Choosing the right track: improving PTSD treatment outcomes for patients with childhood abuse-related posttraumatic stress disorder

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Chapter 3

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 two booster sessions) or a phase based treatment, in which 8 sessions of PE were preceded by 8 session 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. 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 outcomes 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 trials registry, number NCT03194113,

Keywords: Posttraumatic stress disorder, CA-PTSD, trauma-focused treatment, childhood trauma, prolonged exposure, STAIR, intensified treatment

Introduction

Childhood physical and sexual abuse are important risk factors for the development of posttraumatic 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 et al., 2005; Ehring et al., 2014; Watkins et al., 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 et al., 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 et al., 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., 2019b). 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 et al., 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 et al., 2018) and non-inferior 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 et al., 2018), and that the results did not differ between patients with and without CA-PTSD (Wagenmans et

al., 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 processing of trauma memories and that improvement in these capacities during the STAIR phase facilitates the effectiveness of PE (Cloitre et al., 2002). STAIR+PE has been demonstrated to be an effective treatment for CA-PTSD (Cloitre et al., 2002; Cloitre et al., 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.

Method

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 Center (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 year; 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 non-suicidal self-injury (NSSI) which required hospitalization during the past three months; 4) severe suicidal behaviour: a suicide attempt during the past three 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 three 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 two 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.

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.

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 minutes. 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 et al., 2007). In the first 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 minutes. iPE started with three sessions per week for four weeks (12 sessions total) followed by two sessions after one and two 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 minutes for STAIR and 8 weekly face-to-face sessions of 90 minutes for PE. STAIR+PE comprised skills training and prolonged exposure. STAIR is a skills training program with four sessions focused on improving emotion regulation skills followed by four 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 female; M_{age} = 36, SD_{age} = 7) had at least a masters' degree in psychology and on average ten 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 percent 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 ($M_{\text{session elements completed}}$ = 98%, SD = 5%) and PE sessions ($M_{\text{session elements completed}}$ = 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).

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 twelve based on the conservative notion that it is impossible to meet PTSD diagnosis with a score below twelve (Norman et al., 2019). Remission was also based on participants' last available measurement. The audiotapes of twenty 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 et al., 2015), the Difficulties in Emotion Regulation Scale (DERS; Lee et al., 2016b) the Inventory of Interpersonal Problems (IIP-32; Barkham et al., 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 0-80 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 0-180 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 0-4 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 0-30 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 et al., 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.

Statistical analyses

We agreed upon a statistical analysis plan before the trial analysis (pre-registered at the Center 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 et al., 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 3 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 dependent variable. For both analyses, 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 condition (iPE versus PE and STAIR+PE versus PE) versus drop-out rates to assess 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 trials registry, number NCT03194113.

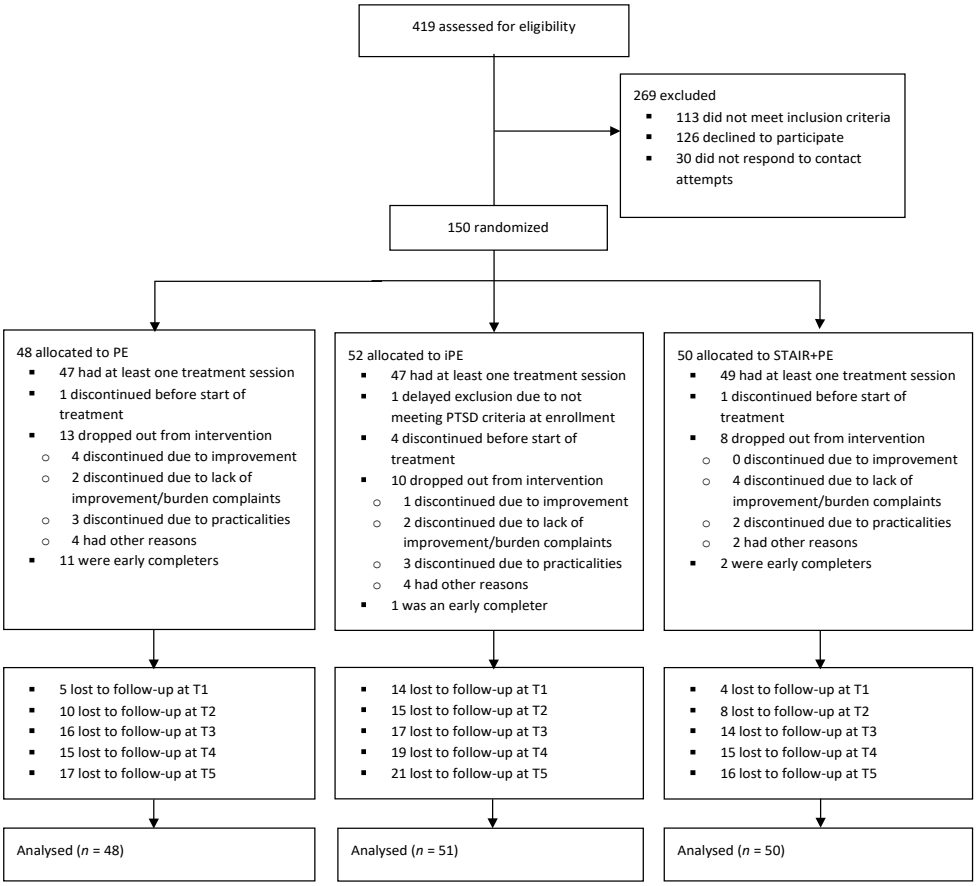

Figure 1. Flow diagram of recruitment and follow-up process

Results

Between November 23, 2016 and December 18, 2018, 150 participants were randomly assigned to PE, iPE or STAIR+PE (see Figure 1 for study flowchart). One participant was excluded after randomization because she no longer met inclusion criteria at time of enrolment. Table 1 lists baseline 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 from 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 ($\chi^2(244) = 241$, 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 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).

There were no significant differences in treatment drop-out (hypothesis 4) from PE (14 participants; 29%) compared to STAIR+PE (9 participants; 18%; $\chi^2(1) = 1.70$, p = .19) and from PE compared to iPE (14 participants; 27%; $\chi^2(1) = .04$, 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 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 non study-related adverse events included overmedication and one non study-related adverse event included a suicide attempt without hospitalization. In the STAIR+PE condition, one serious study-related adverse event included short hospitalization after suicide attempt. No deaths occurred.

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.

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

Time Point	PE			iPE			STAIR+PE		
	Mean (95% CI)	Eff. size[1]	Cum eff. size	Mean (95% CI)	Eff. size[1]	Cum eff. size	Mean (95% CI)	Eff. size[1]	Cum eff. 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
6M FU	19.1 (13.5-25.1)			17.4 (11.9-23.2)			19.4 (13.8-25.2)		
12M 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
6M FU	22.1 (15.2-28.9)			21.0 (14.7-27.2)			24.9 (18.1-31.6)		
12M 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
6M FU	93.7 (86.8-101.0)			86.8 (79.8-93.8)			91.2 (84.0-98.4)		
12M 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
6M FU	1.2 (0.9-1.6)			1.2 (0.9-1.5)			1.3 (1.0-1.7)		
12M 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
6M FU	15.2 (12.7-17.8)			17.8 (15.4-20.3)			14.8 (12.2-17.4)		
12M 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, 6M FU = 6-month follow-up, 12M 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.

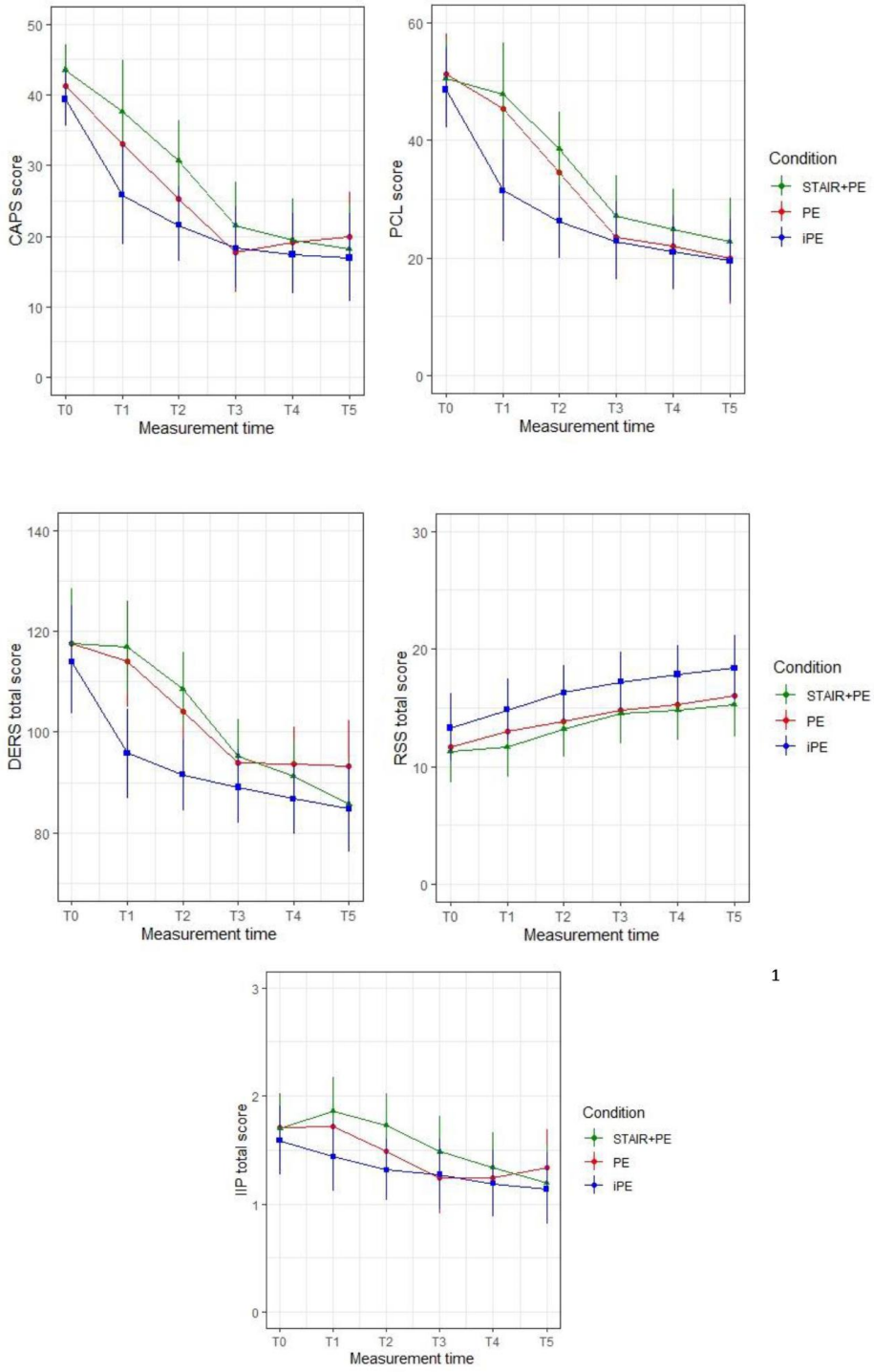

Figure 2. Modelled trajectories of the outcomes as a function of treatment condition per measurement time T0 = baseline, T1 = 4 weeks, T2 = 8 weeks, T3 = 16 weeks, T4 = 6-month follow-up, T5 = 12-month follow-up

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 et al., 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 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 eight PE sessions in STAIR+PE (versus sixteen in the PE condition). Conversely, iPE and PE improved emotion regulation, interpersonal problems, and self-esteem without any skills 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 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 dropout 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 four weeks (12 of the 14 sessions). In conclusion, fast improvement seems most likely to occur with intensified treatment, what may be clinical relevant for some patients (Ehlers et al., 2014), but the other treatments catch up relatively quickly and all lead to sustained response.

This study differs from previous CA-PTSD trials in the large sample size, inclusion of patients with severe psychiatric symptoms, the cultural and socioeconomic diverse sample, multiple measurement 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., 2019b). 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 three sessions a week, whereas other studies on intensified trauma-

focused treatment used five 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; $M_{STAIR+PE}$ = 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 overall outcome of PE. All treatments were effective for patients with CA-PTSD.