Guided Internet Cognitive Behavior Therapy (ICBT) treatment of Posttraumatic Stress Disorder (PAXPTSD) for Romanian population

A study protocol of a randomized controlled trial

Introduction

In the general population the estimated lifetime prevalence of posttraumatic stress disorder (PTSD) ranges from 5.6% to 8.3% (Alonso, Angermeyer & Lepine , 2014; Kessler et al., 1995; Niles et al., 2018). Around 65% of the world population experience at least one potential traumatic event at some point during their life (Kuester, Niemeyer & Knaevelsrud , 2016; Sijbrandij,Kunovski & Cuijpers, 2016). In Europe, the lifetime prevalence of PTSD is estimated between 1.9% (Ferry et al., 2010) and 11% (Lewis et al., 2018). In cases of people with PTSD approximately 50% of people recover within two years, while about a third continue to meet criteria for diagnosis six years later (Alonso, Angermeyer& Lepine, 2014).

Posttraumatic stress disorder is a serious disorder and if people do not receive appropriate care, the symptoms get worse and PTSD becomes chronic. Frequently, when patients have a diagnosis of PTSD they also meet criteria for depression, another anxiety disorder (e.g. general anxiety disorder) or substance abuse (Ehring, Ehlers & Glucksman; Kleim, Ehlers & Glucksman , 2012; Lommen et al, 2016;, 2008; Nosen et al., 2014).

Guidelines for treatment of PTSD strongly recommend TF-CBT (Trauma Focused Cognitive Behavioral Therapy). This family of psychotherapies/interventions include: cognitive behavior therapy (CBT); cognitive processing therapy (CPT), cognitive therapy (CT) and prolonged exposure therapy (PE) (Nosen et al., 2014; Ofer levi, Yair Bar-Haim, Yitshak Kreiss, & Eyal Fruchter, 2015; Wang et al, 2005; Wild et al, 2016;). In the treatment of PTSD, these are also the most commonly studied types of psychotherapy (Bradley V. Watts et al., 2013; Ofer levi, Yair Bar-Haim, Yitshak Kreiss,& Eyal Fruchter, 2015). Despite the efficacy of these interventions and the potential to successfully treat this condition, only a minority of people receive an adequate treatment. Many patients with PTSD are unable to access treatment because resources are limited, they may fear stigmatization, shame, have negative beliefs about mental health services, high costs, symptoms of avoidance or live in remote areas (Ciuca, Berger, Crisan, & Miclea, 2016; Florescu et al., 2009; Tulbure et al., 2015). In Romania, where the current study will be conducted, epidemiological data present that only 2-3% of the individuals with anxiety problems and substance abuse and only 10.2% of the individuals with affective disorders search for treatment in the first year since the debut

of disorder (Florescu et al., 2009). Also 76.4% of the individuals with mental health disorders do not have access to any form of treatment and only 11.5% receive psychological or psychiatric help (Florescu et al., 2009).

Internet-based cognitive behavioral treatments (ICBT) represent relative recent attempts to innovate the psychotherapeutic process. Research on internet-based treatments has rapidly grown in the past decades. ICBT programs have been developed since the late 1990s and there are empirical studies supporting their efficacy and effectiveness (Andrews et al., 2018; Ciuca, Berger, Crisan & Miclea, 2016; Carbring et al., 2005; National Collaborating Centre for Mental Health, 2005; Richards & Richardson , 2012; Tulbure et al., 2015). There is growing evidence of studies which demonstrate the efficacy of therapist-guided ICBT for depression and anxiety disorders (Andrews, et al., 2018; Ciuca, Berger, Crisan & Miclea, 2018, Tulbure et al., 2015), as well as for patients diagnosed with PTSD symptoms (Ivarsson et al., 2014; Klein et al., 2009; Lewis et al., 2018; Litz, Engel, Bryant, Papa, 2007; Spence et al., 2011).

One of the first people who developed and tested a therapist-guided internet-based treatment protocol for persons exposed to trauma in controlled studies was Lange et al. The intervention was named Interapy (Lange et al., 2003; Lange, et al., 2001) and was based on the principles of expressive writing intervention. The participants had to write about the trauma, confront the trauma, reappraise the event, share and take a symbolic leave of the traumatic event (Lange et al., 2003). The program was translated and tested in studies conducted in Germany (Knaevelsrud, Maercker, A., 2007; Saunders et al., 1993) and Iraq (Saunders et al., 1993; Wagner, Schulz, KInaevelsruf, 2012). The effect size of Interapy was large and the results were stable over a period of 3 months (Wagner, Schulz, KInaevelsruf, 2012).

Results from meta-analyses provide support for the efficacy of ICBT in treating PTSD (Lewis et al., 2019). ICBT interventions for PTSD are demonstrated to also be effective not just in PTSD symptoms but also in symptoms associated to PTSD like depression and other anxiety symptoms (Ivarsson et al., 2014; Sijbrandij, Kunovski, Cuijpers, 2016;). Moderate to large effect sizes were found for PTSD global symptom severity as well as for subscales for avoidance, intrusion and hyperarousal, when compared to passive control (Ivarsson et al., 2014). The effect size of CBT and ICBT for PTSD is displayed in **Table 1.**

In Romania we have efficient internet-based treatments for anxiety disorders: panic disorder, social anxiety disorder (Ciuca, Berger, Crisan, & Miclea, 2018; Tulbure et al., 2015). A research team proposed a multiuser platform, *PAXonline*, to prevent and treat anxiety disorders (generalized anxiety disorder, obsessive-compulsive disorders,

panic, different phobias, posttraumatic stress disorder etc.) (Miclea, Ciuca & Miclea, 2009; Miclea, Miclea, Ciuca, Budau, 2010). The platform and the program for PTSD were constructed in 2012, (Ciuca, 2019). We modified the program in accord to DSM-V (APA, 2013) criteria and want to test the program in a random clinical trial which is the golden standard in testing the efficacy of a treatment.

Table 1 The effect size of ICBT and CBT for PTSD

CBT	*Study*	*Conditions*	*N*	*Primary Outcome Measure*	*g*	*FU (Months)*
	Blanchard et al. (2003)	CBT ST WLC	78	CAPS PCL IES	0.84 [0.30, 1.40]	3 months
	Bryant et al. (2003)	IE IE+ CR SC	58	CAPS-I CAPS-F IES-I IES-A	0.71 [0.07, 1.35]	6 months
	Cottrauxet al. (2008)	CBT ST	60	PCL GCI BDI FQ QL	0.54 [0.03, 1.06]	24 months
	Ehlers et al (2014)	ICT Weekly cognitive therapy Weekly supportive therapy WLC	121	CAPS PDS	0.63 [0.12, 1.14]	6 months
	Foa et al. (1991)	SIT PE SC WLC	45	PDS	0.42 [-0.41, 1.26]	3 months
	Markowitz et al. (2015)	PE Relaxation	110	CAPS	0.66 [0.15, 1.18]	-
	Marks et al. (1998)	PE CR CR+PE Relaxation	87	CAPS	0.75 [0.11, 1.40]	6 months

	McDonagh et al.(2005)	CBT PCT WLC	74	CAPS	0.14 [-0.41, 0.69]	3months, 6 months
	Neuner et al. (2004)	NET SC Psychoeducation	43	PDS	0.33 [-0.39, 1.06]	4 months, 12 months
	Rauch et al. (2015)	PE PCT	36	CAPS	0.99 [0.19, 1.79]	-
	Resick et al. (2015)	Group CPT Group PCT	108	PCL BDI-II	0.24 [-0.13, 0.62]	2 months, 6 months, 12 months
	Schnurr et al. (2003)	TF groups psychotherapy PCT	360	CAPS	0.04 [-0.18, 0.26]	18 months 24 months
	Schnurr et al. (2007)	PE PCT	277	CAPS	0.33 [0.10, 0.57]	3 months 6 months
	Surís et al. (2013)	CPT PCT	86	CAPS PCL QIDS	0,35 [-0.09, 0.78]	2 months, 4 months, 6 months
ICBT	*Study*	*Conditions*	*N*	*Primary Outcome Measure*	*Hedges'g*	FU (Months)
	Carpenter et al. (2014)	CBSM WLC	132	IES	0.31	5 months
	Hirai and Clum (2005)	SHICBT WLC	27	SRQF	0.57-0.59	-
	Kersting et al. (2011)	ICBT WL	82	IES-R	0.55	3 months
	Kersting et al. (2013)	ICBT WLC	228	IES	0.83 – 1.01	3 months, 12 months

	Knaevelsrud et al. (2015)	ICBT WLC	159	PDS	0.77- 0.81	3 months
	Knaevelsrud and Maercker (2007)	ICBT WL	95	IES-R	0.97- 1.39	3 months
	Lange et al. (2003)	ICBT WLC	101	IES	1.25- 1.38	6 weeks
	Lange et al. (2001)	ICBT WLC	25	IES	0.67- 1.10	6 weeks
	Litz et al. (2007)	ICBT SC	45	PSSI	0.40	3 months, 6 months
	Spence et al. (2014)	ICBT Exposure ICBT Non Exposure	125	PSSI, IES-R	0.24 0.29	3 months
	Spence et al. (2011)	ICBT WLC	42	PCL	0.46	3 months
	Steinmetz et al. (2012)	ICBT CG TAU	56	MPSS	0.39	-
	Wagner et al. (2006)	ICBT WL	55	IES	1.50	3 months
	Wang et al. (2013)	ICBT WLC	197	PDS	0.81 (urban sample) 1.33 (rural sample)	3 months

Effect size estimates (Hedges' *g*) and 95% confidence intervals (CI) for efficacy of CBT relative to placebo on PTSD *Note* N: number randomized; g: Heges g; FU: follow up in months; ICBT: internet-delivered CBT; TAU: treatment as usual; CBT: cognitive behavioral therapy; ST: supportive therapy; WLC: waitlist control; IE: imaginal exposure; IE+CR: imaginal exposure + cognitive restructuring; SC: supportive counseling; ICT: intensive cognitive therapy; SIT: stress inoculation training; PE: prolonged exposure; CR: cognitive restructuring; CR+PE: cognitive restructuring+ prolonged exposure; Relaxation; PCT: present- centered therapy; NET: narrative exposure therapy; CBSM: cognitive behavioral stress management; SHICBT: self-help ICBT; ICBT exposure: internet- delivered cognitive behavioral therapy with exposure; ICBT non-exposure: internet -delivered cognitive behavioral without exposure; CG: control group, information only; Group PCT: group present-centered therapy; Group CPT: group cognitive processing therapy; TF groups psychotherapy: trauma-focused groups psychotherapy. GCI – General Criterion of Improvement; CAPS- Clinician-Administered PTSD Scale; PCL- PTSD Checklist; IES- Impact of Event Scale; BDI-Beck Depression Inventory; FQ- The Fear Questionnaire; PDS= Posttraumatic Diagnostic Scale; QL- quality of life; QIDS Quick Inventory of Depressive Symptomatology; SRQF- Stressful Responses Questionnaire-Frequency; PSSI PTSD Symptom Scale—Interview Version; MPSS- The Modified PTSD Symptoms Scale

Objectives and research questions

Taking into consideration all the above arguments, the aim of the study is to investigate the clinical efficacy of a guided ICBT program for Romanian adults on measure of PTSD, depression, anxiety symptoms and quality of life. The program PAXPTSD (Paxonline for Posttraumatic stress disorder) has been adapted according cu DSM-5 criteria for PTSD (APA, 2013) based on empirically validated cognitive behavioral models of PTSD (Clark & Beck, 2011; Leahy, Holland & McGinn, 2011; Resick, Monson, Chard, 2014) and it is currently the only available psychological intervention of this type in Romania (Ciuca, 2019).

The current study focused on individuals with an established diagnosis of PTSD. The aim of the study is to investigate the effects of guided ICBT on measures of PTSD symptoms, depression, and other anxiety symptoms, as well as quality of life against a control group and the maintenance of the improvments. We expect that the effect size for program PAXPTSD to be in accord with other programs delivered to PTSD patients (Ivarsson et al., 2014; Knaevelsrud et al., 2015; Kuester, Niemeyer & Knaevelsrud, 2016; Spence et al., 2011; Sijbrandij, Kunovski & Cuijpers, 2016).

METHODS/DESIGN

The study is reported in line with the CONSORT 2019 statement (Consolidated Standards of Reporting Trials) and the SPIRIT 2013 Statement (Standard Protocol Items: Recommendations for Interventional Trials).

This study is a two-armed randomized controlled trial (RCT) with one active treatment condition (TC) and a waiting list control group (WL). Individuals from WL will receive the intervention 3 months after the study begins.

1. Guided internet-based cognitive behavioral program for Posttraumatic Stress Disorder (PAXPTSD): Participants will complete the PAXPTSD with guidance from a psychologist. The guidance includes a kickoff meeting discussion of approximately 30 minutes, via Skype, videoconference or telephone after the evaluation, to discuss the results of assessments and to discuss the next steps. After the completion of every module, the psychologists will schedule a session for Q & A with every participant to answer their questions, monitor their progress and offer them feedback. At the end of the program there will be another 30 minutes discussion for debriefing using Skype, videoconference or telephone. All participants will complete the standard program for general symptoms of PTSD and it is composed from 11 modules. Besides these modules, there are 5 facultative modules for specific aspects associated with PTSD (depression, guilt, shame or anger). Facultative modules are activated for every participant by his psychologist according to co-morbidity symptoms.

2. *Waiting list control group*: participants from this group will not receive any kind of intervention for 12 weeks. At the end of the waiting period the participants will receive the intervention program if they want this (after 3 months of study begins) and we will check if they receive any treatment for PTSD and associated problems in this period. Participants from WL complete the assessment phase similar to those in TC.

The participants can contact the study administration team at any time through using email or messaging on the platform. Participation in the study is voluntary. Participants can withdraw anytime from the study without any consequences. They will receive an information sheet detailing psychological treatments available, according to symptom severity assessed in the evaluation phase or upon contacting study administration team.

We will have diagnostic interviews and self-reports assessments as it follows: screening (T0), preintervention assessment (T1), middle intervention assessment (T2), post intervention assessment (T3) and a 3 months follow-up assessment (T4) (See **Figure 1** for a detailed overview of the study). For the evaluation phase we will use diagnostic interviews conducted face to face or by telephone and self-report assessment. Self-report assessment will be conducted using a secure online-based assessment system, incorporated in the platform. The participants' symptoms will be monitored every week. All the procedures from the study will be congruent with the generally accepted standards of ethical practice.

Ethical approval

The study have to be approved by the Ethical Review Board of The Center for the Management of Scientific Research Babes-Bolyai University.

PARTICIPANTS and PROCEDURE

Inclusion and Exclusion Criteria

In the study we will include (1) adults age within 18-65, (2) who have a diagnostic of PTSD according to DSM-V criteria assessed by diagnostic raters using Posttraumatic Stress Disorder Symptom Scale Interview for DSM-V (PSSI-5), (3) have access to internet connection (via computer, laptop, telephone, tablet), (4) have a valid email address, (5) are native Romanian speakers; (6) and have signed a written informed consent.

Participants will be excluded if any of the following criteria are met: (1) they are currently enrolled in a different psychotherapeutic program or they received psychotherapy in the previous 3 months; (2) they present severe comorbidities, other than mild depression or other anxiety disorder (e.g. bipolar disorders, psychotic disorders, severe personality disorder, substance abuse); (3) they suffer from mental retardation; (4) they present suicidal

ideation or behaviors (assessed by Patient health questionnaire- 9, PHQ-9) (Kronke, Spitzer, Williams, Lowe, 2010); (5) present excessive drinking problems scoring 19 or higher on Alcohol Use Disorders Identifications Test, AUDIT (Saunders et al., 1993). Medication use is permitted only if the dosage was constant in last month and it will remain the same during the trial. All eligible participants must fill in and return a detailed informed consent before starting the trial.

The inclusion and exclusion criteria are in accord to those used in the literature about ICBT intervention on PTSD problems (Ciuca et al., 2016; Ehring, Ehlers, Cleare, Glucksman, 2008; Ivarsson et al., 2014; Wild et al., 2016).

Recruitment

Participants will be recruited from the general population. The participants will be Native Romanian speakers with Posttraumatic Stress Disorder (n=108). They will be recruited by recommendation from local specialists in mental health (psychiatrist, psychotherapist) and via media (Facebook advertise, TV news, radio news, internet advertisements and social media), advertising delivered in hospitals, organizations for victims of domestic violence and sexual abuse, emergency rooms and direct recommendations made by mental health practitioners.

Procedure

The participants can contact the study administration team at any time through using email or messaging on the platform. Participation in the study is voluntary. Participants can withdraw anytime from the study without any consequences. They will receive an information sheet detailing psychological treatments available, according to symptom severity assessed in the evaluation phase or upon contacting study administration team.

We will have diagnostic interviews and self-reports assessments as it follows: screening (T0), preintervention assessment (T1), middle intervention assessment (T2) after 5 weeks of study begins, post intervention assessment (T3) and a 3 months follow-up assessment (T4) (See **Figure 1** for a detailed overview of the study). For the evaluation phase we will use diagnostic interviews conducted face to face or by telephone and self-report assessment. Self-report assessment will be conducted using a secure online-based assessment system, incorporated in the platform. The participants' symptoms will be monitored every week. All the procedures from the study will be congruent with the generally accepted standards of ethical practice.

Clinician interviewing and self-report assessments will take place at screening (T0), pre-treatment assessment (T1), post-assessment 11 weeks after randomization (T3) and 3 months follow-up (T4). There will be also weekly mood assessment. All self-report measures are administered through internet (secure links are used and all the data are

encrypted) and the diagnostic interviews are conducted face to face or via telephone. The questionnaires, which were not yet validated for Romanian population, were previously translated in Romanian and underwent a rigorous back-translation process to ensure a good adaptation. The version we acquired was approved by the author(s) of questionnaires. See **Table 2** for an overview of all assessments. Adherence to assessment completion will be monitored throughout the study. In case of noncompliance participants will be contacted after 7 days (14, 21) to remind them of assessment completion. After 28 days a short message will be sent via text message. The entire communication between psychologist and participants will be inside the platform. In maximum 48 hours after completing the module the psychologist and the participants will schedule the Q and A session for any questions, they will also give feedback and monitor the progress.

Persons who are interested in the program can freely access the study website. The website offers information about PTSD and treatment options and a description of the present clinical trial and information about enrollment. Participants must offer an online informed consent, and then provide demographic information (age, gender, location and contact information). Then, they have to complete key questionnaires: (1) a screening for the exclusion criteria; (2) one scale to evaluate Posttraumatic Stress Disorder and its severity (PDS-5); and (3) a screening questionnaire for psychiatric comorbidities using Psychiatric Diagnostic Screening Questionnaire (PDSQ). Eligible participants are contacted by email to schedule a semi-structured clinical interview face to face or via telephone. The interviews are conducted by two trained clinical psychologists, independent from the study intervention, to verify and confirm the presence of PTSD and the conformity with all the inclusion and exclusion criteria. The eligible participants will receive an email from the administrator of the study with a link where there is a detailed informed consent to the participation in the study. The pre-treatment questionnaires will be completed on the platform by those who are eligible. Participants who offer consent and fulfill all the inclusion criteria are then randomly allocated to one of the two study groups, the treatment condition (TC) or the wait-list control (WL). Participants in the TC will receive immediate access to the platform and online intervention while the participants in WL will receive login access after 3 months of study intake. After completing the evaluation phase all participants receive a short description and debriefing from psychologists in a kick off meeting of 30 minutes. Participants will receive access to each module after they complete the previous one (one module per week).

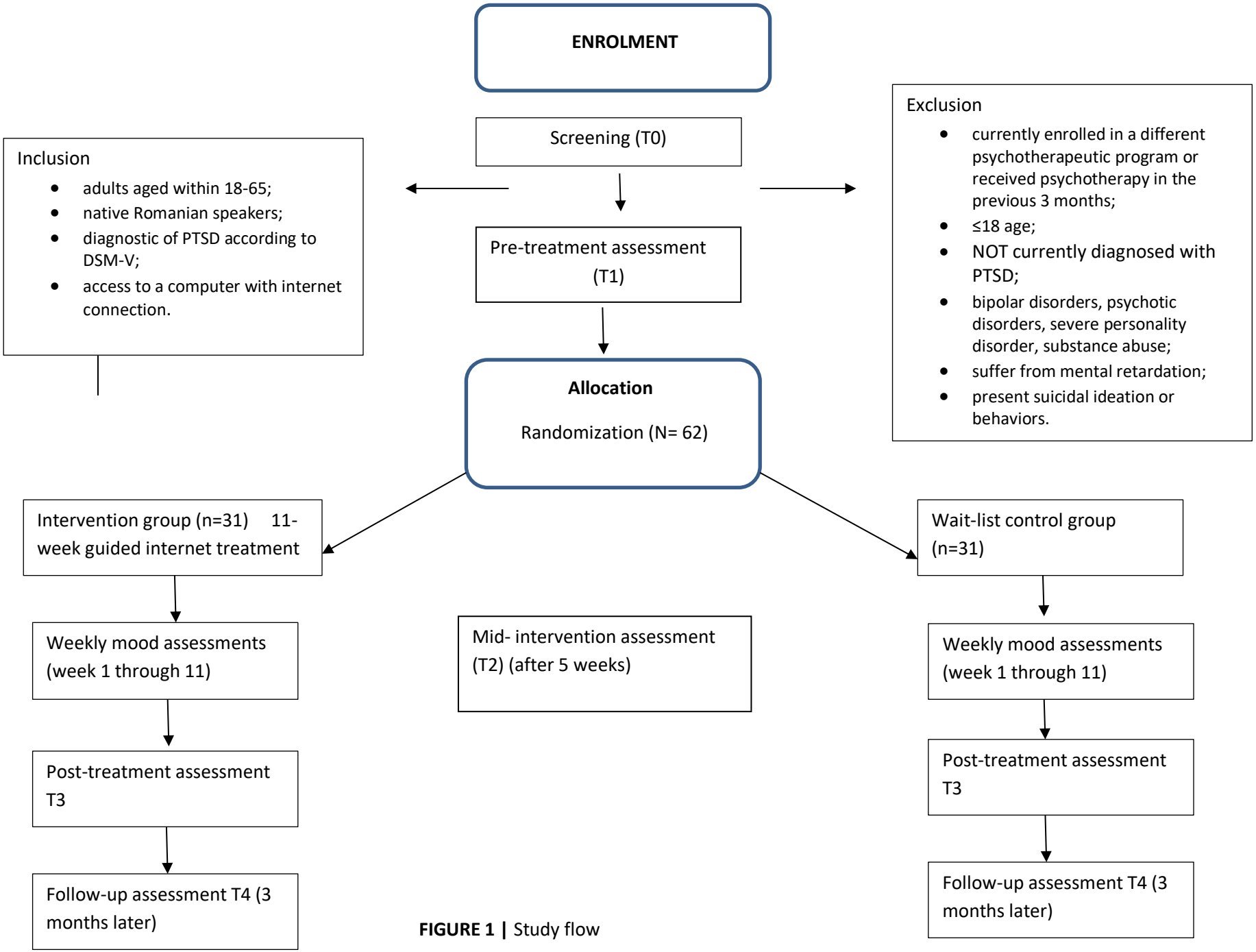

FIGURE 1 | Study flow

Interventions Development and Content

The PAXonline Standard Program for Post Traumatic Stress Disorder contains 11 modules. Besides these modules, there are 5 facultative modules for specific symptoms associated with PTSD (depression, other secondary emotions such as guilt, shame or anger). The program PAXPTSD contains modules which address important cognitive and behavioral psychotherapy elements which are detailed in **Table 3.** The treatment modules and the manual used to guide the intervention in our RCT were written based on *PAXOnline manual* and on the empirically validated cognitive behavioral models of anxiety disorders (Ciuca, 2019; Clark & Beck, 2011; Leahy, Holland & McGinn, 2011; Resick, Monson & Chard, 2014). The intervention content contains text, audios, short educational video clips, videos and interactive elements like quizzes. Each module can be completed in 15-40 minutes and the participants are provided with a recommended timetable (one or two modules per week, depending if there are necessarily additional modules) (Ciuca, 2019; Miclea, Miclea, Ciuca, Budau, 2010).

Table 3 PAXOnline Posttraumatic Stress Disorder Intervention

Standard program	Short description
Module 1 *Posttraumatic stress disorder – explanation and treatment*	Psychoeducation about symptoms, various reactions to trauma, evolution of disorder and maintenance of symptoms.
Module 2 *Breathing training*	Participants are taught how to breathe in a calming way.
Module 3 and 4 *Reducing hyperarousal through Autogenic Training*	Information of the effects of hyperarousal, benefits of relaxation, learn and practice autogenic training.
Module 5 *Progressive Desensitization*	Progressive desensitization regarding traumatic experience.
Module 6 *Changing maladaptive conscious cognitions*	Identify catastrophic cognitions, learn and practice cognitive restructuration.
Module 7 *Confrontation with traumatic memory*	Expressive writing about traumatic event. Describe vividly the traumatic event, cognition, emotions and behaviors.
Module 8 *Avoidance reduction through interoceptive exposure*	Reduce fear of bodily sensation associated with traumatic experience through interoceptive exposure.

Module 9 *Avoidance reduction through exteroceptive exposure*	Reduce safety behaviors and prepare for exteroceptive exposure.
Module 10 *Reclaiming your life*	Trauma as an opportunity to grow.
Module 11 *Positive emotions development*	Increase positive emotions through exercises from positive psychology.
Module 12 *Relapse prevention*	Resume the intervention techniques, set the expectancies for the future and a plan in cases of relapse.
Facultative modules	
1. *Reducing depressive symptoms associated with trauma- behavioral activation*	Depression symptoms co-morbid to traumatic experience. Behavioral activation technique.
2. *Reducing depressive symptoms associated with trauma- cognitive restructuring*	Cognitive restructuring of dysfunctional cognition associated with traumatic experience that induce and maintain depression.
3. *Shame associated with trauma*	Cognitive restructuring for specific cognitions that induce and maintain shame associated with traumatic experience.
4. *Guilt associated with trauma*	Identify the personal role and any other factors implicated in traumatic experience.
5. *Anger associated with trauma*	Psychoeducation about anger and anger management in context of trauma.

Guidance and Adherence Monitoring

The psychologists from the study will be either licensed psychologists or master students at clinical psychology and psychotherapy. They will support the participants' adherence by providing reminders using the messaging application available in the platform or via telephone, offering feedback, and monitoring the progress as well as risk for deterioration. Any crisis or any other adverse events are reported to the research team. In cases when participants forget to complete one session, the psychologists will offer reminders and send messages to participants by using platform messages and telephone messages.

Assessments

Instruments

The selected instruments have already been well established and frequently used in CBT trials for posttraumatic stress disorder in particular, as well as for other anxiety and mood disorders.

Table 2 *Measurements and time assessment*

Instruments	Abbreviation	Aim	Time of assessment
Clinical administered Posttraumatic Stress Disorder Symptom Scale Interview for DSM-5	PSS-I-5	PTSD symptoms	Pre and post treatment assessment (11) weeks
Alcohol Use Disorder Identification Test	AUDIT	Abuse and dependence of alcohol	Screening and exclusion participants with excessive drinking problems
Semi-structured clinical interview for DSM-IV	PDSQ	DSM-IV axis I severity	Pre and post treatment assessment (11) weeks
Self-report ratings			
Primary outcome			
Posttraumatic Diagnostic Scale for DSM-5	PDS-5	Severity of PTSD symptoms	Pre-treatment, middle intervention assessment (after 6 weeks), post-treatment and

			follow-up assessment (3 months)
The Posttraumatic Cognitions Inventory	PTCI	Catastrophic cognitions	Pre-treatment, middle intervention assessment (after 6 weeks),post-treatment and follow-up (3 months)
PTSD Checklist	PCL-5	Screening, monitor	Pre-treatment, every week, middle intervention assessment (after 6 weeks), post-treatment and follow-up (3 months)
Secondary outcome			
Patient health questionnaire-9	PHQ-9	Symptoms and severity of depression	Pre-treatment, every week, middle intervention assessment (after 6 weeks), post-treatment and follow-up (3 months)
General Anxiety Disorder	GAD-7	Symptoms of general anxiety disorder	Pre-treatment, every week, middle intervention assessment (after 6 weeks), post-treatment and follow-up (3 months)
The work and social adjustment scale	WSAS	Functional impairment	Pre-treatment, middle intervention assessment (after 6 weeks), post-treatment and follow-up (3 months)
Psychiatric diagnostic and screening questionnaire	PDSQ	Axis 1 disorders	Pre-treatment, post-treatment and follow-up (3 months)
Perceived stress scale - 10	PSS-10	Perceived stress levels	Pre-treatment, middle intervention assessment (after 6 weeks), post-treatment and follow-up (3 months)

Additional measures			
Credibility/ expectancy questionnaire	CEQ	Expectancy for change and treatment credibility	Administered to 2 and 5 weeks during intervention
A 5-item shortened version of the Medical Outcomes Study Social Support Scale (MOS-SSS)	SS-5	Social support	Pre-treatment, middle intervention assessment (after 6 weeks), post-treatment and follow-up (3 months)
The Patient Feedback Questionnaire	PFQ	Evaluate the patients' satisfaction with the platform, quality and utility of program.	Post-treatment assessment
Positive and Negative Effects of Psychotherapy Scale	PANEPS	Evaluate negative side effects of intervention.	Post-treatment

Diagnostic interview

Comorbidities are assessed using the Romanian adapted version of Psychiatric Diagnostic Screening Questionnaire (PDSQ) (Ciuca, Berger, Crisan, & Miclea, 2016; Ciuca, Berger, Crisan, & Miclea, 2018), which comprises a self-report screening scale, followed by a semi-structured interview delivered by a clinician. The PDSQ scale has good psychometric properties. In the Romanian validation study the mean of the alpha coefficients was .85 and test-retest reliability was above .80 for nine subscales, with a mean test-retest of .85 (Ciuca et al., 2016). Following the screening procedures, all eligible participants are interviewed by one of the psychotherapists. Any mental disorder that reached PDSQ screening cutoff point is assessed during the interview. In order to increase interraters` agreement on assessment protocol, the assessors have to participate in a two days training before study starts. The diagnostic interview is conducted before and after the treatment by clinicians blind to the treatment group. At post-treatment diagnostic interview we are going to count missing data as equivalent to still meeting diagnostic criteria for Posttraumatic Stress Disorder. The procedure is recommended according to intention-to-treat paradigm and was used in several other studies (Hedman et al., 2013; Weisel et al., 2018).

Primary outcomes

The primary outcome measures PTSD Symptom Scale - Interview for DSM-5 (PSS-I-5); Posttraumatic Diagnostic Scale for DSM-5 (PDS-5) (Foa et al., 2016); and PTSD Checklist for DSM-5 (PCL-5) (Bovin et al., 2016). Posttraumatic Stress Disorder is assessed using the Romanian adapted version of PTSD Symptom Scale - Interview for DSM-5 (PSS-I-5). PSS-I-5 is originally a face-to-face semi-structured interview that assesses PTSD symptoms in the past months developed by Foa et al. The semi-structured interview contains 24 items that assess PTSD according to DSM-5 criteria. This traumatic event is called “trauma index” and the remaining criteria for the diagnosis are evaluated according to this event. There are 20 items which address symptoms criteria according to DSM-5 clusters: intrusions (items 1-5), avoidance (items 6-7), change in mood and cognition (items 8-14) and arousal and hyperactivity (items 15-20). These items evaluate the frequency of symptoms in the last month for the trauma index. Participants answer on a 5 point Likert scale ranging from 0 (not at all) to 4 (6 or more times a week/severe). Symptoms are considered present when rated as 1 or higher. PSS-I-5 symptom severity is calculated by summing the items 1-20 (scores range between 0 and 80). Items 21 and 22 assess for overall distress and interference and items 23 and 24 report delayed onset and duration of symptoms, respectively. PTSD diagnosis is consistent with DSM-5 criteria and it requires presence of 1 intrusion symptom, 1 avoidance symptom, 2 cognition and mood

symptoms and 2 arousal symptoms for a period of 1 month. A significant distress or interference is also necessarily to be present (operationalized as a score of 2 or higher on either item 21 or 22).

Posttraumatic Diagnostic Scale for DSM-5 (PDS-5). The PDS-5 (Foa et al., 2016) is a 24-item self-report questionnaire that supplements the administration of PSS-I-5. The questionnaire includes a trauma screen, followed by 20 questions corresponding to PTSD symptom according to DSM-5 criteria and offers an estimation of PTSD severity of symptoms. Participants are asked to complete the questionnaire in correspondence with "trauma index". There are 4 clusters which assess distress, interference, onset and duration of symptom. The participants answers on a 5 point Likert scale ranging from 0 (not at all) to 4 (6 or more times a week/severe). In cases where there are multiple traumatic events, "trauma index" is evaluated as the most traumatic event, the event which currently produces the most distressing experience.

PTSD Checklist for DSM-5 (PCL-5). This scale has different versions; in our study we will use the version for the civilian population. PCL is 20 item self-report questionnaires that prompt informants to endorse the level of distress that has co-occurred according to each PTSD symptom in the previous month. PCL is used for screening, temporary diagnostic and for monitoring the symptoms on 5 point Likert scale (0 to 4) (Ruggiero, Del Ben, Scotti & Rabalais, 2003). PCL-5 total score ranges from 0 to 80, with higher score indicating greater PTSD symptom severity. PCL has excellent internal consistency (Cronbach α=.96) and a high level of stability over time, test-retest reliability .84. Scores of 31 or 33 was demonstrated to be optimally efficient to diagnose PTSD (Bovin et al., 2016). In the study we will use PCL-5 for screening and to monitor progress and symptoms of PTSD. Participants will complete PCL-5 weekly.

Secondary outcomes

Secondary outcome measures include depressive symptoms, functional impairment, quality of life, cognitions related to trauma, stress level and other anxiety symptoms.

General mood

The Patient Health Questionnaire (PHQ-9) is a widely used measure to evaluate and monitor depression (Kronke, Spitzer, Williams, Lowe, 2010). The questionnaire contains nine items and the participants are required to rate the frequency of present difficulties in the past 2 weeks. Scores on this questionnaire indicate the presence and the severity of the symptoms with a range of scores between 0 and 27. Cutoff points for mild, moderate, moderately severe and severe depression are 5, 10, 15 and 20. The internal reliability of the English version of PHQ-9 in a

clinical population was in a range between 0.86-0.89. (Ciuca, Berger, Crisan & Miclea, 2016; Ciuca et al., 2011), which indicates good reliability. The test-retest reliability was also good, 0.84, and the correlation with interview results is very high, 0.84. We will use PHQ-9 for screening and monitoring the symptoms once a week.

Anxiety is also measured in a self-report manner using generalized anxiety disorder measurement GAD-7 (Spitzer, Kroenke, Williams, & Löwe, 2006) with items ranging from 0 to 3 (Frans, Rimmo, Aberg & Fredrikson, 2005; Weisel et al., 2018). Internal consistency of GAD-7 was excellent (Cronbach α=.92). Test-retest reliability was good 0.83 (Frans, Rimmo, Aberg & Fredrikson, 2005).

Functional impairment

Work and Social Adjustment Scale (WSAS) was developed by Mundt, Marks, Shear and Greist (Mundt, Marks, Shear & Greist, 2002). The scale has 5 items, which are simple and reliable. We decided to use this scale to evaluate the functional impairment caused by PTSD symptoms. The scale items' encompass different domains of functioning and include the following: ability to work, home management, social leisure and ability to form and maintain close relationships. Each item is rated on a 9-point Likert scale and the scores range between 0 (no impairment) and 8 (very severe impairment). The sums of the 5 items represent total impairment with higher scores representing greater impairment. The maximum score is 40. The WSAS has demonstrated good internal consistency (range between 0.70 and 0.94) and test-retest reliability (0.73) and is a scale which is sensitive to patients' perceptions of disorder severity (Ciuca et al., 2011 ;Mundt, Marks, Shear & Greist, 2002).

Cognitions relevant to Posttraumatic Stress Disorder

The Posttraumatic Cognitions Inventory (PTCI). The questionnaire was developed by Foa et al. in 2016. The questionnaire contains 36 items and three factors: negative cognitions about self, negative cognitions about the world, and self-blame. Items were developed taking into account the theoretical considerations of cognitions biases and specific cognitions which are present in the traumatic experience, from the clinical experience (Foa et al., 2016). Participants are asked to rate each item on a 7 point Likert scale (from 1 *totally disagree* to 7 *totally agree*). High score indicates stronger endorsement of negative cognitions and the sum of scores is calculated. The three factors of PTCI classified correctly those people with PTSD from people without PTSD (86%). Scores for test-retest reliability were in range: total score= .74- .85 negative cognitions about the self= .75- .86; negative cognitions about the world= .81 - .89 and self-blame=. 80- .89 (Foa et al., 2016). All three factors and the sum of scores correlated substantially with PTSD severity, depression and general anxiety (Foa et al., 2016).

Perceived stress

Perceived Stress Scale – 10 (PSS- 10). The questionnaire is short and easy to use and it is recommended for the assessment of perceived stress in practice and research (Lee, 2012; Zimmerman & Mattia, 2001). The questionnaire measures the people's perception of uncontrollability, unpredictability and overloading. Participants are asked to respond to each question on a 5-point Likert scale from 0 (never) to 4 (very often), indicating how often in the previous month they have felt or thought in a certain way. Scores range from 0 to 40, higher composite score indicating greater level of perceived stress. The PSS-10 demonstrated good internal consistency (0.89) and also good divergent and convergent validity (Ciuca et al., 2011; Lee, 2012; Roberti, Harrington & Storch, 2006).

Additional measures

Treatment credibility and patient expectancies

The Credibility/Expectancy Questionnaire (CEQ) (Devilly & Borkovec, 2000) is used to measure expectancy for change and treatment credibility. Questionnaire contains 6 items, 4 about thinking and 2 about feelings, all 6 items are rated on a Likert scale and scores range from 1 to 9. The questionnaire has good internal consistency (expectancy α= .79-.90; credibility α= .81-86) and test-retest reliability (expectancy= 0.82; credibility= 0.75) (Ciuca et al., 2011; Devilly & Borkovec, 2000). We administer CEQ in IG twice, after the first and fifth session.

Perceived social support

We use SS-5, which is an abbreviated version of the Medical Outcome Study Social Support Scale (MOS-SSS) (Sherbourne & Stewart, 1991). SS-5 is a 5 item short and reliable measure for assessing perceived social support, a predictor or possible moderator of treatment outcome. Participants are asked to rate each item on a 5-point Likert scale (1 to 5), the items are summed for a total score ranging from 5 to 25. Test-retest reliability for SS-5 is adequate (0.92) and also the internal consistency (α= .88). In the scientific literature the equivalence between paper pencil administration and web-based administration was demonstrated of SS-5 (Ciuca et al., 2011).

Sociodemographic questionnaire

To evaluate sociodemographic characteristics of the participants we use a survey with 7 items which refer to: environment (urban or rural), ethnicity, marital status, education, occupation, income levels and computer skills (1 to 10) (Ciuca et al., 2011).

Adherence to treatment and homework compliance

We will assess adherence to treatment and homework compliance. We will analyze several aspects to identify potential mediating effects: number of modules completed, total time spent on the platform, time spent on each module, and usage of the support (Ciuca et al., 2011).

Patient satisfaction

We will use The Patient Feedback Questionnaire (PFQ). The questionnaire was used in a previous study which evaluates the efficacy of an iCBT program for panic attacks and it was developed by a team of researchers (Ciuca et al., 2011). The questionnaire contains 14 items which evaluate the patients' satisfaction with the platform and several other aspects (quality and utility of different components of the platform). Other items refer to giving improvement suggestions, what they like most, if they would use it again or recommend it to a friend with symptoms related to traumatic experiences. The questionnaire will be administered at post-treatment evaluation.

Drop-out reasons

In order to evaluate the reasons for drop-out we will use a questionnaire developed by Ciuca et al. The questionnaire contains 18 items and each item is considered to be a possible reason (e.g. lack of motivation, lack of time, different expectations, exacerbation of symptoms, interface is too complicated, the treatment pace is too slow or too fast, finding another treatment, getting better, important life events etc.) (Ciuca et al., 2011).

Side effects

We will evaluate negative side effects after completion of the intervention to identify any negative effects of PAXPTSD program. For this at the end of the program, participants will complete the Positive and Negative Effects of Psychotherapy Scale (PANEPS) (Moritz et al., 2018). PANEPS was evaluated in a population of individuals with depression who had completed at least one course of face-to-face psychotherapy. Factor analysis yielded four dimensions: positive effects, side effects, malpractice, and unethical conduct. Internal consistency of PANEPS range between 0.72 - 0.92 (Herzong, Lauff, Rief & Brakemeier, 2019).

Randomization

Participants who return the informed consent and meet all the required criteria are randomly allocated to one of the two conditions . The randomization process is done by a software that was developed to implement a minimization algorithm (Pocock & Simon, 1975) that assures a balanced randomization between groups with respect to certain predefined prognostic (stratification) factors. In this study, two stratification factors have been considered: SEVERITY(4 levels according to PDS-5 screening scores; level 1: 11 to 23 points; level 2: 24 to 42 points; level 3:

43 to 59 point; level 4: 60-80) and CHRONICITY (2 levels; more or less than 3 months since the traumatic event). The minimization method has been shown to outperform simple randomization in achieving balanced groups (Scott, McPherson, Ramsay, & Campbell, 2002) and its use in clinical trials has been previously recommended as a better option than other randomization methods (Hagino et al., 2004; Scott, McPherson, Ramsay, & Campbell, 2002; Treasure & MacRae, 1998). Before each allocation, the algorithm computes an imbalance score for the two available treatments, taking stratification factors levels into account. The treatment with the lowest imbalance score is then given preference when assigning treatments, but the allocation probability varies for each patient, depending on the actual level of imbalance (Hofmeijer, Anema & van der Tweel, 2008). This method is preferred because it avoids the deterministic allocation of pure minimization (Pond, 2011). The allocation is done by an independent researcher and is concealed, i.e. patients and researchers have no knowledge and no control over the allocation of participants when they randomize a participant with the computer program.

Blinding

Taking into consideration the characteristics of our research it is impossible to keep patients blind to the study procedures and psychotherapists' intervention. All participants are provided with detailed information about the aims and the methodology of the study. They can request more information about the study and they have the right to terminate participation at any time. The personnel in charge of the clinical interviews will be blind to the treatment group allocation. We specifically instruct the participants not to mention group allocation at the post-assessment interview, but also test whether blinding was successful. The clinicians who conduct the diagnostic interviews are required to describe in their report if their participants disclosed their study group, directly or indirectly (Ciuca et al., 2011; Weisel et al., 2018).

Sample size

The effect size for iCBT intervention for PTSD is considered to be small to medium (Kuester, Niemeyer & Knaevelsrud, 2016; Lewis et al., 2019; Sibrandij, Kunovski & Cuijpers). Take this information in consideration we expected an effect size of .60. Based on this effect size, a power of .80 and a level alpha of 0.05 we would need 45 participants in each condition for testing the two tails hypothesis. This recommended sample size has been increased to accommodate an attrition rate of 20%. Thus, the study aims to achieve a total sample of 108.

Statistical analysis

All statistical analyses will be performed using the IMB SPSS Statistics version 20. The aim analysis will be conducted on intention-to-treat samples. We will use a linear mixed effects models approach with full information maximum likelihood estimation. This approach was recommended since it uses all available data and can handle missing data appropriately (Gueorguieva & Krystal, 2004; Meyer et al., 2015; Pond, 2011). The approach emphasizes the assumption that data are randomly missing and does not assume that missing data remain stable as in the last-observation-carried-forward (LOCF) approach (Blankers, Koeter & Schippers, 2010; Meyer et al., 2015). Significance testing of dichotomous data such as diagnostic status will be conducted with chi-square tests. Calculation of within and between- groups effect sizes (Cohen d) will be based on the pooled standard deviations. Regression analyses will be used to identify predictors of treatment outcome. Moderation and mediation analysis will be conducted with multiple regression models, using the PROCESS macro for SPSS (Hayes, 2017), a computational technique that can compute both simple and complex moderation and meditation models. Effect sizes for significant effects will be indicated by Cohen's d.

Consistent with recommendations from CONSORT (Schulz, Altman, Moher, 2011) and SPIRIT (Chan et al., 2013) we mention our intention to perform secondary analyses for minimal treatment users, defined as participants that complete as least 5 of recommended modules and use the intervention program for at least 80 minutes. This definition is based on the specific of our intervention program and the criteria used in other studies (Ciuca et al., 2011; Meyer et al., 2015; Ivarsson et al., 2014).

Discussion

We expect that our program PAXPTSD to be effective for PTSD global severity symptom as well as for subscale for re-experiencing, avoidance, changes in mood and cognitions and hyperarousal. We expect that these results to be maintained (3 months follow-up). These results will be in line with the literature on effectiveness of Internet-delivered cognitive behavior therapy for PTSD showing that Internet-delivered cognitive behavioral interventions are more effective than waitlist control group (Sijbrandij, Kunovski, Cuijpers, 2016). We expect that the effect size for our study to me medium to large and to be in line with other ICBT programs. Internet-based treatments also resulted in moderate to large effects for other disorders such as anxiety (Cuijpers et al., 2009; Reger & Gahm, 2009; Tulbure, 2011) and small to moderate ones for depression (Andersson & Cuijpers, 2009; Cowpertwait & Clarke, 2013; Richards & Richardson, 2012; So et al., 2013). ICBT that provided support resulted in a large effect, whereas a medium effect was obtained without support. Because there are no firm conclusions about the role of the therapist

in ICBT, we decide to keep to minimum the psychotherapist implication. In our study the psychologist will discuss the results of the evaluation in a kickoff meeting as well as offer feedback, respond to question, monitor the progress and offer reminders every week.