate between facts, emotions, and thoughts. For example: "I am responsible for the trauma" "it is my fault to go there late". patients are going to be taught the fact is: you were raped and assaulted, while your own thought is "my fault and mistake" your thoughts do not mean the fact or the reality at all.

Sessions 11-12: develop a new thought or plan

Encourage the patients to set personal future goals to achieve personal growth by developing new supportive and positive, more optimistic thoughts. later patients are going to be learned to deal with the meaning of the stressful events and current beliefs about self and others.
In both CPT individual and group sessions, we aimed to teach the patients to become their own therapists

6.1. Recruitment

Patients were recruited from Ain Shams University teaching Hospital, Cairo, Egypt. All patients' data and demographic information are stored at a much-secured place at the British University in Egypt (BUE). The present study is a Randomized Controlled Trial (RCT) with three groups: control group, Sertraline group and the CPT group.

6.2. Screening and Eligibility Assessment

The participants who will be eligible for the study will be approached and those who agreed to participate in the experiment protocol will be randomly assigned to either one of the three groups (CPT, Sertraline, Control).

6.3. Informed Consent

The patients signed the participants' information sheet and consent form and were informed that the experiment will include two psychological assessments of SUD and PTSD. Patients who will be assigned to the experimental groups are going to be informed about the treatment protocol to investigate the efficacy of the treatment. All patients will sign the Informed Consent form before any study specific procedures are performed. Written and verbal versions of the patients Information and Informed Consent will be presented to the patients detailing the following points: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent will be the Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site.

6.4. Randomisation

This is a three-group, repeated-measure, parallel-group, Randomized Control Trial design. Patients, study psychiatrists, and assessors will be blind to treatment condition assignment. Randomization blocks of three will be used to maintain equal group size. Participants will be re-assessed at 3, 6, 12 months post-treatment. The pharmacy of Ain Shams Hospital will create sertraline and matching placebo kits with single-identifier numbers based on a random code that was provided to an unblinded statistician (Prof. Elmazar) who will instruct the psychiatrist how to distribute kits to patients.

6.5. Blinding and codebreaking

This is a three-group, repeated-measure, parallel-group, Randomized Control Trial design. Patients, study psychiatrists, and assessors were blind to treatment condition assignment. Randomization blocks of three were used to maintain equal group size. Outcome's assessments were PTSD severity, substance use severity, and depression. The pharmacy of Ain Shams Hospital will create sertraline and matching placebo kits with single-identifier numbers based on a random code that will be provided to an unblinded statistician (Prof. Elmazar) who will instruct the psychiatrist how to distribute kits to patients.

6.6. Description of study intervention(s), comparators and study procedures (clinical)

If we could find comorbid PTSD & SUD patients in our study, then they will be divided into three groups: 1) CPT group
2) the "medication group" who will receive Sertraline.
3) The third group will be the placebo control group.
All participants in all groups will complete standardized tests and checklists of PTSD and SUD symptoms as pre-treatment, post-treatment, 6-months, and 12-months assessments.

6.6.1. Description of study intervention(s)

6.6.2. Cognitive Behavioural Therapy (CPT) is a manual-guided therapy (Resick et al., 2014) focused on PTSD symptom reduction. It is delivered in weekly 45–50-minute individual sessions during a 12-week timeframe. The outlines of the therapy during the sessions were as follows. Therapy is delivered in weekly 45–50-minute individual sessions during a 12-week timeframe. Sessions 1-4: education and Impact Statement, how the trauma affects their perceptions and emotions in different domains such as safety, trust, power and control, esteem, and intimacy. Sessions 5-7 cognitive therapy. Sessions 8-10 over accommodation. Patients asked to rewrite impact statements. Patients were asked to describe their emotions and thoughts about traumas but with more insight to identify the cognitive distortions and destructive thoughts by using worksheets. Sessions 11-12: develop a new thought or plan. Encourage the patients to set personal future goals (See Appendix D).

6.6.3. Description of comparator(s)

Medication: To test drug adherence, the matching capsules will include sertraline or placebo as well as riboflavin. Compliance will be also checked by pill count. Participants receiving sertraline started on 50 mg daily and titrated up to 200 mg daily over 2 weeks. Participants will continue their full sertraline dose until the end of the trial (12 months). The “medication group” who will receive Sertraline. Prof. Hanan Elrassas is the psychiatrist at the Department of Neuropsychiatry, Faculty of Medicine, Ain Shams University, who is responsible for prescription of medicine for the patients.

6.6.4. Description of study procedure(s)

All participants in all groups will complete standardized tests and checklists of PTSD and SUD symptoms

Assessments will include:

During the time of the study, patients will meet weekly with a psychiatrist for the collection of a urine sample to examine drug use and any adverse events. After the study treatment phase, assessment interviews will be conducted by a blind independent assessor (Prof. Badary) at the end-of-treatment, 3, 6, 12 months posttreatment.

Patient demographics: Personal Information and questions that will include closed-ended questions about participants' sociodemographic characteristics, personal, family-related, social, financial, educational, and academic-related problems.

Mini-International Neuropsychiatric Interview (MINI) standard version 7.0.2 for DSM-5 is used for screening for SUD, and PTSD. The M.I.N.I. is the structured psychiatric interview of choice for psychiatric evaluation and outcome tracking in clinical trials with an administration time of approximately 15 minutes (Sheehan et al., 1998).

Clinician-Administered PTSD Scale (CAPS-5; Weathers et al., 2015) is currently the gold-standard assessment for PTSD and is used to assess PTSD's symptoms at pre-and post-treatment. This 30-item structured interview was developed by staff at the U.S. Department of Veterans Affairs National Center for PTSD. The interview can generally be administered in 45-60 minutes. Each question in CAPS asks about both the frequency and the severity of each PTSD symptom. These questions are split into categories. Each criterion has several questions, and scores for each criterion are added up at the end. The CAPS-5 has demonstrated strong psychometric properties (Weathers, et al., 2018). In the present study, CAPS-5 demonstrated strong interrater reliability (κ=.90). A random sample of 35 tapes was selected for evaluation of interrater reliability for the CAPS. Categorical diagnostic analyses revealed that the kappa coefficient for the overall PTSD diagnosis was 1.00 with 100% agreement. Kappa values and percentages of agreement for each of the three clusters of PTSD symptoms were as follows: reexperiencing (κ = .90; 95% agreement), avoidance (κ = .85; 89% agreement), and arousal (κ = .80; 87%

agreement). Also, in the current sample, internal consistency (Cronbach's alpha) across subscales was excellent at both time points (α = 0.94 and 0.96).

Posttraumatic Stress Disorder Checklist (PCL-5) to measure the severity of the PTSD symptoms by the 20 items. The PCL-5 is a self-report measure that evaluates the degree to which an individual has been bothered in the past month by PTSD symptoms as described by DSM–5 (Weathers et al., 2013). Items are put on a 5-point Likert scale and are rated from 0 (not at all) to 4 (extreme), then items, are summed for a total severity score. Subscale severity scores are calculated by summing items in each of the four DSM–5 PTSD symptom clusters: intrusions (Items 1–5), avoidance (Items 6 –7), negative alterations in cognitions and mood (NACM; Items 8 –14), and alterations in arousal and reactivity (AR; Items 15–20). PTSD was defined as endorsing a severity of at least a 2 (moderate) for enough symptoms in each cluster to meet DSM–5 criteria. Evidence for the PCL for DSM-5 suggests that a 5-10-point change represents reliable change, and a 10-20-point change represents clinically significant change (Weathers, et al. 2013). The PCL has demonstrated acceptable psychometric properties (Sveen et al., 2016). For the present study, internal consistency was acceptable at both time points (α = 0.81 and 0.94) and Categorical diagnostic analyses revealed that the kappa coefficient for the overall PTSD diagnosis was .98 with 95% agreement.

Beck Depression Inventory (BDI-II): was used to evaluate the severity of depressive symptoms. BDI-II is a 21-item, self-report rating inventory that measures characteristic attitudes and symptoms of depression (Beck, et al., 1996). The BDI takes approximately 10 minutes to complete. Depression levels were defined as follows: minimal range = 0–13, mild depression = 14–19, moderate depression = 20–28, and severe depression = 29–63. The BDI-II has demonstrated good reliability and validity (Beck et al., 1996). Cronbach's alpha was excellent at pre-and post-treatment in the present study (α=0.90 and 0.91, respectively) and one-week test-retest stability was high (.90).

Timeline Follow Back Interview (TLFB; Sobell and Sobell, 1992), was administered to assess substance use patterns. Participants estimated their daily substance use in the previous 30 days with a detailed calendar to help them identify their uses and specific episodes of heavy use. TLFB has demonstrated good reliability as an instrument for the estimation of daily substance use (Sobell, Sobell, Leo, & Cancilla, 1988).

Brief Addiction Monitor (BAM) to measure the SUD symptoms. The BAM is a 17-item self-report measure that assesses substance use. It includes the following subscales: 1) Use any alcohol or drug: if a patient scores a 1 or greater, it calls for further clinical attention 2) Risk Factors including cravings, physical health, sleep, mood, risky situations, or Family/social problems. If a patient scores a 12 or greater in the risk factors, he needs clinical attention 3) Protective factors include self-efficacy, self-help behaviors, religion/spirituality, work/school participation, adequate Income, sober support. If a patient scores a 12 or below in protective factors, it calls for clinical attention. The previous studies showed acceptable characteristics of psychometric properties of BAM (e.g., Cacciola et al., 2013). In the current study, internal consistency (Cronbach's alpha)

across subscales was excellent at both time points (α = 0.90 and 0.91) and Kappa values and percentages were obtained for SUD (κ = .95; 98% agreement).

Urine drug screen (UDS) tests (CLIAwaived Inc.) will be administered weekly to assess for the presence of cocaine, marijuana, benzodiazepines, opioids, and amphetamines. Urine samples will be also tested for riboflavin to assess medication compliance.

6.7. Baseline Assessments

Interview by clinicians who had at least a Ph.D.'s degree in clinical psychology or Psychiatry. Assessments including: Mini-International Neuropsychiatric Interview (M.I.N.I), The Brief Addiction Monitor (BAM), PTSD Checklist–Civilian (PCL-5), Clinician-Administered PTSD Scale (CAPS). The primary outcome will be the total scores on the BAM, CAPS for *DSM-5,* the secondary outcome will be the total scores on the PCL, TLFB and BDI-II for *DSM-5*. Evaluations are going to be conducted at baseline and 6 months after the first assessment.

Subsequent Visits

participants will return to the hospital after 3, 6, and 12- months and the following assessments will be conducted: Interviews by clinicians - Clinician-Administered PTSD Scale (CAPS), Posttraumatic Stress Disorder Checklist (PCL-5), Beck Depression Inventory (BDI-II), Timeline Follow Back Interview (TLFB), and Brief Addiction Monitor (BAM)

6.8. Sample Handling

N/A

6.9. Early Discontinuation/Withdrawal of Participants

During the course of the study a participant may choose to withdraw early from the study treatment at any time. This may happen for several reasons, including but not limited to:

- The occurrence of what the participant perceives as an intolerable AE.
- Inability to comply with study procedures
- Participant decision

According to the design of the study, Participants can withdraw from the study but permit data and samples obtained up until the point of withdrawal to be retained for use in the study analysis. No further data or samples would be collected after withdrawal.

In addition, the Investigator may discontinue a participant from the study treatment at any time if the Investigator considers it necessary for any reason including, but not limited to:

- Pregnancy
- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- Clinical decision

6.10. Definition of End of Study

The study will be ended when we can get at least 50 patients with comorbid SUD and PTSD to be treated by the Cognitive processing therapy condition.

7. SAFETY REPORTING

Participation in this study involves answering questionnaires a risk of taking part could be related to any questions that they might consider too sensitive, intrusive, or upsetting. We will inform them "If you consider any of the questions as being inappropriate, please feel free not to give any answer". Also, Patients in CPT group are going to be asked to write about their traumas they experienced. In these written accounts, participants will provide sensory details, thoughts, and feelings associated with the traumas. Unlimited time is allotted for the narrative and once it is completed patients are asked to read the account daily until the next session. In addition, between-session assignments are given after each treatment session. Cognitive processing therapy are going to be delivered individually weekly and group weekly sessions.

7.1. Definition of Serious Adverse Events

N/A

7.2. Reporting Procedures for Serious Adverse Events

N/A

8. STATISTICS AND ANALYSIS

SPSS will be used to analyse the data. The normality of the data distribution will be investigated using the Kolmogorov-Smirnov test. Homogeneity assumptions will be examined using, Levene's tests. Mauchly's test will be employed to examine the assumption of sphericity.

8.1. Statistical Analysis Plan (SAP)

Descriptive statistics (means, standard deviations, frequencies, percentages) were used to describe the sociodemographic and baseline characteristics of this sample. Bivariate analyses were employed to compare demographics and baseline symptom severity between the CPT, sertraline, and placebo group, and to explore the data for potential covariates for the main omnibus analyses. The main outcome variable for PTSD was CAPS & PCL total scores and was administered at pre-treatment (baseline) and all follow-up assessments. The main outcome variable for Depression was BDI-II total score and was administered at baseline and all follow-up assessments. The main outcome variables for SUD were, the total score on (BAM), the average number of substances used in the past 30 days (PDU), and self-reported abstinence from the substance or/and alcohol in the prior 7 days, and negative urine tests at follow-up assessments.

All analyses were conducted on the intent-to-treat sample. Generalized estimating equations (GEE) were utilized to model PTSD and SUD outcomes (Ballinger, 2004). A

temporal within-subjects autoregressive [AR (1)] correlation matrix was used to model participants across timepoints. Models were specified according to the distributions of the outcome measures. Identity link functions for normal distributions were used to model CAPS, PCL, BDI-II, and BAM severity scores, negative binomial models with log link were applied to the SUD measures of SU, PDU, and past 7 days abstinence rate was modelled using logit link for binary distribution. We use GEE, as it extends the generalized linear model, which processes corresponding data from repeat measurements, needs no assumption of parametric distribution and robust inference for an incorrect description of the internal correlation of subjects, and has good indications to the within-subject correlations (Zeger et al., 1988). Therefore, results are reported using parameter estimates for CAPS, PCL, BDI-II, RF, PF, incidence rate ratios for SU, PDU, and odds ratios for abstinence rate. All models included variables of time, treatment, time-by-treatment interaction, and any demographic or baseline diagnostic covariates for which there was a significant difference between groups. Consistent with prior studies applying similar analytic methods to comparable sample sizes (Schneier et al., 2012), and to reduce the probability of Type-II errors (Selvin, 1996), interactions that were at least trend-level (i.e., $\alpha < .10$) were investigated for simple effects at end-of-treatment and follow-up time points. When an interaction did not meet this criterion, outcomes were modelled as main effects with covariates of time and baseline values of the outcome measures included in the model. All simple and main effects were considered significant at the $\alpha = .05$ level (two-tailed). Bonferroni corrections were applied to all models of PTSD, depression, and SUD outcomes to control for Type I error. Sensitivity analyses with multiple imputations were conducted to further assess the influence of missing data in significant models.

8.2. Sample Size Determination

A priori statistical power analyses ensured that the sample size was sufficient to detect meaningful differences in primary outcomes. We set the following parameters based on previous research: the two-tailed test of significance, desired power=0.80, unstructured covariance matrix, four time-points, correlation= 0.40 between repeated assessments, and attrition at 30% from pre-treatment to posttreatment. With a (50 per group), the study has 80% power to detect a medium effect size of 0.55 for group (treatment types) difference on primary outcomes.

Analysis populations

All participants as randomised / registered / enrolled; all participants who will attend the intervention; all eligible participants

8.3. The Level of Statistical Significance

The level of significance to be used is < .05

8.4. Procedure for Accounting for Missing, Unused, and Spurious Data.

Missing data are unavoidable in clinical research, potentially leading to bias and loss of precision. Multiple imputation (MI) will be utilized.

8.5. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

All deviation(s) from the original statistical plan (if any) will be described in the final report.

8.6. Health Economics Analysis

N/A

9. DATA MANAGEMENT

All patients' data and demographic information are stored at a much-secured place at the British University in Egypt (BUE). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number, not by name.

9.1. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host hospital for monitoring and/or audit of the study to ensure compliance with regulations.

9.2. Data Recording and Record Keeping

All trial data will be entered on CRFs

The participants will be identified by a unique trial specific number in any database. The name and any other identifying detail will NOT be included in any trial data electronic file.

The data will be retained for 7 years

10. QUALITY ASSURANCE PROCEDURES

The study will be monitored, in accordance with the current protocol, relevant regulations and standard operating procedures.

10.1. Risk assessment

A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities.

10.2. Study monitoring

The British University in Egypt (BUE) is the sponsor for the study. Regular monitoring will be performed according to the study specific Monitoring Plan. Data will be evaluated for

compliance with the protocol and accuracy in relation to source documents as these are defined in the study specific Monitoring Plan. Following written standard operating procedures, the monitors will verify that the clinical study is conducted, and data are generated, documented and reported in compliance with the protocol and the applicable regulatory requirements.

11. PROTOCOL DEVIATIONS

Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

12. SERIOUS BREACHES

If a serious breach is suspected the Sponsor must be contacted within 1 working day. The serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving Ethical committee and the relevant host hospital within seven calendar days.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

13.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

13.3. Approvals

Following Sponsor approval the protocol, informed consent form, participant information sheet will be submitted to an appropriate Research Ethics Committee (REC), and host hospital for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

13.4. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

13.5. Participant Confidentiality

Issues of confidentiality were addressed by attributing a coding number to each participant's data and by keeping all data in secured location (both physical and digital). All participants were made aware of these confidentiality procedures.

13.6. Expenses and Benefits

NA

14. FINANCE AND INSURANCE

14.1. Funding

NA

14.2. Insurance

NA

15. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

16. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

'not applicable'

17. ARCHIVING

Issues of confidentiality were addressed by attributing a coding number to each participant's data and by keeping all data in secured location (both physical and digital). All participants were made aware of these confidentiality procedures. The data will be stored for 7 years.

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