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Effect of Prolonged Exposure, intensified Prolonged Exposure and STAIR +Prolonged Exposure in patients with PTSD related to childhood abuse: a randomized controlled trial

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ABSTRACT

Background: It is unclear whether the evidence-based treatments for PTSD are as effective in patients with CA-PTSD.

Objective: We aimed to investigate the effectiveness of three variants of prolonged exposure therapy.

Method: We recruited adults with CA-PTSD. Participants were randomly assigned to Prolonged Exposure (PE; 16 sessions in 16 weeks), intensified Prolonged Exposure (iPE; 12 sessions in 4 weeks followed by 2 booster sessions) or a phase-based treatment, in which 8 sessions of PE were preceded by 8 sessions of Skills Training in Affective and Interpersonal Regulation (STAIR+PE; 16 sessions in 16 weeks). Assessments took place in week 0 (baseline), week 4, week 8, week 16 (post-treatment) and at a 6-and 12-month follow-up. The primary outcome was clinician-rated PTSD symptom severity.

Results: We randomly assigned 149 patients to PE (48), iPE (51) or STAIR+PE (50). All treatments resulted in large improvements in clinician assessed and self-reported PTSD symptoms from baseline to 1-year follow-up (Cohen's $d > 1.6$), with no significant differences among treatments. iPE led to faster initial symptom reduction than PE for self-report PTSD symptoms ($t_{135} = -2.85, p = .005, d = .49$) but not clinician-assessed symptoms ($t_{135} = -1.65, p = .10$) and faster initial symptom reduction than STAIR+PE for self-reported ($t_{135} = -4.11, p < .001, d = .71$) and clinician-assessed symptoms ($t_{135} = -2.77, p = .006$, Cohen's $d = .48$) STAIR+PE did not result in significantly more improvement from baseline to 1-year follow-up on the secondary outcome emotion regulation, interpersonal problems and self-esteem compared to PE and iPE. Dropout rates did not differ significantly between conditions.

Conclusions: Variants of exposure therapy are tolerated well and lead to large improvements in patients with CA-PTSD. Intensifying treatment may lead to faster improvement but not to overall better outcomes.

The trial is registered at the clinical trial registry, number NCT03194113, https://clinicaltrials.gov/ct2/show/NCT03194113

Efecto de la Exposición Prolongada, la Exposición Prolongada intensificada y STAIR + la Exposición Prolongada en pacientes con TEPT relacionado con el abuso infantil: un ensayo controlado aleatorio

Antecedentes: No está claro si los tratamientos basados en la evidencia para el TEPT son tan efectivos en pacientes con TEPT relacionado con abuso infantil (TEPT-AI).

Objetivo: Nuestro objetivo fue investigar la efectividad de tres variantes de la terapia de exposición prolongada.

Método: Reclutamos adultos con TEPT-AI. Los participantes fueron asignados aleatoriamente a Exposición Prolongada (EP; 16 sesiones en 16 semanas), Exposición Prolongada intensificada (EPi; 12 sesiones en 4 semanas seguidas de dos sesiones de refuerzo) o un tratamiento basado en fases, en el que 8 sesiones de EP fueron precedidas por 8 sesiones de Entrenamiento de Habilidades en Regulación Afectiva e Interpersonal (STAIR+EP; 16 sesiones en 16 semanas). Las evaluaciones se llevaron a cabo en la semana 0 (línea de base), semana 4, semana 8, semana 16 (postratamiento) y en un seguimiento de 6 y 12 meses. El resultado primario fue la gravedad de los síntomas de TEPT calificada por el médico.

Resultados: Asignamos aleatoriamente 149 pacientes a EP (48), EPi (51) o STAIR+EP (50). Todos los tratamientos dieron como resultado grandes mejoras en los síntomas de TEPT

evaluados por el médico y autoinformados, desde el inicio hasta el seguimiento de 1 año (*d* de Cohen > 1.6), sin diferencias significativas entre los tratamientos. La EPi condujo a una reducción más rápida de los síntomas iniciales que la EP para los síntomas de TEPT autoinformados (t_{135} = −2.85, *p* =.005, *d* =.49) pero no los síntomas evaluados por el médico (t_{135} = −1.65, *p* =.10) y una reducción más rápida de síntomas iniciales que STAIR+EP para los síntomas autoinformados (t_{135} = −4.11, *p* <.001, *d* =.71) y evaluados por el médico (t_{135} = −2.77, *p* =.006, *d* de Cohen =.48) STAIR+EP no dio como resultado una mejora significativamente mayor desde el inicio hasta el seguimiento de 1 año en los resultados secundarios de regulación emocional, problemas interpersonales y autoestima en comparación con la EP y la EPi. Las tasas de abandono no difirieron significativamente entre las condiciones.

Conclusiones: Las variantes de la terapia de exposición se toleran bien y conducen a grandes mejoras en pacientes con TEPT-AI. La intensificación del tratamiento puede conducir a una mejora más rápida, pero no a mejores resultados en general.

延长暴露、强化延长暴露和STAIR +延长暴露对童年期虐待相关PTSD 患者的影响：一项随机对照 试验

背景: 目前尚不清楚PTSD的循证治疗在CA-PTSD患者中是否有效。

目的: 我们旨在考查延长暴露治疗三种变式的有效性。

方法: 我们招募了CA-PTSD成年患者。参与者被随机分配到延长暴露组 (PE; 16周内16次)，强化延长暴露组 (iPE; 4周内12次, 随后两个推进期) 或阶段性治疗，即8次PE之前有8次情感和人际关系调节技能培训 (STAIR + PE; 16周内 16次) 。在第0周 (基线)，第4周，第8周，第16周 (治疗后) 以及6个月和12个月的随访中进行评估。主要结果为临床医师评定的PTSD症状严重程度。

结果: 我们将149例患者随机分配至PE组 (48), iPE组 (51) 或STAIR + PE组 (50) 。从基线到1年后随访，所有治疗在临床医生评估和自我报告PTSD症状上都有了很大改善 (Cohen *d*> 1.6)，各治疗之间无显著差异。iPE组比PE组更快地缓解自我报告PTSD症状的初始症状 (t_{135} = −2.85, *p*=.005, *d*= 0.49), 但对于临床医生评估的症状无此效应 (t_{135} = −1.65, *p*=.10)，并且比STAIR+PE组更快地缓解自我报告 (t_{135} = −4.11, *p*<.001, *d*=.71) 和临床医生评估症状 (t_{135} = −2.77, *p*=.006, Cohen's *d*=.48) 的初始症状。与PE和iPE相比，从基线到1年后随访，STAIR + PE 在情绪调节，人际交往问题和自尊的次要结果上并没有更多显著提升。不同条件下的流失率无显著差异。

结论: 暴露治疗变式耐受性良好, 可为CA-PTSD患者带来大幅改善。强化治疗可能更快改善, 但不会带来总体上更好的结果。

1. Introduction

Childhood physical and sexual abuse are important risk factors for the development of post-traumatic stress disorder (PTSD; Cougle, Timpano, Sachs-Ericsson, Keough, & Riccardi, 2010; Kessler et al., 2017). Both childhood abuse and childhood abuse-related PTSD (CA-PTSD) are associated with severe psychiatric symptoms and negative long-term outcomes (Cloitre et al., 2009; Gilbert et al., 2009; Norman et al., 2012), emphasizing the need for effective treatment. Clinical guidelines prescribe trauma-focused treatment as the first-line treatment of PTSD (Hamblen et al., 2019). Substantial empirical support exists for the effectiveness of trauma-focused treatment in PTSD (Ehring et al., 2014; Mavranezouli et al., 2020; Watts et al., 2013); however, there is ample room for improvement since about half of the patients still meet diagnostic criteria for PTSD after treatment and 25% drop-out (Bradley, 2005; Ehring et al., 2014; Watkins, Sprang, & Rothbaum, 2018). Furthermore, there is a limited number of studies assessing trauma-focused treatment among those with CA-PTSD and it is therefore uncertain how effective trauma-focused treatment is in this group of patients (Ehring et al., 2014).

Patients with CA-PTSD more often experience emotion regulation difficulties and interpersonal problems than patients with non-CA-PTSD (Cloitre, Miranda, Stovall-McClough, & Han, 2005; Gekker et al., 2018; Messman-Moore & Bhuptani, 2017). In addition, co-morbid diagnoses are more common in these patients – in particular depression, substance abuse and personality disorders (Dvir, Ford, Hill, & Frazier, 2014). Although comorbidity is also prevalent in non-CA-PTSD, prevalence rates of comorbidity are much higher in CA-PTSD, with moderate to large effect sizes (e.g. Gekker et al., 2018; Messman-Moore & Bhuptani, 2017)

A recent meta-analysis indicated that patients with PTSD related to childhood trauma do not benefit optimally from treatment. Compared with patients with PTSD related to trauma in adulthood, they improve less on PTSD symptoms, emotion regulation and interpersonal functioning (Karatzias et al., 2019). Another meta-analysis of dropout rates from psychotherapy found somewhat higher dropout rates from trauma-focused treatment in patients with CA-PTSD (24%; Ehring et al., 2014) than in patients with PTSD in general (18%; Lewis, Roberts, Gibson, & Bisson, 2020), suggesting that dropout rates are potentially high among those with CA-PTSD.

The aim of this study was to investigate whether the effectiveness and the dropout rates of trauma-focused treatment for PTSD can be improved in patients with CA-PTSD. Prolonged Exposure (PE), an established treatment of PTSD was compared with two adaptations of PE. The first was an intensified version of PE (iPE). We expected that offering several sessions per week would lead to faster improvement and lower drop-out rates (Ragsdale, Watkins, Sherrill, Zwiebach, & Rothbaum, 2020). In patients with (non-CA) PTSD, iPE led to faster improvement (Ehlers et al., 2014; Foa, McLean, Zang, & Consortium, 2018) and noninferior post-treatment outcomes (Foa et al., 2018) compared to standard (weekly) PE. Open studies in patients with chronic PTSD following multiple traumata and treatment attempts indicated that iPE may lead to fast improvement and low dropout rates (Hendriks, de Kleine, Broekman, Hendriks, & van Minnen, 2018) and that the results did not differ between patients with and without CA-PTSD (Wagenmans, Van Minnen, Sleijpen, & De Jongh, 2018). It is unclear, however, whether iPE improves treatment outcome of PE in patients with CA-PTSD. The second adaptation was a phase-based treatment in which PE is preceded by Skills Training in Affective and Interpersonal Regulation (STAIR). This treatment is based on the notion that emotion regulation and interpersonal problems interfere not only with daily life functioning but also the processing of trauma memories and that improvement in these capacities during the STAIR phase facilitates the effectiveness of PE (Cloitre, Koenen, Cohen, & Han, 2002). STAIR+PE has been demonstrated to be an effective treatment for CA-PTSD (Cloitre et al., 2002, 2010) and led to better outcomes and a lower dropout rate relative to a PE treatment that did not include STAIR (i.e. Supportive Counseling+PE) (Cloitre et al., 2010).

We tested the following hypotheses:

(1) iPE and STAIR+PE lead to more clinician-rated and self-reported PTSD symptom reduction than PE from baseline to follow-up.
(2) iPE leads to faster improvement, that is, iPE leads to more clinician-rated and self-reported PTSD symptom reduction than PE and STAIR+PE from baseline to the first assessment (week 4).
(3) STAIR+PE leads to more improvement in emotion regulation, interpersonal problems and self-esteem than PE and iPE from baseline to follow-up.
(4) iPE and STAIR+PE result in lower drop-out rates from treatment than PE.

2. Method

2.1. Study design and participants

In this randomized-controlled trial (RCT), 'IMPACT' (improving PTSD treatment for adults with childhood trauma), we compared the effectiveness of PE, iPE and STAIR+PE. The authors assert that all procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving patients were approved by the Medical Ethical Committee of Leiden University Medical Centre (NL57984.058.16). More detailed information about the design can be found in the published study protocol (Oprel et al., 2018).

Participants were recruited in two outpatient mental health services specializing in the treatment of trauma-related disorders located in the Hague and Rotterdam, the Netherlands. Inclusion criteria were: 1) ages 18 to 65 years; 2) a PTSD diagnosis according to the DSM-5 classification established with the Clinician-Administered PTSD Scale (CAPS-5 see below), and at least moderate severity of PTSD-symptoms (CAPS-5 score ≥26) and at least one specific memory of the traumatic event; 3) Traumata related to childhood sexual and/or physical abuse that occurred before 18 years of age, committed by a primary caretaker or an authority figure as index event; 4) sufficient fluency in Dutch to complete the treatment and research protocols. Exclusion criteria were: 1) involvement in a compensation case or legal procedures concerning admission or stay in The Netherlands; 2) pregnancy given the limited available information about safety (Baas, van Pampus, Braam, Stramrood, & de Jongh, 2020), 3) severe nonsuicidal self-injury (NSSI) which required hospitalization during the past 3 months; 4) severe suicidal behaviour: a suicide attempt during the past 3 months or acute suicidal ideations with serious intent to die with a specific plan for suicide and preparatory acts; 5) severe disorder in the use of alcohol or drugs in last 3 months according to the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998), 6) cognitive impairment (estimated IQ < 70); 7) changes in psychotropic medication in the 2 months prior to inclusion; and 8) engagement in any current psychological treatment. Written informed consent was obtained from all patients after receiving a complete description of the study.

2.2. Randomization and masking

Randomization was carried out on study-enrolment in a 1:1:1 ratio by an independent researcher from Leiden University based on a computerized randomization sequence of permutated blocks of six participants stratified by gender. All assessments were carried out by research assistants who were blind to treatment condition.

2.3. Procedures

Upon referral, a member of the research team provided study-information by telephone and scheduled the baseline assessment. In- and exclusion criteria were checked during this assessment. Eligible participants obtained more detailed study-information in a subsequent preparatory session. After this preparatory session and informed consent, randomization took place.

PE was delivered in 16 weekly face-to-face sessions of 90 min. PE is a form of cognitive behavioural therapy involving psychoeducation about PTSD, imaginal exposure (repeatedly recounting most disturbing traumatic memories) and exposure in vivo (repeatedly approaching trauma-related stimuli) (Foa, Hembree, & Rothbaum, 2007). In the 1st session, the therapist and patient constructed a case conceptualization including a hierarchy of traumatic experiences. Between sessions, patients were instructed to listen to the audiotaped exposure sessions on a daily basis and to complete exposure in vivo assignments. PE sessions were manualized (based on the protocol of Foa et al. (2007)) and one therapist was assigned to each patient.

iPE was delivered in 14 face-to-face sessions of 90 min. iPE started with 3 sessions per week for 4 weeks (12 sessions total) followed by 2 sessions after one and 2 months. iPE was implemented similarly to the PE condition, except for the time format of the sessions. iPE sessions were delivered alternately by two therapists per patient.

STAIR+PE was delivered in 8 weekly face-to-face sessions of 60 min for STAIR and 8 weekly face-to-face sessions of 90 min for PE. STAIR+PE comprised skill training and prolonged exposure. STAIR is a skill training programme with 4 sessions focused on improving emotion regulation skills followed by 4 sessions focused on developing interpersonal skills (Cloitre et al., 2002; Levitt & Cloitre, 2005). Between sessions, patients were instructed to practice skills. STAIR was followed by 8 sessions PE which was implemented similar to the PE condition. STAIR+PE sessions were manualized and one therapist was assigned to each patient.

Therapists' adherence to the PE and STAIR protocols was ensured through training, an exam with pilot patients graded by supervisors, and weekly group supervision (supervisors: AvM and RAdK in PE; MC and IGW in STAIR). The therapists ($n = 20$; 18 females; $M_{age} = 36$, $SD_{age} = 7$) had at least a masters' degree in psychology and on average 10 years' experience in mental health services ($M = 10$, $SD = 7$). They were trained in both methods and the therapists provided treatment in all conditions when practically possible. We randomly selected 10% of the total sessions (178 sessions) which were rated by independent observers for treatment adherence in the three conditions based on the original adherence rater checklist scale by Cloitre and colleagues and the Dutch translation of the original adherence rater checklist scale by Foa and colleagues. Protocol adherence was high during STAIR sessions ($M_{session\ elements\ completed} = 98\%$, $SD = 5\%$) and PE sessions ($M_{session\ elements\ completed} = 90\%$, $SD = 18\%$). Early therapy completion was allowed when patients scored below 16 on the PTSD checklist for DSM-5 (PCL-5; see below) for three consecutive weeks. Patients who completed treatment (including early completers) were considered treatment completers.

Demographic and clinical characteristics of participants were assessed at baseline (T0). All primary and secondary outcomes of this paper (see below) were assessed at T0, at T1 after 4 weeks (4 sessions STAIR+PE and PE or 12 sessions iPE), at T2 after 8 weeks (8 sessions STAIR+PE/and PE or 13 sessions iPE), at T3 after 16 weeks (post-treatment) and at 6-month (T4) and 12-month follow-ups (T5).

2.4. Outcome measures

The primary outcome was clinician-rated PTSD symptom severity as measured with the CAPS-5 (Boeschoten et al., 2018). The CAPS-5 is a 20-item clinical interview that assesses both DSM-5 PTSD diagnostic criteria and PTSD symptom severity. The score range is 0–80, with higher scores indicating greater severity. The CAPS-5 was administered over events that were most strongly related to current PTSD symptoms. For all participants, index events included sexual and/or physical abuse in childhood. Treatment response was defined as at least 6 points improvement on the CAPS-5 between baseline and participants' last available measurement between baseline and 12-month follow-up (adapted from Schnurr & Lunney, 2016). Remission was defined as a response to treatment, a loss of PTSD diagnosis (measured with the CAPS-5) and CAPS-5 score below 12 based on the conservative notion that it is impossible to meet PTSD diagnosis with a score below 12 (Norman et al., 2019). Remission was also based on the participants' last available measurement. The audiotapes of 20 randomly selected CAPS-5 interviews were independently re-assessed by one of the researchers who did not conduct any interview in the study himself and showed a high correlation of the total severity scores (Pearson's correlation = .99) and diagnosis (Pearson's correlation = .90) between assessors. Internal reliability of the CAPS-5 at baseline was moderately high (Cronbach's α = .75).

Secondary outcome measures were the PTSD Checklist for DSM-5 (PCL-5; Blevins, Weathers, Davis, Witte, & Domino, 2015), the Difficulties in Emotion Regulation Scale (DERS; Lee, Witte, Bardeen, Davis, & Weathers, 2016) the Inventory of Interpersonal Problems (IIP-32; Barkham, Hardy, & Startup, 1996) and the Rosenberg Self-esteem Scale

(RSES; Schmitt & Allik, 2005). The PCL-5 is a 20-item self-report questionnaire which assesses PTSD symptoms. Total PCL-5 score ranges between 0 and 80 with higher scores indicating higher symptom severity. Internal reliability of the PCL-5 at baseline was high (Cronbach's α = .89). The DERS is a 36-item self-report questionnaire assessing emotion regulation difficulties. Total score ranges between 0 and 180 with higher scores indicating more difficulties. Internal reliability of the DERS at baseline was high (Cronbach's α = .90). The IIP is a 32-item self-report questionnaire which measures interpersonal problems with an averaged total score between 0 and 4 with a higher score indicating more difficulties. Internal reliability of the IIP at baseline was high (Cronbach's α = .87). The RSES is a 10-item self-report questionnaire which measures self-esteem with a total score between 0 and 30 with higher scores indicating higher self-esteem. Internal reliability of the RSES at baseline was high (Cronbach's α = .87).

Baseline comorbid axis-1 disorders were assessed with the MINI (Sheehan et al., 1998) and baseline personality disorders were assessed with the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-2; Weertman, Arntz, Dreessen, van Velzen, & Vertommen, 2003). Data about adverse events (untoward medical occurrence) and serious adverse events (i.e. an adverse event which is life-threatening requires inpatient hospitalization or potentially results in permanent impairment) were recorded by therapists during therapy and by research assistants during assessments.

2.5. Statistical analyses

We agreed upon a statistical analysis plan before the trial analysis (pre-registered at the Centre For Open Science; Hoeboer, 2019). We performed the analyses with R version 3.6.1 (R Core Team, 2018). The analyses were conducted on an intention-to-treat basis. Alpha was set at .05 for all analyses (two-tailed). To identify between-group differences with at least moderate effect size ($d = .40$) with an alpha of .05 (2-tailed) and a power of 0.8, 150 participants were recruited.

We used package lme4 for modelling the linear mixed effect models (Bates, Machler, Bolker, & Walker, 2015). The models were estimated with random intercepts for persons and random slope effects of time to account for the dependency in the data within persons (Hox, 2002; Kato et al., 2005). We modelled time with a piecewise linear growth curve model to account for a nonlinear decrease of symptoms over time since we expected a fast symptom decrease of the iPE condition from T0-T1. Additionally, we expected a different effect of time during treatment than during the follow-up period. This resulted in three different slopes with time point T0-T1 as the first slope (i.e.

baseline to 4 weeks in treatment), T1-T3 (i.e. 4 weeks in treatment to post-treatment) as the second slope and T3-T5 (post-treatment to 1-year follow-up) as the third slope. To evaluate post-treatment differences between conditions, we recoded the intercept as T3 for all outcomes.

To test the first hypothesis, we performed two independent linear-mixed effect models with 1) CAPS-5 and 2) PCL-5 as the dependent variable. For both analyses, the condition was dummy coded with PE as comparator. The three slopes (i.e. T0-T1; T1-T3 and T3-T5), condition and their interaction effects were included in the models as fixed independent variables. We used the same models for the second hypothesis but recoded iPE as comparator condition. For the third hypothesis, we performed three independent linear mixed effect models with the DERS total score (emotion regulation), IIP total score (interpersonal skills) and RSES total score (self-esteem) as dependent variables and STAIR+PE as comparator condition. The three slopes, condition and their interaction effects were included in the model as fixed independent variables. To test the fourth hypothesis we used two chi-square tests of independence with the condition (iPE versus PE and STAIR+PE versus PE) versus drop-out rates to assess the difference in drop-out rates between the three conditions. Patients were regarded as treatment drop-out if they stopped therapy prematurely (including never starting treatment after randomization). We used fisher exact tests to assess differences between conditions in early completers (iPE versus PE and STAIR+PE versus PE) since one of the assumptions of chi-square tests of independence (five expected observations per cell) was not met in more than 20% of the cells (McHugh, 2013).

The assumptions of all analyses were met. We evaluated between-group effect sizes with modelled data following the method of Feingold and t-to-d conversion using function lme-dscore from R package EMAtools (Feingold, 2013; Kleiman, 2017). We used semi-parametric bootstrapping to derive the prediction intervals of the modelled data from the linear mixed-effect models to account for the uncertainty in the variance of the parameters due to the random effects using R package Bootmer (Bates et al., 2015). The trial is registered at the clinical trial registry, number NCT03194113.

3. Results

Between 23 November 2016 and 18 December 2018, 150 participants were randomly assigned to PE, iPE or STAIR+PE (see Figure 1 for the study flowchart). One participant was excluded after randomization because she no longer met inclusion criteria at the time of enrolment. Table 1 lists the baseline
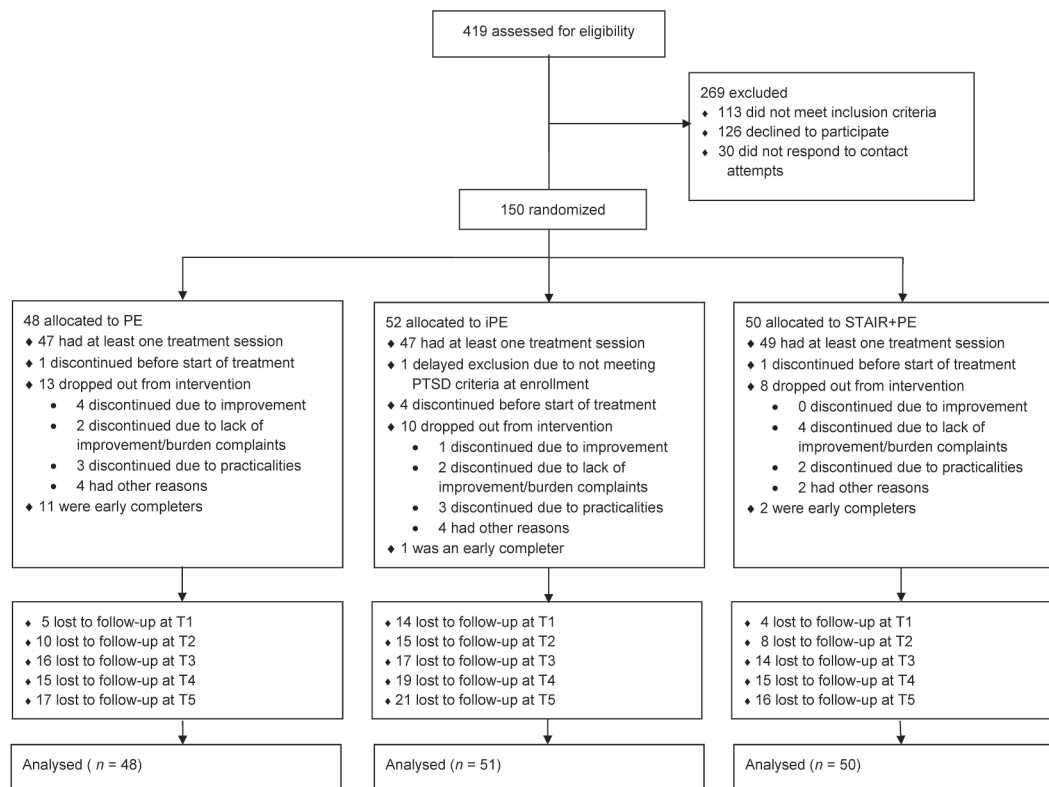
Figure 1. Flow diagram of recruitment and follow-up process.

characteristics of the included participants ($n = 149$). There were significantly more early completers in the PE condition (23%) compared to iPE (2%; $p = .001$) and STAIR+PE (4%; $p = .007$). In total, 37 patients (25%) dropped out of treatment. We found no demographic or clinical characteristics which were related to drop-out from therapy. Change in PTSD symptoms from baseline to week 4 did not predict subsequent therapy drop-out. Little's MCAR test indicates that missing cases may meet criteria for missing completely at random ($\chi2(244) = 241$, $p = .54$).

Table 2 lists the modelled CAPS-5 and PCL-5 scores with bootstrapped 95% confidence intervals and effect sizes produced with the linear mixed model analyses. All conditions resulted in large improvements in PTSD symptoms from baseline to 1-year follow-up (see Figure 2 for modelled outcomes). iPE and STAIR+PE did not produce significantly larger reductions in CAPS-5 and PCL-5 scores than PE (comparator condition, hypothesis 1) from baseline to 1-year follow-up (via the three slopes) and did not result in lower CAPS-5 and PCL-5 scores post-treatment or at 1-year follow-up. Significant differences between iPE and PE in the decrease of symptoms from baseline to week 4 are described under hypothesis 2. Moreover, we found a smaller decrease in CAPS-5 scores ($b = 3.92$, $t_{120} = 2.41$, $p = .02$, $d = .44$) and PCL-5 scores ($b = 7.32$, $t_{120} = 3.29$, $p = .001$, $d = .60$) from week 4 to post-treatment in iPE compared to PE. From post-treatment to 1-year follow-up, STAIR+PE resulted in more

improvement in CAPS-5 scores than PE ($b = 2.77$, $t_{175} = 2.16$, $p = .03$, $d = .33$).

iPE (comparator condition, hypothesis 2) resulted in a larger decrease of PTSD symptoms than PE from baseline to week 4 on the PCL-5 ($b = -10.11$, $t_{135} = -2.85$, $p = .005$, $d = .49$), but not on the CAPS-5 ($b = -4.82$, $t_{135} = -1.65$, $p = .10$). iPE led to larger improvements than STAIR+PE from baseline to week 4, as measured with the CAPS-5 ($b = -7.96$, $t_{135} = -2.77$, $p = .006$, $d = .48$) and the PCL-5 ($b = -14.32$, $t_{135} = -4.11$, $p < .001$, $d = .71$).

We did not find larger improvements of emotion regulation (DERS), interpersonal problems (IIP) and self-esteem (RSES) in STAIR+PE (comparator condition, hypothesis 3) compared to PE and iPE from baseline to 1-year follow-up (via the three slopes). STAIR+PE did not result in significantly improved DERS, IPP and RSES scores compared to PE and iPE post-treatment or at 1-year follow-up. All three conditions resulted in large improvements (see Table 2). STAIR+PE led to less DERS symptom improvement than iPE from baseline to week 4 ($b = 17.71$, $t_{133} = 3.30$, $p = .001$, $d = .57$), but STAIR+PE caught up from week 4 to post-treatment ($b = -6.23$, $t_{117} = -2.77$, $p = .007$, $d = .51$). STAIR+PE showed significantly more symptom improvement in DERS scores from post-treatment to 1-year follow-up compared to PE ($b = -5.42$, $t_{100} = -2.58$, $p = .01$, $d = .52$). STAIR+PE led to less symptom improvement on IIP scores than iPE from baseline to week 4 ($b = 0.32$, $t_{162} = 2.78$, $p = .006$, $d = .44$), while STAIR+PE showed more improvement on IIP scores than PE post-treatment to follow-up ($b = -.22$, $t_{163} = -3.50$, $p < .001$, $d = .58$).

Table 1. Baseline characteristics of the participants.

	Total (N = 149)	PE (n = 48)	iPE (n = 51)	STAIR+PE (n = 50)
Demographic characteristics, No. (%)				
Age, mean (SD), y	36.86 (11.75)	34.52 (11.05)	38.87 (11.57)	37.07 (12.39)
Gender (female)	114 (76.5)	37 (77.1)	38 (74.5)	39 (78.0)
Marital status (married/cohabitating)	56 (37.6)	15 (31.3)	25 (49.0)	16 (32.0)
Education (high)[1]	30 (20.1)	9 (18.8)	12 (23.5)	9 (18.0)
Job				
Employed	57 (38.3)	19 (39.6)	21 (41.2)	17 (34.0)
Incapacitated/on disability	37 (24.8)	14 (29.2)	7 (13.7)	16 (32.0)
Unemployed	55 (36.9)	15 (31.3)	23 (45.1)	17 (34.0)
Cultural background (non-Western)[2]	65 (43.3)	20 (41.7)	19 (36.5)	26 (52.0)
Trauma category (single or multiple) DSM 5A criterion CAPS				
Childhood sexual abuse	108 (72.5)	39 (81.3)	35 (68.6)	34 (68.0)
Childhood physical abuse	93 (62.4)	29 (60.4)	32 (62.7)	32 (64.0)
Sexual abuse in adulthood	29 (19.5)	12 (25.0)	9 (17.6)	8 (16.0)
Physical abuse in adulthood	42 (28.2)	16 (33.3)	15 (29.4)	11 (22.0)
Duration of PTSD, mean (SD), y	15.06 (12.49)	15.33 (10.21)	15.40 (12.89)	14.47 (14.19)
Any medication	96 (64.0)	32 (66.7)	34 (66.7)	30 (60.0)
Psychotropic medication	71 (47.7)	24 (50.0)	25 (49.0)	22 (44.0)
Antidepressants	39 (26.2)	16 (33.3)	13 (25.5)	10 (20.0)
Sedatives	42 (28.2)	17 (35.4)	11 (21.6)	14 (28.0)
Axis-1 MINI diagnosis				
Mean number, excluding PTSD (SD)	3.12 (1.91)	3.15 (1.89)	2.84 (1.79)	3.38 (2.03)
Current depression	85 (57.1)	27 (56.3)	25 (49.0)	33 (66.0)
Severe suicidality past month	64 (43.0)	23 (47.9)	21 (41.2)	20 (40.0)
Current bipolar disorder (type1/2)	10 (6.7)	4 (8.3)	3 (5.9)	3 (6.0)
Disorder alcohol/drug use past year	34 (22.8)	13 (27.1)	12 (23.5)	9 (18.0)
Current psychotic disorder	19 (12.8)	6 (12.5)	7 (13.7)	6 (12.0)
Any personality disorder diagnosis	90 (60.4)	33 (68.8)	26 (51.0)	31 (62.0)

PE = Prolonged Exposure condition, iPE = intensive Prolonged Exposure condition, STAIR+PE = Skills Training in Affective and Interpersonal Regulation + Prolonged Exposure, SD = standard deviation, y = year, N = sample size, No. = number, NA = not applicable, MINI = Mini-International Neuropsychiatric Interview. [1]high education = higher vocational education or university. [2]non-Western cultural background = at least one parent was not born in a Western country.

There were no significant differences in treatment drop-out (hypothesis 4) from PE (14 participants; 29%) compared to STAIR+PE (9 participants; 18%; $\chi2(1) = 1.70$, $p = .19$) and from PE compared to iPE (14 participants; 27%; $\chi2(1) = .04$, $p = .85$).

There were no significant differences between conditions in number of responders to treatment (PE = 71%, iPE = 73%, STAIR+PE = 70%), loss of PTSD diagnosis (PE = 48%, iPE = 59%, STAIR+PE = 58%) and remission rates (PE = 29%, iPE = 27%, STAIR+PE = 28%). This was based on the participants' last available measurement. In the PE condition, one serious study-related adverse event was reported which included short hospitalization after a suicide attempt and one study-related adverse event included voluntary hospitalization due to increased suicidal ideations. In the iPE condition, one nonstudy-related adverse events included overmedication and one nonstudy-related adverse event included a suicide attempt without hospitalization. In the STAIR+PE condition, one serious study-related adverse event included short hospitalization after a suicide attempt. No deaths occurred.

4. Discussion

Three variants of PE – 'traditional' PE, iPE and STAIR+PE – were each effective treatments of PTSD in patients with CA-PTSD. The baseline to follow-up effect sizes were large. Cohen's d was larger than 1.6 in each condition (baseline assessment to 1-year follow-up), which far exceeds published effect sizes of control conditions in this population (which are small-medium; Ehring et al., 2014). The drop-out rate in the current study is not different than generally found for trauma-focused treatment in CA-PTSD (Ehring et al., 2014), but higher than found for patients with PTSD in general (Lewis et al., 2020). However, the definition of drop-out differs substantially between studies, which complicates direct comparisons (Ehring et al., 2014; Lewis et al., 2020). Adverse events were rare in all conditions. This adds to recent evidence that suggests that trauma-focused psychotherapy is not contra-indicated and a viable option in severely ill, vulnerable patient populations (van den Berg et al., 2015; van Minnen, Harned, Zoellner, & Mills, 2012).

The hypothesis that iPE and STAIR+PE result in larger PTSD symptom reductions compared to PE from baseline to 1-year follow-up was not supported. This was true both for interviewer-assessed and self-reported symptom severity. There were no significant differences between PE and iPE/STAIR+PE at post-treatment or at 1-year follow-up. We found that STAIR+PE led to more improvement than PE in the post-treatment to follow-up phase on interviewer-assessed but not self-reported PTSD symptoms. This finding is in line with a previous study which found a beneficial follow-up trajectory of STAIR+PE

Table 2. Modelled outcomes for the three treatment conditions for all time points.

Time Point	PE Mean (95% CI)	Eff. size[1]	Cum eff. size	iPE Mean (95% CI)	Eff. size[1]	Cumeff. size	STAIR+PE Mean (95% CI)	Eff. size[1]	Cumeff. size
CAPS-5									
Baseline	41.3 (37.8–45.1)			39.4 (35.6–43.2)			43.5 (40.1–47.1)		
Week 4	33.1 (26.3–40.3)	.75	.75	25.8 (18.9–33.3)	1.11	1.11	37.6 (31.0–44.8)	.50	.50
Week 8	25.3 (20.0–30.9)			21.6 (16.4–27.1)			30.7 (25.4–36.4)		
Week 16	17.8 (12.1–23.8)	1.10	1.85	18.3 (12.6–24.3)	.49	1.60	21.5 (15.6–27.6)	1.19	1.69
6 M FU	19.1 (13.5–25.1)			17.4 (11.9–23.2)			19.4 (13.8–25.2)		
12 M FU	19.9 (13.6–26.3)	−.22	1.63	16.9 (10.8–23.3)	.09	1.69	18.2 (12.0–24.5)	.25	1.94
PCL-5									
Baseline	51.3 (45.0–58.0)			48.6 (42.0–55.8)			50.4 (44.0–56.9)		
Week 4	45.3 (36.9–54.2)	.46	.46	31.4 (22.8–40.0)	1.11	1.11	47.9 (39.2–56.6)	.17	.17
Week 8	34.6 (28.5–40.9)			26.2 (20.0–32.3)	.		38.5 (32.2–44.8)		
Week 16	23.5 (16.9–30.5)	1.25	1.71	22.9 (16.3–29.6)	.43	1.54	27.1 (19.7–34.0)	1.14	1.31
6 M FU	22.1 (15.2–28.9)			21.0 (14.7–27.2)			24.9 (18.1–31.6)		
12 M FU	19.9 (12.2–27.7)	.13	1.84	19.5 (12.6–26.6)	.17	1.71	22.9 (15.5–30.2)	.32	1.63
DERS									
Baseline	117.5 (107.0–127.8)			114.0 (103.6–125.0)			117.5 (107.1–128.3)		
Week 4	114.0 (104.9–123.5)	.17	.17	95.8 (86.9–104.6)	.79	.79	116.9 (107.6–126.0)	.01	.01
Week 8	104.0 (97.1–111.4)			91.6 (84.5–98.6)			108.5 (101.4–115.8)		
Week 16	93.8 (86.6–101.2)	1.05	1.22	89.0 (82.0–96.5)	.30	1.09	95.2 (87.8–102.6)	1.05	1.06
6 M FU	93.7 (86.8–101.0)			86.8 (79.8–93.8)			91.2 (84.0–98.4)		
12 M FU	93.2 (84.4–102.3)	−.07	1.15	84.8 (76.2–93.6)	.25	1.34	85.7 (76.9–94.2)	.68	1.74
IIP									
Baseline	1.7 (1.4–2.0)			1.6 (1.3–1.9)			1.7 (1.4–2.0)		
Week 4	1.7 (1.4–2.0)	.01	.01	1.4 (1.1–1.7)	.31	.31	1.9 (1.5–2.2)	−.32	−.32
Week 8	1.5 (1.2–1.8)			1.3 (1.0–1.6)			1.7 (1.4–2.0)		
Week 16	1.2 (0.9–1.6)	.87	.88	1.3 (1.0–1.6)	.29	.60	1.5 (1.2–1.8)	.62	.30
6 M FU	1.2 (0.9–1.6)			1.2 (0.9–1.5)			1.3 (1.0–1.7)		
12 M FU	1.3 (1.0–1.7)	−.27	.61	1.1 (0.8–1.5)	.14	.74	1.2 (0.8–1.5)	.55	.85
RSS									
Baseline	11.7 (9.0–14.5)			13.3 (10.4–16.2)			11.3 (8.6–14.0)		
Week 4	13.0 (10.4–15.8)	.36	.36	14.8 (12.2–17.4)	.23	.23	11.7 (9.1–14.4)	.07	.07
Week 8	13.9 (11.5–16.2)			16.3 (13.9–18.6)			13.2 (10.8–15.6)		
Week 16	14.8 (12.1–17.4)	.33	.69	17.2 (14.7–19.7)	.34	.57	14.6 (11.9–17.3)	.56	.63
6 M FU	15.2 (12.7–17.8)			17.8 (15.4–20.3)			14.8 (12.2–17.4)		
12 M FU	16.0 (13.2–18.9)	.20	.89	18.4 (15.7–21.1)	.22	.79	15.2 (12.5–18.1)	.14	.77

Eff. = effect, Cum = cumulative, Baseline = T0, Week 4 = T1, Week 8 = T2, Week 16 = T3, 6 M FU = 6-month follow-up, 12 M FU = 12-month follow-up, PE = Prolonged Exposure condition, iPE = intensive Prolonged Exposure condition, PBT = Phase-Based Treatment, CAPS-5 = Clinician-Administered PTSD Scale, PCL-5 = PTSD Checklist for DSM-5, DERS = Difficulties in Emotion Regulation Scale, IIP = Inventory of Interpersonal Problems, RSS = Rosenberg Self-esteem Scale, CI = Confidence Interval.

1 Within-group effect size (Cohen's *d*) of week 4 (baseline – week 4), week 16 (week 4 – week 16) and follow-up (week 16 – follow-up) based on modelled scores from LMM procedure. Positive values indicate improvements in symptoms.

compared to Support+PE (Cloitre et al., 2010), but this did not lead to better outcomes of STAIR+PE at 1-year follow-up. The hypothesis that iPE would lead to faster symptom improvement than PE and STAIR+PE was partly supported. Compared with PE, iPE led to faster improvement on self-reported but not interviewer-assessed PTSD symptom severity. iPE led to faster improvement than STAIR+PE on both self-reported and interview-based assessments. These results replicate previous studies with iPE in non-CA-PTSD populations (Ehring et al., 2014; Foa et al., 2018). Taken together, iPE is promising for a fast and sustained symptom improvement.

The hypothesis that STAIR+PE leads to more improvement in emotion regulation, interpersonal problems and self-concept compared to PE and iPE was not supported. There were no significant differences between STAIR+PE and PE/iPE post-treatment or at 1-year follow-up. STAIR+PE showed more improvement in emotion regulation and interpersonal problems post-treatment to 1-year follow-up compared to PE, but not compared to iPE. The baseline to 1-year follow-up effect of the three treatments

on emotion regulation ($d_{PE} = 1.15$, $di_{PE} = 1.34$, $d_{STAIR+PE} = 1.74$), interpersonal problems ($d_{PE} = .61$, $di_{PE} = .74$, $d_{STAIR+PE} = .85$) and self-esteem ($d_{PE} = .89$, $di_{PE} = .79$, $d_{STAIR+PE} = .77$) was (moderately) large. STAIR+PE led to comparable PTSD symptom reductions as PE despite the fact that patients received only 8 PE sessions in STAIR+PE (versus 16 in the PE condition). Conversely, iPE and PE improved emotion regulation, interpersonal problems, and self-esteem without any skill training and these improvements were reached significantly faster in iPE. This is in line with recent findings indicating that PE and iPE improve emotion regulation in patients with PTSD (Jerud, Zoellner, Pruitt, & Feeny, 2014; van Toorenburg et al., 2020).

The finding that STAIR+PE did not result in more improvements in emotion regulation and interpersonal problems is in contrast with the results of a previous study which found superior effects of STAIR+PE on these outcomes compared to support+PE at follow-up assessments (Cloitre et al., 2010). We considered two possible explanations for this. First, considering that both STAIR and PE improve
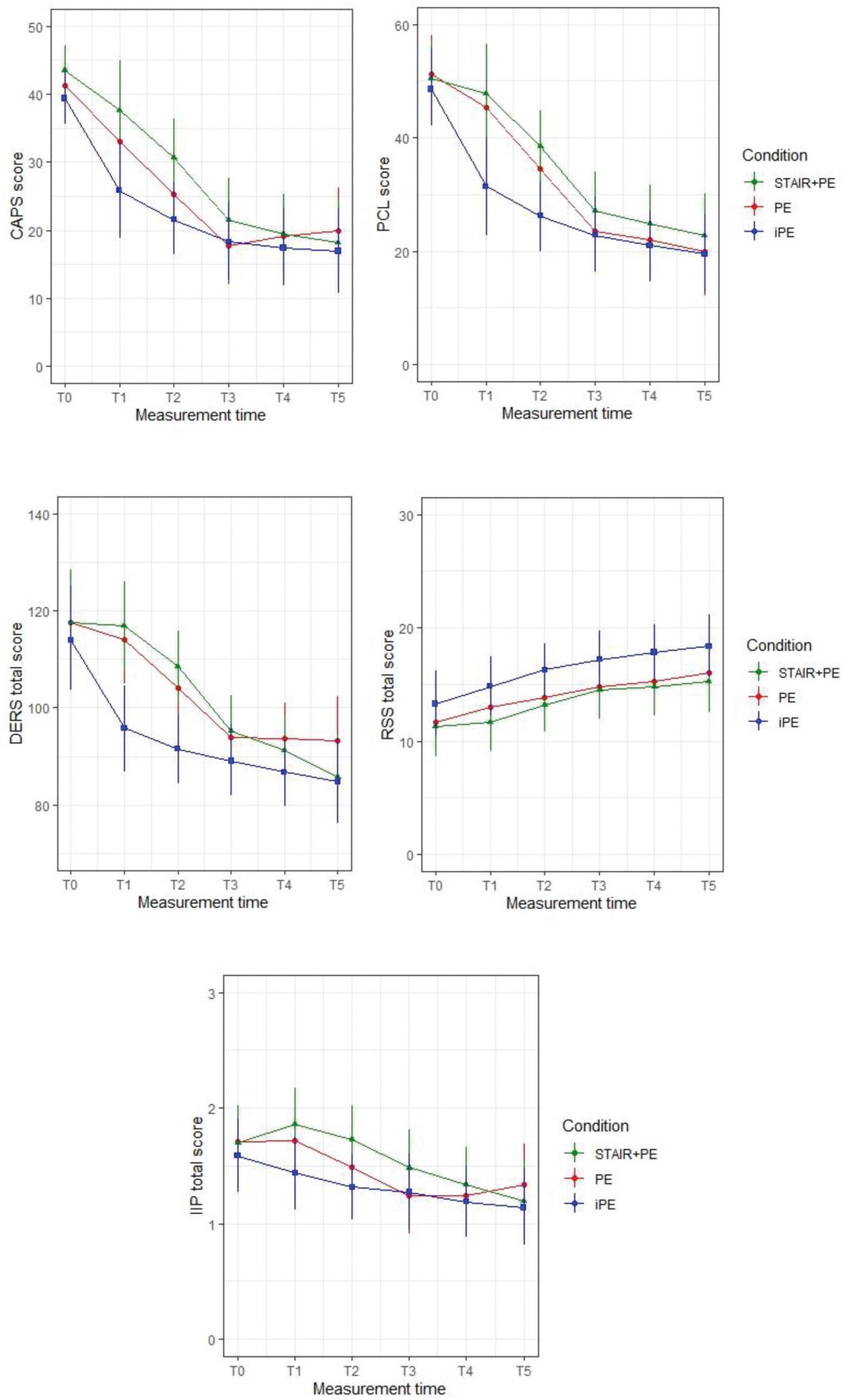
Figure 2. Modelled trajectories of the outcomes as a function of treatment condition per measurement time; Footnotes: T0 = baseline, T1 = 4 weeks, T2 = 8 weeks, T3 = 16 weeks, T4 = 6-month follow-up, T5 = 12-month follow-up.

emotion regulation and interpersonal problems, this inconsistency might be explained by the higher dosage of PE in our study compared to the control condition (support+PE). In other words, the difference between the two studies may be explained by the strength of the comparison condition. Second, the previous STAIR+PE studies used a modified version of PE which excluded in vivo exposure and introduced cognitive re-appraisal at the end of each exposure session identifying alternative interpersonal beliefs that had been generated during the STAIR work. These adaptations to PE after STAIR strengthened the linkage between STAIR and PE and may have contributed to its effectiveness.

Finally, the hypothesis that iPE (27% dropout) and STAIR+PE (18% dropout) would lead to lower drop-out rates than PE (29% dropout) was not supported. PE led to significantly more early completers (23% early completers) compared to iPE (2% early completers) and STAIR+PE (4% early completers), but this may be related to the relatively large amount of exposure sessions in PE (16 sessions) compared to iPE (14 sessions) and STAIR+PE (8 sessions). Moreover, early completion in the iPE condition was hardly possible, since the PCL score had to be below 16 for three consecutive weeks and most iPE sessions were provided in only 4 weeks (12 of the 14 sessions). In conclusion, fast improvement seems most likely to occur with intensified treatment, what may be clinically relevant for some patients (Ehlers et al., 2014), but the other treatments catch up relatively quickly and all lead to a sustained response.

This study differs from previous CA-PTSD trials in the large sample size, the inclusion of patients with severe psychiatric symptoms, the cultural and socio-economic diverse sample, multiple measurements during therapy and treatment adherence assessment. The effect sizes of all three conditions were better than expected since a previous meta-analysis indicated that patients with CA-PTSD may have suboptimal outcomes with standard trauma-focused interventions (Karatzias et al., 2019). However, iPE and STAIR+PE did not lead to larger PTSD symptom reductions or lower drop-out rates than PE. The two innovations provided comparable outcomes but did not improve treatment outcome in patients with CA-PTSD. This is in line with a meta-analysis that indicated that changed formats of PE do not improve outcomes of PE (Zhou et al., 2020).

This study has several limitations. Firstly, we did not include a control comparator condition, which precludes the calculation of controlled effect sizes. However, given the observed effect sizes and the speed of recovery, one may question the ethics of continued use of waiting list conditions in this population (Devilly & McFarlane, 2009). Secondly, our iPE condition included 3 sessions a week, whereas other studies on intensified trauma-focused treatment used 5 or more sessions a week (Ehlers et al., 2014; Foa et al., 2018). The effect of this format change on treatment outcome and drop-out rate is unknown. Thirdly, the study required that a participant agreed to be randomized to three different exposure treatments and therefore, there may have been a selection bias of patients who are willing to engage in this type of treatment. Fourthly, some patients received therapy for PTSD or other psychological problems between the 6-month and 12-month follow-up (number of sessions: M_{PE} = 7.6; $M_{\text{STAIR+PE}}$ = 4.7; M_{iPE} = 7.9), so the symptom trajectory during follow-up cannot be unequivocally attributed to the allocated treatment.

The results of this study demonstrate that PE, iPE and STAIR+PE are effective treatments for CA-PTSD. Intensifying treatment may speed up recovery but does not lead to an overall better outcome. Moreover, all treatments led to improvements in emotion regulation, interpersonal problems and self-esteem from baseline to follow-up. Despite the large and sustained effects, there is ample room for further improvements and innovations. Attention to patient preferences regarding type and intensity of interventions may lead to greater patient engagement, treatment benefit and patient satisfaction (Delevry & Le, 2019). Studies that focus on personalizing treatment based on baseline patient characteristics or on patient preference are an important next step in treatment research among traumatized patient populations. In conclusion, iPE and STAIR+PE did not improve the overall outcome of PE. All treatments were effective for patients with CA-PTSD.

Contributors

MS, DACO, WvD and AvM obtained funding and designed the study. DACO implemented the study at the PsyQ departments. DACO and CMH coordinated the recruitment of participants and data collection during the study. MS, RAdK, AvM and WvD supervised the study. CMH and DACO wrote the first draft of the manuscript. CMH did the statistical analyses. RAdK, MS, WvD, AvM, MC and IGW contributed to the writing of the manuscript. All authors read and approved the final version.

Disclosure statement

Dr. van Minnen reports personal fees from Royalties and fees, outside the submitted work; Dr. Cloitre reports

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Data availability

The study protocol, statistical analysis plan and analytical codes are available at OSF and BMC Psychiatry. Anonymized individual patient data that underlie the results of this article will be available for individual participant data meta-analyses that have been approved by independent review committees after the publication of this article. Proposals for the use of data and requests for access should be directed to vanderdoes@fsw.leidenuniv.nl.

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