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

Hoeboer, C.M.

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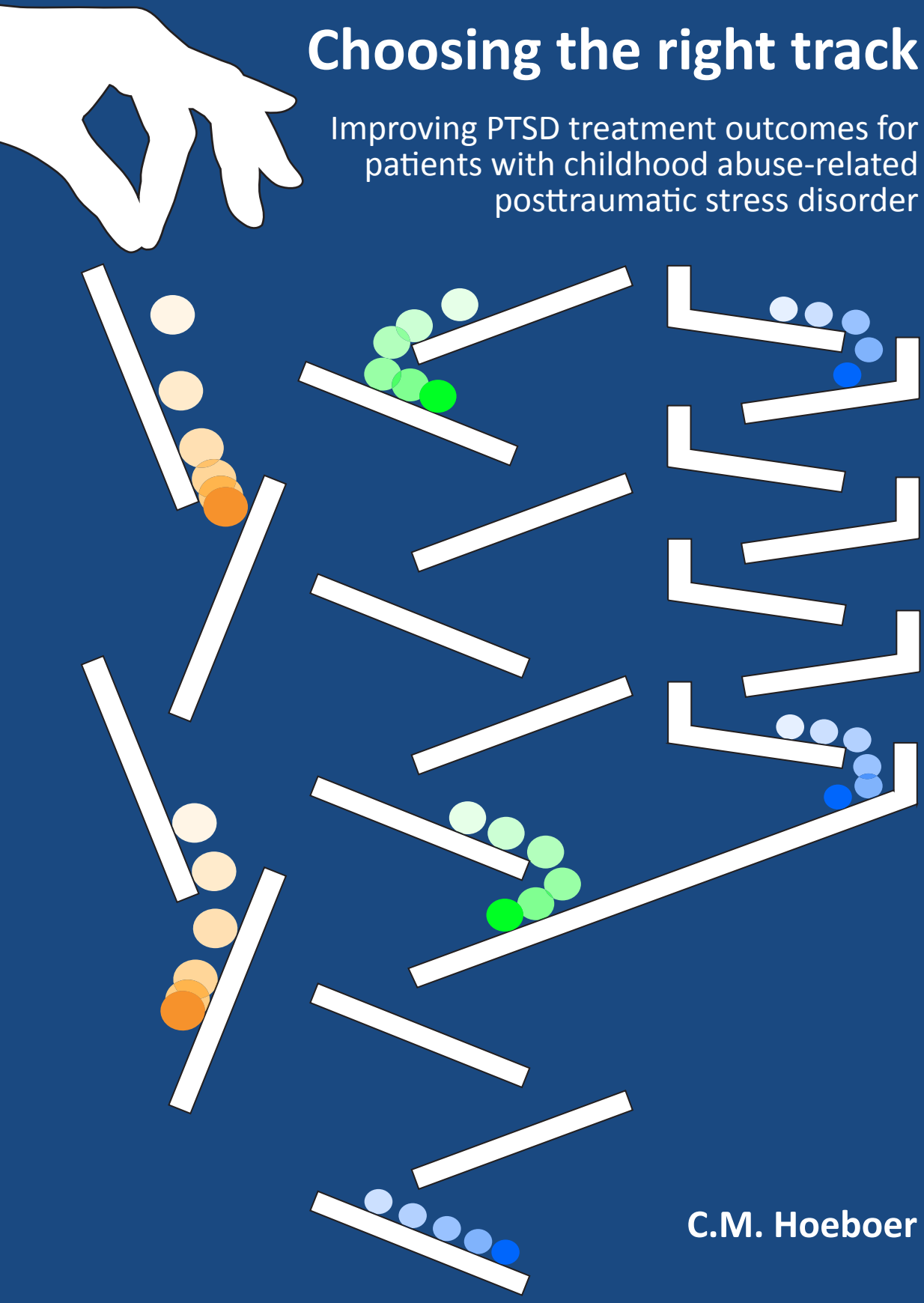

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All roads lead to Rome

But some get you there faster than others

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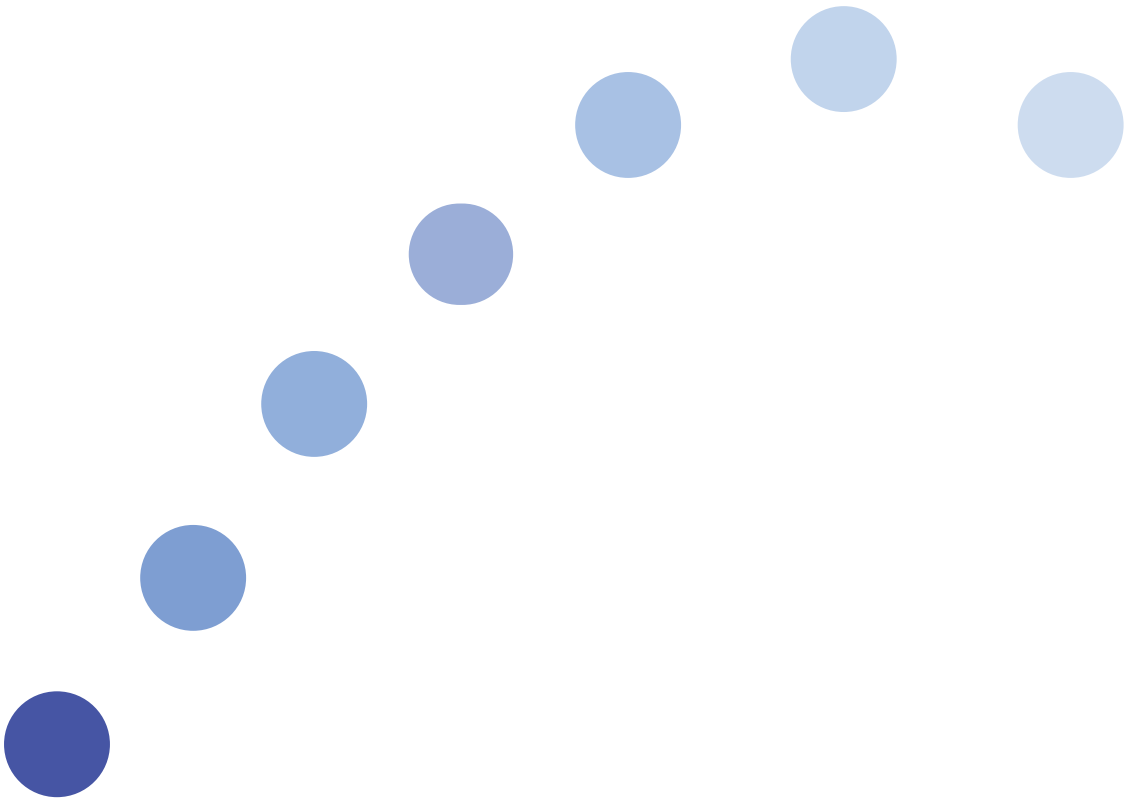


Chapter 1

General introduction

PTSD related to childhood abuse

Throughout life, many people experience stressful and potentially traumatic events such as accidents, sudden death of loved ones or assaults. On average, people are exposed to two to three different types of trauma during their life (de Vries & Olff, 2009). Some people suffer from persisting symptoms related to the event they experienced and develop posttraumatic stress disorder (PTSD). PTSD symptoms include: 1) intrusions about the traumatic event such as nightmares or flashbacks; 2) avoidance of feelings and thought related to event; 3) negative alterations in mood and cognitions such as blaming themselves for the event and 4) alterations in arousal and reactivity such as sleeping disturbances and hypervigilance (APA, 2013).

When PTSD was first introduced in a diagnostic manual (APA, 1980), it was mainly included to describe psychiatric symptoms of combat troops after their return from war (Crocq & Crocq, 2000). Researchers soon identified similar symptoms in other traumatized populations such as victims of rape (Burgess & Holmstrom, 1974) and childhood sexual abuse (Briere & Runtz, 1987). Early on, it was noted that repeated interpersonal traumatization, particularly at a young age, may elicit more complex symptoms than single incidents of traumatic events (Courtois, 1988; Herman, 1992). The experience of such abuse during childhood, often committed by a caregiver or authority figure, was thought to interrupt emotional and cognitive development, affecting self-organization skills such as emotion regulation, interpersonal functioning and self-esteem (Cloitre et al., 2009; Dvir, Ford, Hill, & Frazier, 2014; Lonergan, 2014). In the past decades, research confirmed that enduring physical or sexual abuse as a child is related to problems with self-organization skills (Cloitre, Miranda, Stovall-McClough, & Han, 2005; Gekker et al., 2018; Messman-Moore & Bhuptani, 2017). In addition, it has been consistently shown that early childhood maltreatment also increases the likelihood of aversive outcomes in adulthood other than PTSD, such as depression (Li, D'Arcy, & Meng, 2016; Nelson, Klumparendt, Doebler, & Ehring, 2017), drug abuse (Halpern et al., 2018) and suicidality (Angelakis, Gillespie, & Panagioti, 2019). Childhood physical and sexual abuse are also risk factors for developing a comorbid PTSD, i.e. meeting criteria for both PTSD and other disorders such as depression (Spinhoven, Penninx, van Hemert, de Rooij, & Elzinga, 2014). Given this comorbidity, one might conclude that symptom representation of patients with PTSD related to childhood abuse (CA-PTSD) is often rather complex. Since PTSD symptoms also tend to persist for years (Kessler et al., 2017), effective treatment is imperative.

Treatment of PTSD related to childhood abuse

Considerable evidence exists for the effectiveness of trauma-focused cognitive behavioural therapy (TF-CBT) such as prolonged exposure (PE) for PTSD (Mavranezouli et al., 2020). Consequently, TF-CBT is the recommended treatment for PTSD in many guidelines across the globe (Hamblen et al., 2019). Nevertheless, previous studies have consistently shown that not all patients benefit (enough) from TF-CBT (Bradley, Greene, Russ, Dutra, & Westen, 2005; Lewis, Roberts, Gibson, & Bisson, 2020; Watkins, Sprang, & Rothbaum, 2018).

A considerable number of patients drop out from treatment, do not respond to the treatment or do not reach remission of PTSD. Some authors argued that patients with CA-PTSD may be specifically at risk for suboptimal treatment outcomes (e.g., Cloitre, Koenen, Cohen, & Han, 2002; Courtois, 2004; Dorrepaal et al., 2014; Karatzias et al., 2019b) because these patients may find it difficult to regulate their emotions during TF-CBT and to tolerate the distress of the treatment (Cloitre et al., 2002). They may also be vulnerable to experience dissociation, another potential risk factor for poor treatment outcomes (Cloitre et al., 2002; Courtois, 2004). Therefore, it has been suggested that treatment outcomes for patients with CA-PTSD might be improved by starting treatment with a skills training focused on self-organization skills such as emotion regulation. By first improving such skills, patients might be better able to tolerate and benefit from TF-CBT in a second phase of the treatment (Cloitre et al., 2002). Skills Training in Affective and Interpersonal Regulation (STAIR) followed by PE (STAIR+PE) is such a phase-based treatment and showed promising results, i.e. relatively low dropout rates and more remission of PTSD, compared to a supportive treatment followed by PE in patients with CA-PTSD (Cloitre et al., 2010).
Others have argued that empirical evidence to substantiate claims about suboptimal treatment outcomes in CA-PTSD is lacking and that these patients might benefit from 'normal' TF-CBT (De Jongh et al., 2016; Ehring et al., 2014). Rather than developing a new treatment for patients with CA-PTSD specifically, treatment outcomes might be improved with adaptations to TF-CBT which showed promise in PTSD in general (including but not limited to interpersonal trauma). One promising adaptation is intensifying TF-CBT by condensing treatment in a shorter period of time (e.g., Ehlers et al., 2014). Reducing time between sessions might reduce dropout, for example by preventing anticipatory anxiety to build up between sessions. It might also lead to a fast symptom improvement and thereby rapidly reduce symptom burden. First results of intensified PE in patients with PTSD in general (Foa, McLean, Zang, & Consortium, 2018) and CA-PTSD specifically (Hendriks, Kleine, Broekman, Hendriks, & Minnen, 2018) were promising both for dropout and fast symptom reduction.

Despite the different views on how to improve treatment outcomes in CA-PTSD, there is a consensus that more research is needed in patients with PTSD resulting from childhood trauma (Cloitre, 2015; De Jongh et al., 2016; Ehring et al., 2014; Markowitz, 2016). In studies into PTSD in general, exclusion criteria frequently include some of the common complaints of patients with CA-PTSD, such as suicidal ideations or dissociation, which leads to an underrepresentation of this population in treatment studies (Dorrepaal et al., 2014; Ehring et al., 2014; Ronconi, Shiner, & Watts, 2014). Past research has also shown that TF-CBT is underutilized in clinical practice and that perceived barriers (e.g. fear of symptom exacerbation) were related with lower perceived suitability of TF-CBT for patients with CA-PTSD specifically (van Minnen, Hendriks, & Olff, 2010). Hence, it is crucial to study TF-CBT in patients with CA-PTSD and to investigate whether treatment might be (further) improved. Note that treatment might also be improved by studying *for whom* and *how* treatment works (Kraemer, 2016). When we know better what treatment has most chance to be

effective for a specific patient, we can tailor treatment indications. When we know more about the active ingredients of a specific treatment, we might track or even enhance these. To this end, we designed the 'IMPACT' study (improving PTSD treatment for adults with childhood trauma; Oprel et al., 2018).

IMPACT study

In the IMPACT study, we compared standard PE with two potential improvements in patients with CA-PTSD: STAIR+PE and intensified prolonged exposure (iPE). The study was designed to compare the effectiveness of these three treatments. A second aim was to assess for whom and how the treatments work. The primary outcome of the study was clinician-assessed PTSD symptoms. Secondary outcomes were self-reported PTSD symptoms, emotion regulation difficulties, interpersonal problems, self-esteem and dropout rate.

Standard PE was delivered in 16 weekly sessions and included imaginal exposure involving repeated and systematic recounting of the most distressing traumatic memories and exposure in vivo involving approaching trauma-related stimuli. Patients listened to audiotapes of the imaginal exposure between sessions and practiced with approaching trauma-related stimuli. iPE is a modification of PE and was delivered in triweekly sessions for four weeks followed by two booster sessions. Session content was similar to the standard PE condition, but the treatment was delivered by two alternating therapists. STAIR+PE was delivered in 16 weekly sessions by one therapist (Cloitre et al., 2002). During the first phase (STAIR; 8 sessions), some of the additional symptoms of patients with CA-PTSD were addressed while the second phase of treatment included standard PE (8 sessions) similar to the PE and iPE conditions.

For whom does the treatment work?

In the IMPACT study, patients completed a baseline assessment during which many clinical characteristics were measured to be able to investigate for whom the treatments work. We will focus on predictors and moderators of treatment outcome. *Predictors* refer to baseline patient characteristics indicating which patients are less or more likely to benefit from (any) treatment. Predictors do not have direct clinical implications, since they do not indicate how to improve treatment of patients at risk for suboptimal treatment outcomes, but they can inform future research and adaptations to interventions for subgroups of patients who are unlikely to respond to existing therapies (Kraemer, 2016; Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001). *Moderators* refer to baseline patient characteristics which indicate better or worse treatment outcome of one treatment compared to another (i.e. better outcome of STAIR+PE compared to standard PE or vice versa). Hence, moderators provide a direct opportunity to improve treatment outcomes by allocating patients to specific treatments (Kraemer, 2016; Kraemer et al., 2001). Despite the clinical relevance of identifying predictors and moderators of treatment, this line of research has received little attention in the field of PTSD (Barawi, Lewis, Simon, & Bisson, 2020; Dewar, Paradis, & Fortin, 2020). Two clinical constructs are an exception to this rule: dissociative symptoms and the construct of 'Complex PTSD' have been mentioned as potential predictors and moderators of treatment

outcomes for decades (see for reviews: Courtois, 2004; Lanius, Brand, Vermetten, Frewen, & Spiegel, 2012; Lanius et al., 2010; Lonergan, 2014; van Minnen, Harned, Zoellner, & Mills, 2012). The dissociative subtype is a novel subtype of PTSD in the Diagnostic and Statistical Manual of Mental Disorders (DSM–5) and involves depersonalization (experiencing unreality or detachment from own thoughts, feelings, sensations, body or actions) and derealisation (experiencing unreality or detachment from own surroundings; APA, 2013). Complex PTSD is a novel diagnosis which was formally introduced in the 11th revision of the International Classification of Diseases (ICD-11) for patients who suffer from comorbid symptoms (emotion regulation difficulties, interpersonal problems and low self-esteem) alongside PTSD (World Health Organization, 2018). Both the dissociative subtype and the diagnosis of Complex PTSD were introduced in diagnostic manuals because of the potential relevance for treatment indications, i.e., both were considered potential predictors/moderators of treatment outcome (Berliner et al., 2019; Brewin, 2019; Friedman, 2013). Dissociative symptoms reduce emotional engagement, which is one of the proposed change mechanisms of PE (Lanius et al., 2010). And, patients with Complex PTSD suffer from emotion regulation difficulties and may not be able to tolerate PE without addressing these difficulties first (Cloitre et al., 2002). Empirical evidence, however, about dissociative symptoms and Complex PTSD as predictor or moderator of treatment outcomes is lacking or inconsistent. For example, in a review on dissociative symptoms it was concluded that empirical evidence showed mixed results (van Minnen et al., 2012). Another review on Complex PTSD concluded that 'a dearth of literature exists examining whether CPTSD is a negative prognostic factor within treatment studies.' (Lonergan, 2014, p. 499). Given the potential of these two constructs to indicate for whom treatment works, we will investigate these in studies in this manuscript. Measures for dissociative symptoms have already been developed and validated decades ago (e.g., Bernstein & Putnam, 1986) and have frequently been used in clinical trials. Therefore, the relevance of dissociative symptoms as predictor is tested in a meta-analysis. In contrast, a Complex PTSD measure has only been recently developed and validated (Cloitre et al., 2018). Hence, the relevance of Complex PTSD as predictor or moderator of treatment outcome can only be tested in a novel clinical trial and will be tested with data from the IMPACT study.

Individual treatment recommendation

Although dissociation and Complex PTSD are promising constructs for treatment selection, patients in the IMPACT study might differ on many other demographic and clinical characteristics relevant for treatment outcome, given the heterogeneous representation of CA-PTSD. Rather than focusing on the importance of single constructs, we will also consider the relevance of a combination of constructs for individual treatment outcomes. In the field of medicine, research into the relevance of a combination of individual characteristics for screening, assessment and treatment of diseases, often referred to as *personalization* or *personalized medicine* has been carried out for decades (Meyer & Ginsburg, 2002). Regarding treatment personalization, the basic idea is that individual patients respond

differently to two distinct but on average equally effective treatments and that this might be predicted by a combination of baseline characteristics (Seidler & Wagner, 2006). In the field of psychiatry, depression has been the major focus of personalization research. These studies have shown that combinations of clinical characteristics seem to be related to differential response to treatments. The effect size difference between groups that were retrospectively identified as being allocated to their optimal treatment versus non-optimal treatment was small to medium in most studies. However, prospective research is absent and findings await replication (e.g., Cohen, Kim, Van, Dekker, & Driessen, 2020; Delgadillo & Duhne, 2020; DeRubeis et al., 2014; Friedl, Berger, Krieger, Caspar, & Holtforth, 2019; Friedl et al., 2020; Huibers et al., 2015; van Bronswijk et al., 2019). There have only been three treatment personalization studies in patients with PTSD focusing on a limited set of patient characteristics (Cloitre, Petkova, Su, & Weiss, 2016; Deisenhofer et al., 2018; Keefe et al., 2018). These studies found differences between retrospective allocation to optimal versus non-optimal treatment with small to medium effect sizes. One of these studies used the primary treatment target (PTSD symptoms) as outcome measure but did not include a validation procedure to determine the benefit of treatment allocation based on predictors/moderators (Cloitre et al., 2016). The other studies used depressive symptoms and dropout as outcome measures (Deisenhofer et al., 2018; Keefe et al., 2018). Hence, the potential benefit of personalization of treatment indications for PTSD symptoms has yet to be established. Note that when combining baseline patient characteristics for the purpose of predicting treatment outcomes, information about what individual characteristics to include in such a combination is crucial. Put differently, when characteristics unrelated to (differential) treatment outcome are combined to determine optimal treatment, this is highly unlikely to result in useful treatment recommendations in terms of treatment outcomes. Since information about predictors and moderators of treatment outcome in PTSD is limited (see for review: Barawi et al., 2020), the aim of our study was two-fold: firstly, to identify relevant predictors of PE and iPE and STAIR+PE separately using a broad range of predictor candidates involving both self-reported and clinician-assessed characteristics and secondly, to retrospectively evaluate the benefit of treatment allocation based on the combination of these predictors. For this second aim, we combine predictors into a personalized advantage index (PAI; DeRubeis et al., 2014) indicating the benefit of one treatment relative to another in terms of treatment outcome for a specific patient. This index is used to assess whether patients are allocated to their optimal or suboptimal treatment. Next, validation techniques are used to determine the benefit of allocation to the optimal versus suboptimal treatment in terms of treatment outcome.

How does the treatment work?

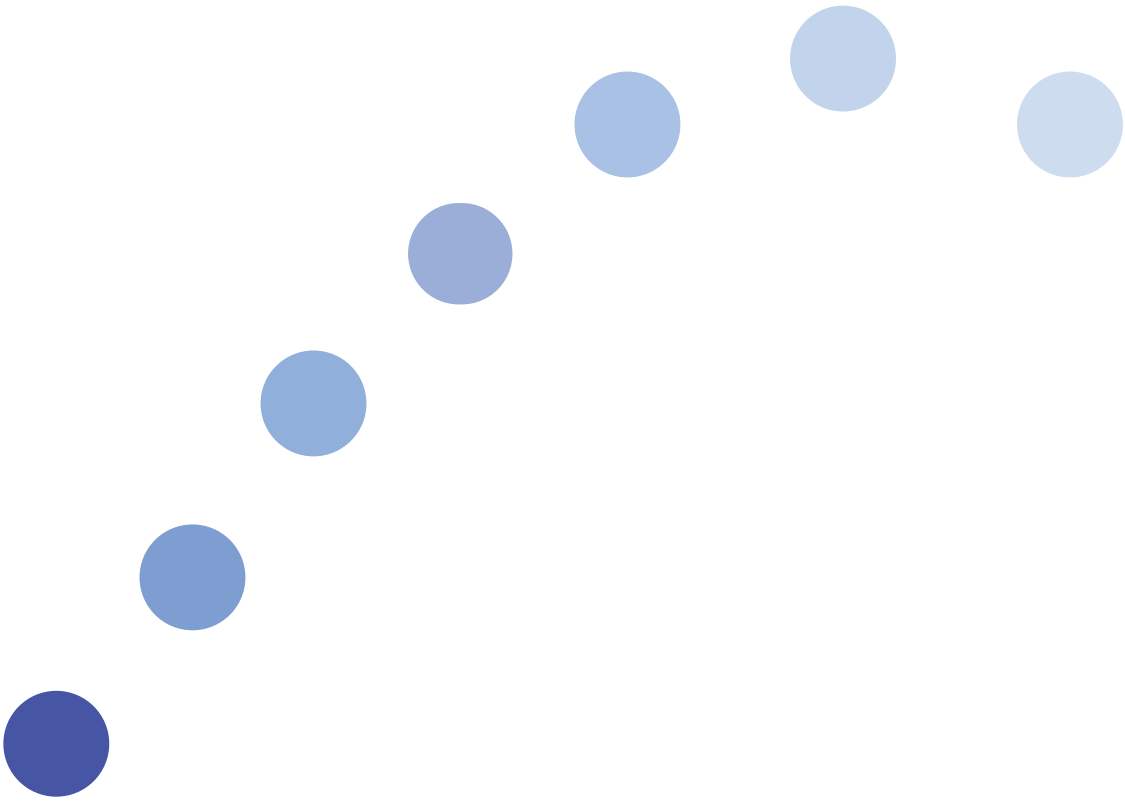
Up to now, we focused on the question for whom treatment works, but the treatment process itself also provides ample opportunity to improve treatment outcomes. Therefore, it is crucial to understand what makes a treatment work, in other words, what ingredients lead to symptom improvement. In the IMPACT study, we assessed indices for some of the

theoretically relevant ingredients, i.e., potential mechanisms of change, every session, which provides the opportunity to investigate whether changes in these indices predict and temporally precede symptom improvements. Indices of change may assist and guide clinicians in monitoring treatment progress and provide directions for treatment improvements (Kazdin, 2007). We will focus on indices of change during PE. Emotional Processing Theory (EPT) provides a theoretical framework about PE's mechanisms of change (Foa & Kozak, 1986; Rauch & Foa, 2006). According to EPT, patients' memories of the trauma (e.g., sexual assault) are represented in a fear network. This network includes excessive behavioral and physiological responses and persistence of associations related to the traumatic event (Foa & Kozak, 1986). For example, someone who was sexually assaulted by a man with a beard may respond very frightened to all men with beards, also in safe contexts. Avoidance may lead to quick relief, but keeps the fear network intact and the avoidance reinforced. During treatment, the fear network needs to be activated in order to modify its content. Then, corrective information can be introduced in the fear network, incompatible with the existing fear structure, forming a new memory. Integration of this corrective information may lead to emotional processing, i.e., attenuation of conditioned fear responses, which is thought to reduce PTSD symptoms. During PE, patients are systematically and repeatedly exposed to (safe) trauma reminders (e.g., men with beards) without the occurrence of the feared outcome, i.e. in this example, sexual assault. In this way corrective information (i.e., men with beards do not necessarily predict sexual assaults) is integrated in the fear network and emotional change can occur. Therefore, EPT describes within-session change in subjective distress (decrease of the fear response within a session) and between-session change in subjective distress (decrease of the peak fear response between two sessions) as indices of change during PE (Foa & McLean, 2016). Many studies have investigated the relevance of within- and between-session change in subjective distress for symptom change during PE, but none used a temporal sequencing design, distinguishing *temporal* effects (i.e., effect of mediator on symptom improvement in the next session) from *averaged* effects (i.e., relationship between averaged mediator scores across sessions and symptom improvement). Establishing temporal relationships is crucial for mediation. As previously noted: *'Demonstrating a timeline between cause and an effect, albeit obvious, is the Achilles' heel of treatment studies'* (Kazdin, 2007, p. 5). Hence, a temporal sequencing study could provide essential information about whether within- and between-session change in subjective distress are relevant processes to monitor during treatment.

Aim and outline of the dissertation

The main aim of this dissertation is to improve treatment outcomes for patients with CA-PTSD. To this end, we compare PE with two different treatment formats: intensified PE (iPE) and Skills training followed by PE (STAIR+PE). We focus on predictors and moderators of treatment outcomes and mechanisms of change to increase understanding about for whom and how treatments work. **Chapter 2** contains the design paper of the IMPACT study. This paper includes the rationale, main research questions and method of the trial which is the

basis for Chapters 3,5,6 and 7. **Chapter 3** describes the main results of the IMPACT study. **Chapter 4** includes a meta-analysis which summarizes clinical trials about the predictive value of dissociation on psychotherapy outcome for patients with PTSD. **Chapter 5** identifies the effect of Complex PTSD as predictor and moderator of treatment outcome. **Chapter 6** focuses on personalization of treatment based on a combination of predictors of treatment outcome. **Chapter 7** presents the results of a time sequencing study about the temporal relationship between change in subjective distress and PTSD symptom decrease during PE. **Chapter 8** summarizes the results of the studies in this dissertation and provides a general discussion.



Chapter 2

Improving treatment for patients with childhood abuse related posttraumatic stress disorder (IMPACT study): protocol for a multicenter randomized trial comparing prolonged exposure with intensified prolonged exposure and phase-based treatment

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Abstract

Background: Childhood abuse related posttraumatic stress disorder (CA-PTSD) is associated with a high burden of disease and with treatment response rates that leave room for improvement. One of the treatments for PTSD, prolonged exposure (PE), is effective but has high drop-out rates and remission rates are relatively low. An intensified form of PE (iPE) was associated with good response and low drop-out rates in PTSD and has not yet been tested in a controlled trial in CA-PTSD. Phase-based treatment (PBT), in which PE is preceded by skills training may improve overall outcomes in this population. We will assess the effectiveness and cost-effectiveness of standard PE, iPE and PBT in patients with CA-PTSD.

Methods/Design: Multi-center randomized controlled trial. Treatment conditions are: prolonged exposure (PE; maximum of 16 sessions in 16 weeks); intensified PE (iPE; maximum of 12 sessions in four weeks and two booster sessions); phase-based treatment (PBT; maximum of eight sessions skills training followed by eight sessions PE in 16 weeks). Primary outcome: Clinician-rated PTSD symptom severity. Secondary outcomes: loss of PTSD diagnosis, self-reported PTSD symptom severity, comorbid symptom severity and quality of life. Moreover, we will examine cost-effectiveness and moderators and mediators of treatment outcome. Target population: adults with CA-PTSD (N = 150). Assessments in weeks 0, 4, 8, 16, 26 and 52.

Discussion: Given that no consensus yet exists about the treatment guidelines for patients with CA-PTSD, the present study may have important implications for the treatment of CA-PTSD.

Trail registration: registered at C.C.M.O. on Sept 7, 2016 (NL57984.058.16); retrospectively registered at June 21, 2017 at clinicaltrials.gov identifier: NCT03194113.

Keywords: Posttraumatic stress disorder, CA-PTSD, Trauma focused treatment, Childhood trauma, prolonged exposure, phase-based treatment, intensive treatment, STAIR

Background

Childhood abuse is associated with severe negative long-term consequences. These include health problems, high health care utilization, a high risk of revictimization, low socio-economic well-being and criminal behavior in adulthood (Coid et al., 2001; Farley & Patsalides, 2001; Gilbert et al., 2009; Gilsanz et al., 2017; Norman et al., 2012; Zielinski, 2009). Childhood abuse is also related to many mental health problems such as depression, suicidality, dissociation, personality disorders, substance abuse and aggression (Briere, Madni, & Godbout, 2016; Carr et al., 2013; Gilbert et al., 2009; Johnson, Cohen, Brown, Smailes, & Bernstein, 1999; Lanius et al., 2010; Norman et al., 2012). In many cases, childhood abuse leads to Posttraumatic Stress Disorder (PTSD): 22 to 49 percent of those who report childhood abuse fulfill criteria for lifetime PTSD (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). The treatment of PTSD in this population is relatively under investigated.

In international guidelines of PTSD, trauma-focused treatment (TFT) is recommended as first treatment option (Forbes et al., 2010). Substantial evidence exists for the effectiveness of TFT in patients with PTSD (Bradley et al., 2005; Ehring et al., 2014; Watts et al., 2013). Treatment adherence and efficacy are relatively low, however. A meta-analysis indicated that 44% of the patients still fulfilled diagnostic criteria for PTSD at the end of treatment (Bradley et al., 2005). TFT may be less effective in CA-PTSD than in PTSD in general, because patients with CA-PTSD have more comorbid symptoms, such as interpersonal problems and emotion regulation difficulties (Messman-Moore & Bhuptani, 2017). These symptoms contribute significantly to functional impairment (Cloitre et al., 2005) but are not specifically addressed in TFT. This may lead to poorer outcomes and specifically less effective use of trauma focused interventions. The current study is designed to investigate the effectiveness of two variants of TFT that may lead to improved effectiveness and/or adherence compared to standard TFT.

Some authors (De Jongh et al., 2016; Ehring et al., 2014; van Minnen, Zoellner, Harned, & Mills, 2015) have argued that trauma focused treatment (TFT) is the preferred treatment for patients with CA-PTSD despite earlier mentioned comorbid symptoms in these patients. A recent meta-analysis indeed revealed more symptom improvement after TFT than non-TFT in patients with CA-PTSD (Ehring et al., 2014). A systematic review also concluded that there is no reason to exclude patients with CA-PTSD from TFT (van Minnen et al., 2015). However, the comorbid symptoms may make it more difficult for those patients to attend weekly treatment sessions, and for therapists to keep the focus on trauma treatment. This has led some researchers to propose that treatment of patients with CA-PTSD may be improved by intensification of TFT. Promising results with an intensified form of TFT in PTSD (Ehlers et al., 2014; Foa et al., 2018; Hendriks et al., 2017; Hendriks et al., 2018; Wagenmans, Van Minnen, Sleijpen, & De Jongh, 2018) suggest that condensing treatment in a shorter period of time may lead to faster or better treatment results. Reduction of treatment length may not only lead to faster improvement, but also to improved treatment adherence, because there is less time between sessions for anticipatory anxiety to build up (Hendriks et

al., 2017; Imel, Laska, Jakupcak, & Simpson, 2013). Intensive TFT (up to 18 hours of cognitive therapy (CT) delivered in one week) led to faster symptom reduction compared to standard TFT (up to 20 hours of weekly CT sessions delivered in 3 months) and equivalent results over 14 weeks (Ehlers et al., 2014). In a veteran population an intensified form of TFT led to faster symptom decline, while it was as effective as regular weekly TFT on the long term (Foa et al., 2018). With regard to CA-PTSD, results of a controlled case series design with intensive TFT in adolescents (*N* = 10) also suggest that intensive treatment is safe and acceptable, with an 80% remission rate (Hendriks et al., 2017). Furthermore, results of two open studies in patients with chronic PTSD following multiple traumas, including CA (Hendriks et al., 2018; Wagenmans et al., 2018) show that intensive TFT was effective and patient retention high (less than 5% drop-out). Taken together, these studies suggest that intensive TFT (iTFT) may improve overall effectiveness of treatment of CA-PTSD.

Other authors (Cloitre et al., 2012a; Dorrepaal et al., 2014; Herman, 1992; Van der Kolk, 2002) have argued that the symptoms and problems frequently observed in patients with CA-PTSD are characteristics of a distinct form of PTSD, referred to as 'complex PTSD'. Complex PTSD is characterized by prominent emotion regulation difficulties, interpersonal problems and a negative self-concept (Van der Kolk, 2002). The International Society for Traumatic Stress Studies (ISTSS) guidelines recommend 'phase-based treatment' as first treatment option for patients with complex PTSD (Cloitre et al., 2012a). In phase-based treatment (PBT) the first sessions are focused on addressing emotion regulation and interpersonal problems, which is followed by TFT (Cloitre et al., 2002). This treatment is based on the notion that emotion regulation and interpersonal problems interfere with daily life functioning and that reduction or resolution of these problems can facilitate more effective use of TFT and can best be addressed before starting TFT (Cloitre et al., 2002). PBT has indeed been associated with lower drop-out rates and more complete PTSD remission than supportive treatment followed by TFT (Cloitre et al., 2010).

Further research on the treatment of CA-PTSD is needed because of limitations of existing studies. Firstly, no studies have directly compared TFT with PBT or iTFT (De Jongh et al., 2016; Ehring et al., 2014; Markowitz, 2016). Secondly, patients with comorbidities such as dissociation, suicidality and personality disorders have often been excluded from RCTs, limiting the generalizability of the results to the population of CA-PTSD (Dorrepaal et al., 2014; Ehring et al., 2014; Ronconi et al., 2014; Spinazzola, Blaustein, & van der Kolk, 2005). Thirdly, in most studies participants were predominantly Caucasian and employed, while PTSD is more severe in patients who are unemployed or from minority ethnical backgrounds (Alegria et al., 2013; Dorrepaal et al., 2014; Ehring et al., 2014; Smith, Schnurr, & Rosenheck, 2005). Fourthly, many studies have methodological shortcomings such as a lack of blind assessments and no reported data on treatment integrity (Ehring et al., 2014). Allegiance effects – the unintentional bias due to investigators' or therapists' preferences (Luborsky et al., 1999; Markowitz, 2016) – is a general problem in clinical research. This may be solved by involving researchers with different areas of expertise and allegiances (Leykin & DeRubeis, 2009).

Current study

The aim of the current study is to examine the effectiveness of three different treatment strategies for patients with CA-PTSD. We will carry out a randomized controlled trial (RCT) comparing the (cost-)effectiveness and treatment adherence of a well-established form of TFT, prolonged exposure (PE), with two potential improvements of TFT: intensified PE (iPE) and phase-based treatment (PBT). For the iPE group, PE sessions are delivered in 4 weeks (3 sessions per week), PBT consists of Skills Training in Affective and Interpersonal Regulation (STAIR), followed by PE. We expect more PTSD symptom reduction and lower drop-out rates in iPE and PBT than in PE. We also expect that iPE and PBT will be more cost-effective, given that the treatment protocols include fewer (iPE) and shorter (PBT) sessions. We expect that iPE will lead to faster improvement than PE and PBT. Finally, we expect that PBT will be superior to both PE and iPE with respect to improvement in emotion regulation, interpersonal skills and self-esteem. The primary outcome is clinician-rated PTSD symptom severity. Secondary outcomes are loss of PTSD diagnosis, self-reported PTSD symptom severity, treatment adherence, comorbid symptoms severity and cost-effectiveness. Outcomes will be assessed at baseline, after 4, 8 and 16 weeks and at 6 and 12 months follow-up.

Moderators and mediators

In line with previous work (Schneider, Arch, & Wolitzky-Taylor, 2015), we will investigate whether treatment effects are affected by baseline characteristics such as PTSD symptom severity, comorbid symptoms, emotional maltreatment and avoidance behavior, using between- and within-group moderation tests. We will calculate a 'personalized advantage index' (PAI; DeRubeis et al., 2014) and trees for treatment-subgroup interactions (QUalitative INteraction Trees; QUINT) to evaluate which pretreatment characteristics are most discriminating in predicting optimal treatment and differential response to treatments with a combination of predictor variables. This may lead to the development of optimal (personalized) treatment sequences (DeRubeis et al., 2014; Doove, Van Deun, Dusseldorp, & Van Mechelen, 2016; Dusseldorp & Van Mechelen, 2014).

As to mediators, moderately strong evidence exists that between-session habitation and change in post-traumatic cognitions mediate the effects of PE, while mixed evidence exists for emotional engagement, inhibition learning and within-session habituation (Cooper, Clifton, & Feeny, 2017a). Mediators of iPE are yet unknown. With regard to PBT, there is some evidence for the mediating effect of both emotion regulation improvement and therapeutic alliance on PBT outcome (Cloitre et al., 2002; Cloitre, Stovall-McClough, Miranda, & Chemtob, 2004). More research on mediators is needed, as the number and quality of the studies are limited (Cooper et al., 2017a). In the current study we will examine all above mentioned mediators.

Methods

Design

The IMPACT study is a multicenter RCT comparing prolonged exposure (PE) with intensified prolonged exposure (iPE) and phase-based treatment (PBT). Participants will be randomly assigned to the conditions. Figure 1 depicts the study flowchart. The research protocol has been approved by the Medical Ethical Committee of Leiden University Medical Center (NL57984.058.16), and is pre-registered at https://clinicaltrials.gov/ct2/show/NCT03194113.

Recruitment

Participants are recruited at the departments of Psychotrauma of PsyQ Den Haag and PsyQ Rotterdam. Referrals from other treatment centers will also be accepted. After initial screening, potential participants will receive written and oral information about the study. Patients who are interested in participating are invited for the baseline assessment including screening of in- and exclusion criteria and an informed consent procedure. Informed consent will be obtained prior to the assessment.

Participants

Inclusion criteria of the study are: 1) age 18 – 65; 2) diagnosis of PTSD as established with the Clinician Administered PTSD Scale (CAPS-5, see instrument section), and at least moderate severity of PTSD-symptoms (CAPS ≥ 26), and with at least one specific memory for a traumatic event; 3) multiple 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 are: 1) involvement in a compensation case or legal procedures concerning admission or stay in The Netherlands; 2) pregnancy; 3) severe non-suicidal self-injury (NSSI) which required hospitalization during the past three months; 4) severe suicidal behavior: 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; 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.

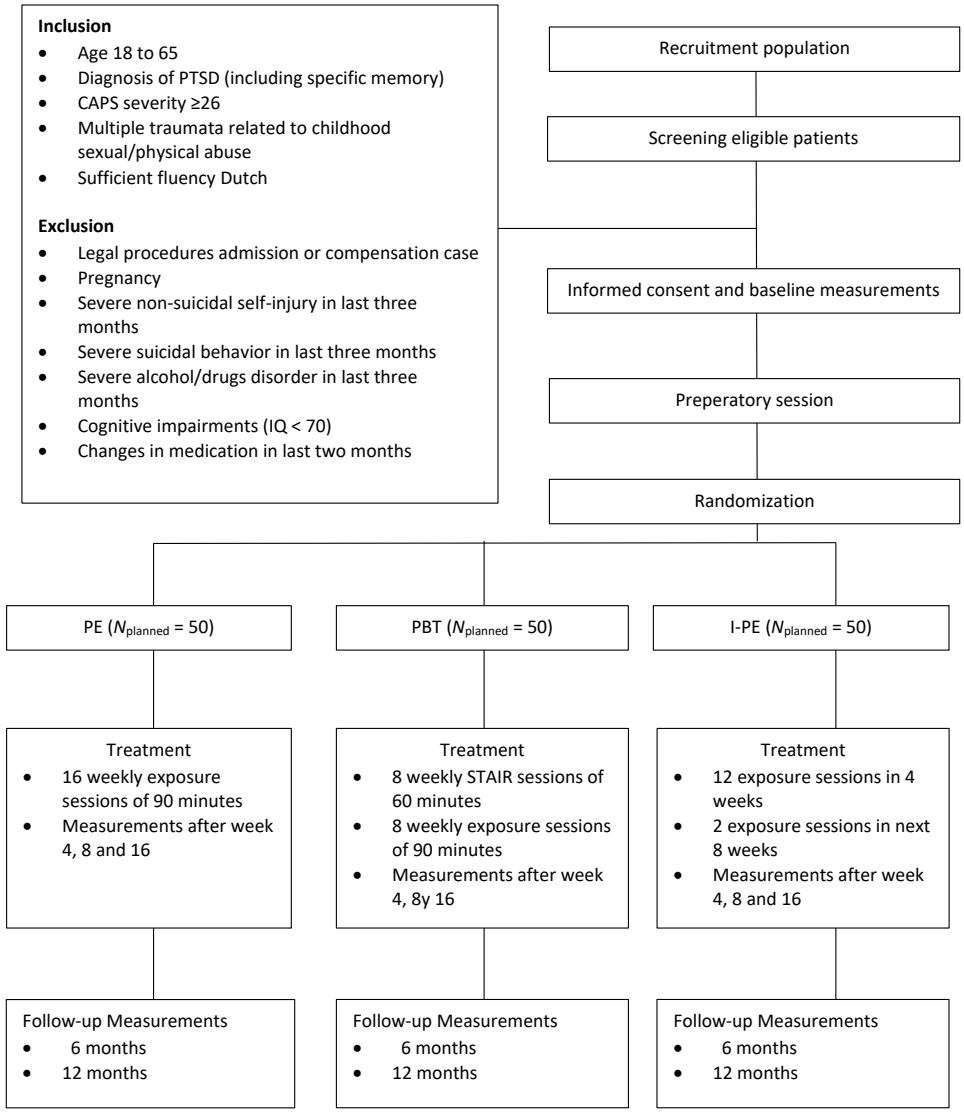

Figure 1. Flowchart of the IMPACT study

Sample size

Our sample size calculations are based on the intention to detect at least moderate effect size differences (*d* = .40) among conditions. To detect this effect size difference in PTSD severity with alpha = .05 (2-tailed) and a power of 0.8, 50 participants per condition are needed. We expect some drop-out which will result in a lower power due to missing values. However, we calculated the sample size based on the conservative assumption that the correlation between the baseline and all further post measurements is 0 and the correlation

between post measurements is 1, since we do not have a good estimation for the correlation between the outcome measurements yet. Thus, the actual power is expected to be considerably higher than 0.8 due to the multiple measurement design correcting for power loss due to drop-out (Morgan & Case, 2013; Yi & Panzarella, 2002).

Procedure

Before randomization, patients complete a baseline assessment of the study. In the preparatory session, patients receive detailed information about the treatment and research procedures and about practical considerations, such as availability. Randomization is carried out by an independent researcher from Leiden University who uses a computerized randomization sequence of permutated blocks of six patients, stratified by gender. Patients are regarded as treatment drop-out if they stop therapy prematurely and as measurement drop-out if they refuse or do not show up for follow-up measurements. Early responders are defined by a score below 16 on the PTSD checklist for DSM-5 (PCL-5) for three consecutive weeks with agreement between patient, therapist and supervisor about finishing the therapy early (de Kleine, Hendriks, Kusters, Broekman, & van Minnen, 2012; Nemeroff et al., 2006). Measurements will take place at baseline, during the therapy (after 4 weeks, 8 weeks and 16 weeks) and follow-up measurements after 6 and 12 months. All measurements are performed by trained and supervised interviewers, who are blind to treatment condition. Patients and their therapists also fill out self-report questionnaires before therapy sessions and fill out questionnaires about harm expectancies and distress during the exposure therapy.

Therapists and training

Before participation in the trial, master's level therapists attend a two-day training in prolonged exposure and a two-day training in STAIR. At the end of these trainings, the therapists have to pass an exam with pilot patients, which is graded by the supervisors of the study. During the study, all therapists receive weekly supervision in (i)PE (by AM and RK) and PBT (by MC and IW). All treatment locations offer the three types of treatment and all therapists receive the same amount of supervision and training. Adherence to the treatment protocols will be checked by independent observers, who will rate randomly selected videotaped therapy sessions.

Prolonged exposure therapy

Prolonged exposure therapy (PE) is delivered in 16 weekly sessions of 90 minutes. The treatment manual is based on the PE protocol by Foa, Hembree, and Rothbaum (2007). Treatment sessions consist of imaginal exposure (repeated recounting of the most anxiety provoking traumatic memories and processing related thoughts and feelings), and exposure in vivo (approaching trauma-related situations). Between sessions, participants listen to audio recordings of the imaginal exposure on a daily basis, and complete in-vivo homework assignments.

Intensified prolonged exposure therapy

Intensified prolonged exposure therapy (iPE) involves three weekly sessions of 90 minutes PE for a period of four weeks (12 sessions total), followed by two PE sessions after one and two months (14 sessions total). The same protocol is used as in the PE condition with some minor changes for practical considerations. For instance, when two treatment sessions are given on consecutive days patients are instructed to do combined homework of both sessions. After the first 12 sessions, patients are instructed to keep doing imaginal exposure and exposure in vivo homework for the 13th and 14th sessions. For practical considerations, two therapists deliver the iPE sessions alternately.

Phase-based therapy

Phase-based therapy (PBT) is delivered in 8 weekly 60 minutes STAIR sessions (Levitt & Cloitre, 2005), followed by 8 weekly 90 minutes PE sessions. STAIR is a manualized skills training, adapted from dialectical behavior therapy and cognitive behavioral therapy (Linehan, 1993). The first four STAIR sessions focus on improving emotion regulation skills, including labeling and identifying feelings, emotion management, distress tolerance and the acceptance of feelings and experiencing positive emotions. The last four STAIR sessions focus on developing interpersonal skills and address exploration and revision of maladaptive schemas, the conflict between trauma generated feelings and interpersonal goals in the present, differences in power and control and flexibility in interpersonal situations with differences in power (Cloitre et al., 2002). Throughout the treatment, patients receive psychoeducation, especially about the connection between the traumatic events during their childhood and the effect it has on their present thoughts, feelings and behavior. After these eight sessions the protocol continues with the standard PE protocol (Foa et al., 2007). This differs from the standard STAIR protocol, which continues with the Narrative Story Telling (NST) protocol (Cloitre, Cohen, & Koenen, 2006).

Instruments

In Table 1, an overview is presented of all the included measures and measurement points.

Clinician-rated PTSD symptom severity

PTSD diagnosis and symptom severity are assessed with the Clinical Administered PTSD scale (CAPS-5; Weathers et al., 2013a). The CAPS-5 has recently been validated for the DSM-5 diagnosis of PTSD and has been translated into Dutch (Boeschoten et al., 2015). The CAPS-5 has good correspondence with CAPS-4 (*kappa* = .83) for the diagnosis of PTSD and a high internal consistency (α = .88) and test-retest reliability (*ICC* = .78) for the total severity score (Weathers et al., 2018). Response to the treatment is defined as an improvement of at least 6 points on the CAPS-5 (Schnurr & Lunney, 2016). Remission is defined as response to treatment, loss of diagnosis and a symptom severity score below 26.

Self-reported PTSD symptom severity

Posttraumatic symptom severity is also measured with the PTSD checklist for DSM-5 (PCL-5). The PCL-5 has a high internal consistency (*α* = .94) and test-retest reliability (*r* = .82)

(Ashbaugh, Houle-Johnson, Herbert, El-Hage, & Brunet, 2016; Blevins, Weathers, Davis, Witte, & Domino, 2015).

Comorbid symptom severity

To measure clinician-rated symptoms that have been proposed to define complex PTSD (Cloitre et al., 2012a) we use three clinical administered items measuring problems with emotion regulation, interpersonal difficulties and low self-esteem (Complex PTSD items, CPI) . Emotion regulation, interpersonal difficulties and self-esteem are also assessed with the Trauma Questionnaire of the International Classification of Diseases, 11th edition (ICD-11) (Cloitre, Garvert, Weiss, Carlson, & Bryant, 2014). Additionally, emotion regulation difficulties are measured with the Difficulties in Emotion Regulation Scale (DERS) (Lee, Witte, Bardeen, Davis, & Weathers, 2016b). Interpersonal problems are measured with the Inventory of Interpersonal Problems (IIP-32) (Barkham, Hardy, & Startup, 1996; Vanheule, Desmet, & Rosseel, 2006) and self-esteem with the Rosenberg Self-Esteem Scale (RSES) (Schmitt & Allik, 2005). Clinician-rated dissociative symptom severity is measured with the two items about the dissociative subtype of PTSD in the CAPS-5. Also, we will also use a new clinical interview for the Dissociative Subtype in PTSD (DSP-I) (Eidhof et al., 2016). Self-reported dissociative symptom severity is measured with the Dissociative Experiences Scale (DES) (van IJzendoorn & Schuengel, 1996) and the Somatoform Dissociation Questionnaire (SDQ) (Bernstein & Putnam, 1986).

Comorbid axis-1 disorders (DSM-IV) are measured with the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Depression severity is measured with the Beck Depression Inventory, 2nd edition (BDI-II-NL) (Beck, Steer, & Brown, 1996). Cognitive reactivity and specifically suicidal reactivity is assessed with the Leiden Index of Depression Sensitivity (LEIDS) (Solis, Antypa, Conijn, Kelderman, & Van der Does, 2017).

Personality disorders are measured with the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II) (Weertman, Arntz, Dreessen, van Velzen, & Vertommen, 2003).

Moreover, anger, negative cognitions, social support and attentional control are measured using self-report questionnaires State-Trait Anger Scale (ZAV) (Van der Ploeg, Defares, & Spielberger, 1982), the Posttraumatic Cognitions Inventory (PTCI) (Foa, Ehlers, Clark, Tolin, & Orsillo, 1999; van Emmerik, Schoorl, Emmelkamp, & Kamphuis, 2006) the MOS (Judah, Grant, Mills, & Lechner, 2014; Kempen, 1992) and the Attentional Control Scale (ACS) (Judah et al., 2014).

Trauma history

The LEC-5 (Gray, Litz, Hsu, & Lombardo, 2004; Weathers et al., 2013b) measures any experienced traumatic event and the CTQ (Childhood Trauma Questionnaire) will be used to measure childhood trauma specifically (Bernstein et al., 2003; Thombs, Bernstein, Lobbestael, & Arntz, 2009).

Treatment variables

Prior, during and immediately after (imaginal) exposure, Subjective Units of Distress (SUD) ratings are assessed and prior and after exposure harm expectancies are assessed. Treatment credibility of the three therapies will be checked with the adapted Treatment Credibility Scale (Devilly & Borkovec, 2000). Additionally, the Working Alliance Inventory (WAI) (Horvath & Greenberg, 1989; Tracey & Kokotovic, 1989; Vervaeke & Vertommen, 1996) will be used to examine therapeutic alliance. The treatment goals of the patients are assessed with an adapted version of the Bern inventory of treatment goals (Holtforth & Grawe, 2002).

Cost-effectiveness

Quality of Life is measured with the EQ-5D-5L (Ergun, Aydemir, Kesebir, Soygur, & Tulunay, 2007; Le, Doctor, Zoellner, & Feeny, 2013). The EQ-5D-5L questionnaire will also be used as cost-effectiveness measurement with the use of the social tariffs of the EuroQol.

Moreover, cost-effectiveness is determined with the Trimbos/iMTA questionnaire for costs associated with Psychiatric Illness (TiC-P) (Bouwmans et al., 2013) which measures the (in)direct costs of illness (health care use and lost productivity), and is specifically developed for the Dutch Healthcare system.

Avoidance task

A classical associative learning paradigm is administered to measure avoidance behaviors. In this task, emotional, anxiety provoking pictures from the International Affective Picture System (IAPS)- set are used as unconditioned stimulus (US), and pictures of an office containing a light, that changes color (blue, red, yellow) as the conditioned stimulus (CS). Participants can avoid the US by pressing a button, but success is dependent on the CS (Vervliet & Indekeu, 2015).

Table 1. Overview of the measurements per time point

Clinical interview	**Construct**	**T0**	**T1**	**T2**	**T3**	**T4**	**T 5**
MINI	Axis-1 disorders	X			X	X	X
CAPS-5	PTSD	X	X	X	X	X	X
CPI	Complex PTSD	X	X	X	X	X	X
SCID II	Personality disorders	X				X	
DSP-I	Dissociation	X	X	X	X	X	X
Self-report							
Demographics	Demographics	X					
LEC-5	Traumata	X					
CTQ	Childhood maltreatment	X				X	
PCL-5[2]	PTSD symptoms	X	X	X	X	X	X
DERS[2]	Emotion regulation	X	X	X	X	X	X
ICD-11	Complex PTSD	X	X	X	X	X	X
BDI-II	Depression	X	X	X	X	X	X
PTCI	Posttraumatic cognitions	X	X	X	X	X	X
DES	Dissociation	X	X	X	X	X	X
SDQ-5	Somatoform dissociation	X	X	X	X	X	X
DERS	Emotion regulation	X	X	X	X	X	X
TIC-P	Direct/indirect costs	X			X	X	X
IIP	Interpersonal problems	X	X	X	X	X	X
MOS	Social support	X	X	X	X	X	X
RSES	Self-esteem	X	X	X	X	X	X
ZAV	Anger	X	X	X	X	X	X
ACS	Attentional control	X	X	X	X	X	X
LEIDS	Cognitive reactivity				X		
Treatment credibility	Treatment credibility	X			X		
Treatment Goals	Treatment goals	X					
EQ-5L5D	Quality of life	X	X	X	X	X	X
WAI[1]	Working alliance						
Cognitive task							
Avoidance task	Avoidance behavior	X					
Process variables		**Measurement moment**					
HE	Harm expectancies	Prior and after (imaginal) exposure					
SUD	Subjective distress	Multiple times during (imaginal) exposure					

MINI: Mini-international Neuropsychiatric Interview, CAPS-5: Clinician Administered PTSD Scale, CPI: Complex PTSD Items, SCID II: Structured Clinical Interview for DSM-IV axis-II personality disorders, DSP-I: Dissociatief Subtype van PTSS interview, LEC-5: Life Events Checklist for DSM-5, CTQ: Childhood Trauma Questionnaire, PCL-5: PTSD Checklist for DSM-5, DERS: Difficulties in Emotion Regulation Scale, ICD-11: International Classification of Diseases-11, BDI-II: Beck Depression Inventory-II, PTCI: The posttraumatic cognitions inventory, DES: Dissociative Experiences Scales, SDQ-5: Somatoform Dissociation Questionnaire-5, DERS: Difficulties in Emotion Regulation Scale; TIC-P: Trimbos and iMTA questionnaire on Costs associated with Psychiatric illness, IIP: Inventory of Interpersonal Problems, MOS: Medical Outcomes Study, RSES: Rosenberg Self-Esteem Scale, ZAV: Zelf Analyse Vragenlijst, ACS: Attentional Control Scale, LEIDS: The Leiden Index of Depression Sensitivity, EQ-5D-5L: EuroQoL 5 Dimensions 5 Levels, WAI: Working Alliance Inventory T0 = baseline, T1 = 4 weeks, T2 = 8 weeks, T3 = 16 weeks, T4 = 26 weeks, T5 = 52 weeks

[1]WAI is self-administered by the patient and therapist 4 times during the course of treatment before the start of the treatment sessions.

[2]PCL-5 and DERS are self-administered weekly before the therapy session by the patient

Analyses

Data analyses will be based on intention-to-treat analyses. All randomized patients will be included in the analyses. Due to the structured data, we will use multiple imputation of multilevel data which takes the levels within the data into account (van Buuren, 2011).

Primary and secondary continuous outcome parameters will be analyzed with multilevel mixed models using a repeated measurement design to correct for the dependencies among the observations (Hox, 2002; Kato et al., 2005). Dichotomous secondary outcome parameters will be analyzed with multilevel logistic regression. The intraclass correlation will be determined to give an indication about these dependencies and determine the residuals which can be explained within and between patients (Hox, 2002). The models will be fitted with the lme4 package in R and with a FML estimation method (Bates, Machler, Bolker, & Walker, 2015). The models will be nested, so the models are compared with the likelihood ratio test (LRT) (West, Ryu, Kwok, & Cham, 2011). All assumptions of the models will be checked to ensure the reliability of the results. When major assumptions are violated, clustered bootstrap will be used, since this method can handle structured data and has less stringent assumptions than multilevel models. Cost-utility analysis will be based on patient reports (societal costs per QALY), and cost-calculator spreadsheet model (BIA). The economic evaluation will also be based on analysis to treat; standard Dutch unit prices will be used.

For moderation and mediation analyses, regression based approaches will be used with the PROCESS macro in SPSS (Hayes & Rockwood, 2017). For moderation analyses with multiple time points, linear mixed models will be used with an interaction effect between time and the moderation variable of interest. For between treatment moderation analyses the three-way interaction between the moderator, treatments and time will be calculated. For calculation of the personalized advantage index we will use leave-one-out cross validation to generate the counterfactual prediction per patient using prognostic and prescriptive variables from moderation analyses and generate the PAI, the magnitude of the predicted difference of receiving the predicted optimal treatment versus the non-optimal treatment (DeRubeis et al., 2014; Efron, 1983). For the trees for treatment-subgroup interactions we will use the R-package quint which uses a stepwise tree building algorithm to detect treatment by subgroup interaction allowing all possible predictor combinations in the model. The algorithm subdivides all patients in terminal nodes based on their patient characteristics and further assigns patients to nodes in which either one of the treatment is better than the other or both treatments are equally effective (Doove et al., 2016; Dusseldorp & Van Mechelen, 2014).

Discussion

Completion of this RCT will provide more knowledge about the relative effectiveness of three treatment strategies for CA-PTSD. We will directly compare the effects of a well-established treatment (prolonged exposure) and two treatment innovations (intensified prolonged exposure and phase-based treatment) in this difficult to treat patient population.

Furthermore, cost-effectiveness of the three interventions will be examined. Finally, moderation and mediation analyses will provide more information for whom and under which conditions these treatments are most effective. Ultimately, this might assist clinicians in personalizing treatment indications and optimizing treatment delivery.

Methodological considerations

We expect to include a cultural and socioeconomic diverse sample, since the participating centers are located in large cities. We protect the generalizability of the findings by using few exclusion criteria. The relatively long follow-up measurements of 6 and 12 months will provide insights in the long-term effects of the therapies. Every type of treatment is supervised by expert supervisors of that specific method. Additionally, all therapists are trained and supervised in both PE and PBT. This prevents biases to the internal reliability of the study and is essential for a meaningful interpretation of the results (Leykin & DeRubeis, 2009).

Limitations of this study are that not all eligible patients will agree to participate in the study which could result in selection bias. Especially the iPE condition could lead to selection bias since it is more demanding in terms of time investment in the first weeks of the treatment. All reasons of patients to decline participation in the study will be carefully monitored to ensure the generalizability of the results and for implementation purposes. Another limitation is that patients have one therapist in PE and PBT, but two alternating therapists in the iPE condition. This may influence the therapeutic alliance and consequently the results of the treatment. We will assess whether therapeutic alliance indeed differs between condition and, if so, whether this has any influence on treatment results.

Conclusion

Patients with CA-PTSD have a high burden of disease. Currently, there is no consensus on treatment-guidelines for this patient group. The results of this study may have important implications for the treatment of patients with CA-PTSD.

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.

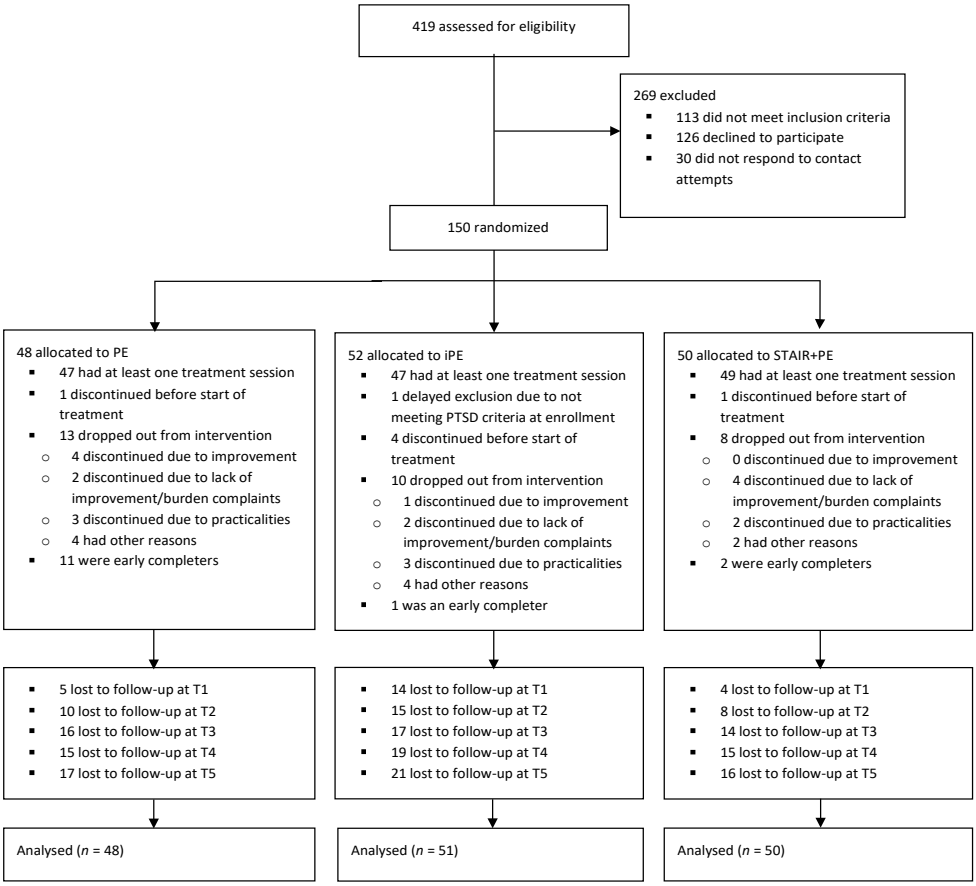


Figure 1. Flow diagram of recruitment and follow-up process

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.

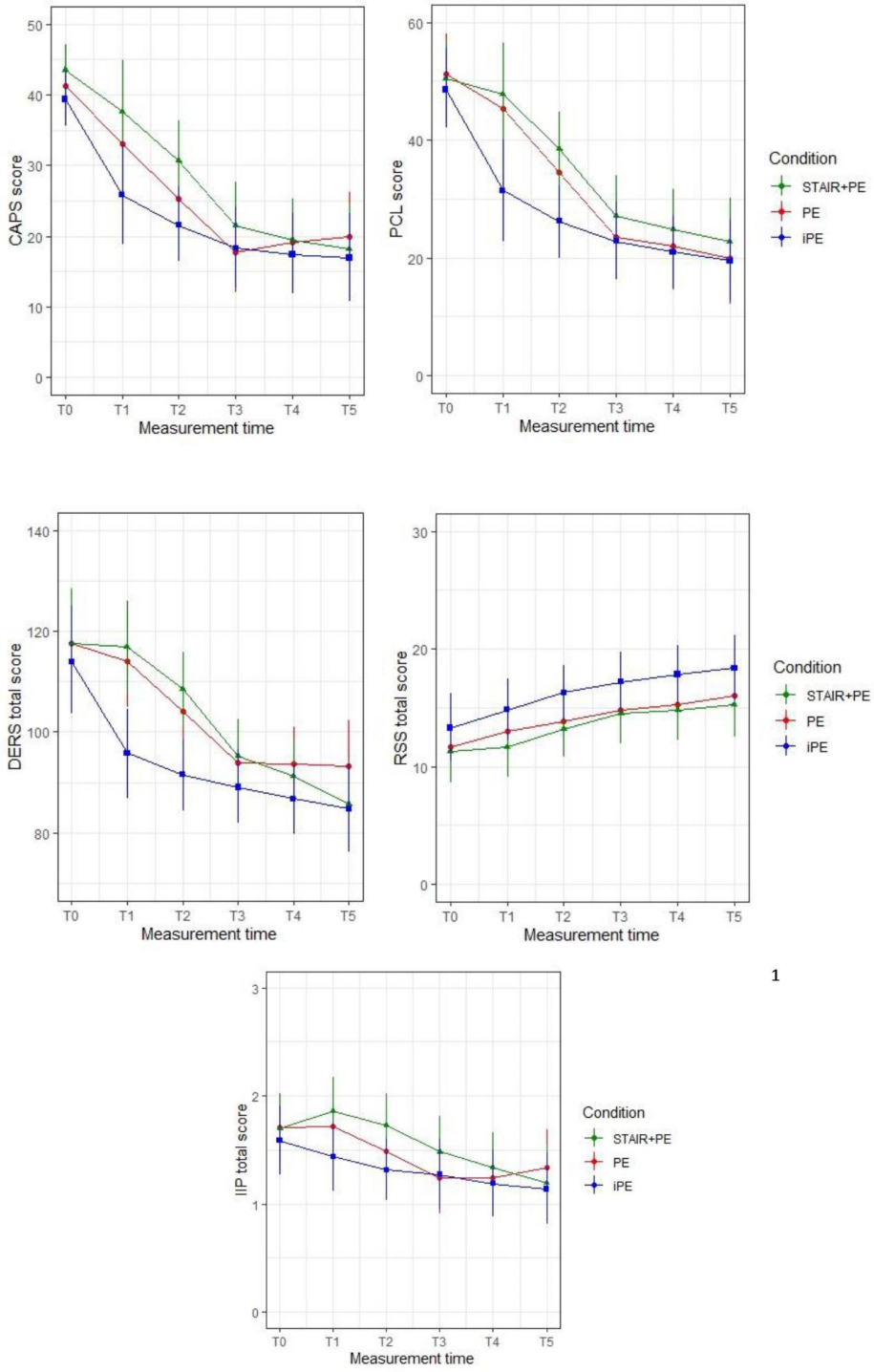


Figure 2. Modelled trajectories of the outcomes as a function of treatment condition per measurement time T0 = baseline, T1 = 4 weeks, T2 = 8 weeks, T3 = 16 weeks, T4 = 6-month follow-up, T5 = 12-month follow-up

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.

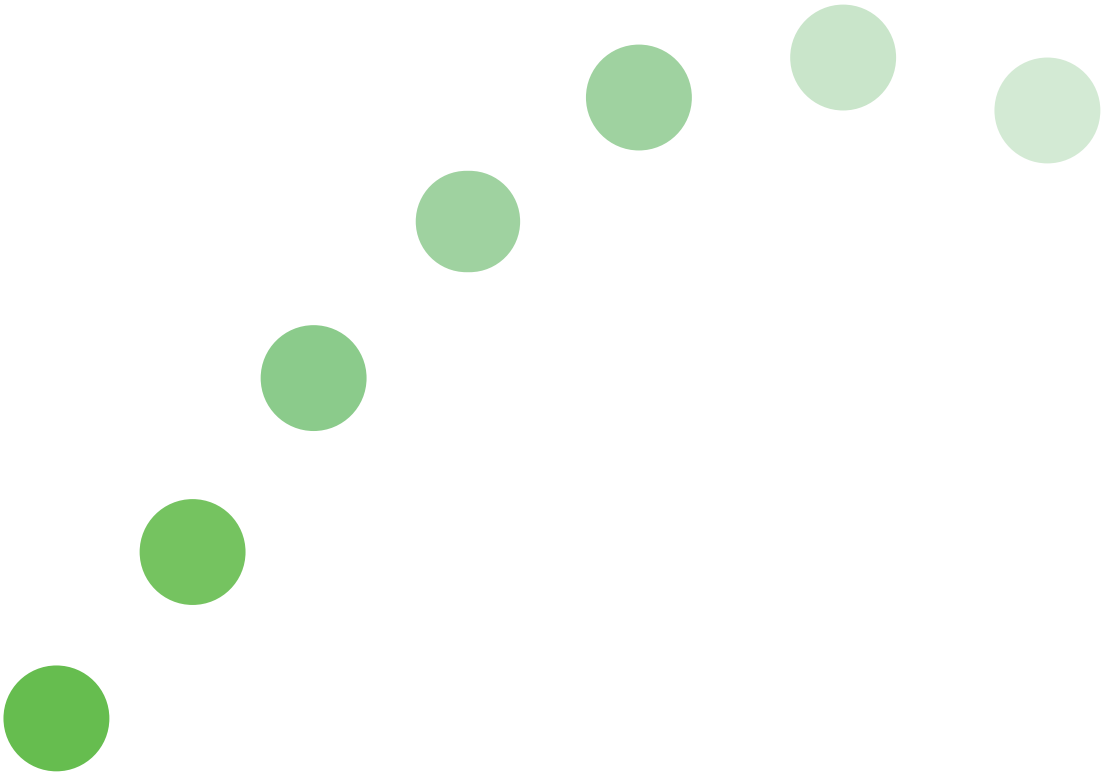
Finally, the hypothesis that iPE (27% dropout) and STAIR+PE (18% dropout) would lead to lower dropout rates than PE (29% dropout) was not supported. PE led to significantly more early completers (23% early completers) compared to iPE (2% early completers) and STAIR+PE (4% early completers), but this 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.



Chapter 4

Impact of dissociation on the effectiveness of psychotherapy for post-traumatic stress disorder: a meta-analysis

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Abstract

Background: Many patients with Post-Traumatic Stress Disorder (PTSD) suffer from dissociative symptoms. The question of whether these dissociative symptoms negatively influence the effectiveness of psychotherapy for PTSD is unresolved.

Aim: To determine the influence of dissociative symptoms on psychotherapy outcome in PTSD.

Method: We conducted a systematic search in Cochrane, Embase, PILOTS, PsycINFO, Pubmed and Web of Science for relevant clinical trials. A random-effects meta-analysis examined the impact of dissociation on psychotherapy outcome in PTSD.

Results: Twenty-one trials (of which 9 randomized controlled trials) with 1,714 patients were included. Pre-treatment dissociation was not related to treatment effectiveness in patients with PTSD (Pearson's correlation coefficient = .04, 95% confidence interval: -.04; .13). Between-study heterogeneity was high but was not explained by moderators such as trauma focus of the psychotherapy or risk of bias score. There was no indication for publication bias.

Conclusions: We found no evidence that dissociation moderates the effectiveness of psychotherapy for PTSD. The quality of some of the included studies was relatively low, emphasizing the need for high-quality clinical trials in patients with PTSD. The results suggest that pre-treatment dissociation does not determine psychotherapy outcome in PTSD.

Pre-registered at Prospero: CRD42018086575.

Introduction

In the DSM-5, a dissociative subtype was added to the classification criteria of Post-Traumatic Stress Disorder (PTSD). This subtype describes patients who meet diagnostic criteria for PTSD, and additionally have persistent or recurrent symptoms of depersonalization (i.e., experience of unreality or detachment from one's thoughts, feelings, sensations, body or actions, e.g. unreal or absent self) and derealisation (i.e., experience of unreality or detachment from one's surroundings, e.g. dreamlike or foggy; APA, 2013). The addition of a dissociative subtype to the DSM-5 was based on multiple sources of evidence, pertaining to factor analyses, brain activation patterns and response to treatment (Friedman, 2013). Approximately 14 percent of the patients with PTSD meet criteria for the dissociative subtype (Stein et al., 2013). While this subtype was only recently added to the DSM-5, research on dissociative symptoms in the context of trauma dates back to the 19th century (Janet, 1894). Several studies have shown that PTSD is associated with high levels dissociation, both compared to nonclinical samples and patients with other psychiatric disorders (Kratzer et al., 2018; Lyssenko et al., 2018; Özdemir, Celik, & Oznur, 2015; Putnam et al., 1996). Additionally, several studies have shown that dissociation is strongly related to the other PTSD symptoms and that these clusters wax and wane together, also in response to treatments (Harned, Korslund, Foa, & Linehan, 2012; Lynch, Forman, Mendelsohn, & Herman, 2008; Rothbaum, Astin, & Marsteller, 2005; Taylor et al., 2003; Zoet, Wagenmans, van Minnen, & de Jongh, 2018). A review of brain-imaging studies has shown that dissociative symptoms/states are related to activation of brain areas related to neurological overmodulation of affect (Lanius et al., 2010). This overmodulation of affect could, amongst others, reduce emotional engagement with the trauma memory, which is considered to be a relevant factor in understanding the effectiveness of current psychotherapies for PTSD (Schnyder et al., 2015). This lack of engagement may be specifically relevant for exposure-based psychotherapy as fear activation is thought to be a crucial mechanism underlying the treatment effect (Cooper et al., 2017a; Ebner-Priemer et al., 2009; Foa & McLean, 2016; Jaycox, Foa, & Morral, 1998; Lanius et al., 2010; Pittig, Treanor, LeBeau, & Craske, 2018).

Currently, there is no consensus about 1) whether patients with PTSD and who dissociate benefit as much from psychotherapy as PTSD-patients who do not dissociate and 2) whether some forms of psychotherapy are particularly ineffective for patients with PTSD and dissociation. Some authors have suggested that treatment programs need to be tailored for PTSD-patients with dissociative symptoms, because, due to their limited emotion regulation capacities, trauma-focused treatments might even lead to an increase in PTSD symptoms, overall distress and functional impairment (Lanius et al., 2010). Others have argued that there is no evidence for an impeding effect of dissociation on the effectiveness of psychotherapy for PTSD (van Minnen et al., 2012). The aim of this study is to provide more clarity to this ongoing debate by quantifying the moderating effect of dissociation on the effectiveness of psychotherapy for PTSD in a meta-analysis.

Method

This project was pre-registered at Prospero (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=86575).

Search strategies

We conducted systematic searches in the following data-bases up to the 28th of August 2018: Cochrane trials register, Embase, PILOTS, PsycINFO, Pubmed and Web of Science. Relevant results during the search from review articles, book chapters and studies were searched for further studies and additionally, key authors and research groups were contacted via email to request any data relevant to the study. Search terms were based on (mesh) terms for PTSD [AND] dissociation [AND] psychotherapy and were adapted to every specific search engine to ensure inclusion of all relevant studies. The search includes the following terms for: (A) PTSD: Posttrauma* Stress Disorde*, Post-Trauma* Stress Disorde*, Post Trauma* Stress Disorde*, DESNOS, CA-PTSD, C-PTSD, PTSD (B) dissociation: Dissocia* Depersonali* Derealization* Derealisation* Fugue* Psychogenic amnesia and (C) psychological treatment: Psychotherap*, Therap*, Posttraumatic Growth, Interven*, Treat*, Exposure, EMDR, CBT, STAIR, Recover*. We manually searched for studies in prior meta-analyses and reviews to ensure that no studies were missed in the systematic search. We de-duplicated data of the search following the protocol of Bramer and colleagues (2016).

Inclusion criteria

The criteria for individual papers for inclusion were: (1) inclusion of patients of 18 years of age and older; (2) assessment of PTSD according to the DSM-5, DSM-IV, DSM-III-R or DSM-III criteria; (3) evaluation of psychotherapy with PTSD symptom severity as main outcome; (4) inclusion of validated self-report measures or structured clinical interviews to assess both PTSD symptom severity and dissociation severity; (5) assessment of PTSD symptom severity at pre and post-treatment; (6) assessment of pre-treatment dissociation severity; (7) inclusion of at least 10 participants per treatment condition which is analysed; (8) published in a peer-reviewed journal; and (9) written in English, Dutch, German, Italian, Spanish or French.

Data extraction and risk of bias assessment

Eligible studies were screened twice and data were extracted twice by two independent screeners. All discrepancies were resolved through discussion and consensus. Risk of bias of the studies was assessed independently by two of the authors using the Cochrane risk of bias tool, which resulted in a methodological score for each study included (Higgins, Green, & Cochrane Collaboration., 2008). The Cochrane scale assesses sources of bias including selection bias, detection bias and attrition bias. We added two items to this measure about: 1) the type of the PTSD measurement (clinical interview versus self-report); and 2) treatment integrity (whether the original article reported on treatment integrity, yes versus no). Consequently, the adapted Cochrane scale consisted of 8 items (see supplement Table S1). Two raters scored each item, and their scores were summed into a risk of bias score (range

0-16; with higher scores indicating higher risk of bias). The risk of bias score was used as a moderator. High bias scores were not considered an exclusion criterion for further analysis.

Potential moderators

To investigate potential moderators of the effect of dissociation on psychotherapy outcome, we coded several study characteristics: (1) completely trauma-focused treatment (yes versus no); (2) randomized controlled trial (yes versus no); (3) sample size (continuous variable); and (4) risk of bias score (continuous variable). The potential moderators were independently coded by two authors and differences were resolved through discussion and consensus.

We compared treatments that were exclusively trauma-focused versus those that were not. Since dissociation is thought to be due to failing emotion regulation capacities, exposure to traumatic memories would result in emotional overmodulation and consequently impede fear activation and emotional learning. This may prevent the therapeutic effect of exposure, unless emotion regulation or other coping skills are also addressed (Lanius et al., 2010). The treatment was coded as trauma-focused if it comprised only evidence-based trauma-focused treatment strategies as described in the manuscript (i.e. prolonged exposure, cognitive processing therapy or eye movement desensitization and reprocessing). Treatments that also comprised other treatment components (i.e. physical activity or stabilization) or treatments that did not include trauma-focused treatment strategies were coded as not exclusively trauma-focused. If a trial included both types of treatments, we extracted the effect size for the two conditions separately for this moderation analysis (see supplement Figure S3 for details).

Statistical analysis

The R package meta was used for all analyses (Schwarzer, 2010). The effect of dissociation on PTSD treatment was determined using pooled effect sizes of the moderating effect of dissociation measured with the Pearson's correlation coefficient (*r*) between pre-treatment dissociation and change in PTSD symptoms from pre- to post-treatment (post-treatment minus pre-treatment PTSD symptom severity score). A positive correlation would indicate a negative relationship between dissociation and treatment effectiveness, whereas a negative correlation would indicate a positive effect of dissociation on treatment effectiveness. Where needed, we calculated the reported effect size from the data provided into *r* as common metric. In case we were unable to calculate the effect size from the publication, we contacted the researchers for additional data. We contacted 38 researchers of whom 27 responded. Twelve of these researchers did not provide the data for various reasons (e.g. no access to data, no time to get data, not willing to share data). Fifteen researchers provided the requested data. Twelve of these studies met the inclusion criteria and were included in the meta-analysis. We used a random effects model that allows heterogeneity between studies (assessed with the Q index) and performed a rank test to detect asymmetry in the funnel plot which is an indication of publication bias. If we had any indications of publication bias either by the rank tests or by visual inspection, we used a trim and fill procedure to

correct for bias due to missing studies. In case of a statistically significant main finding of dissociation on treatment effectiveness, we performed the fail-safe tests of Rosenthal and Orwin to assess the robustness of the results. We conducted moderation analyses with a meta-regression approach by fitting mixed effect models including potential treatment moderators to test for differences in the effect size associated with characteristics of the studies.

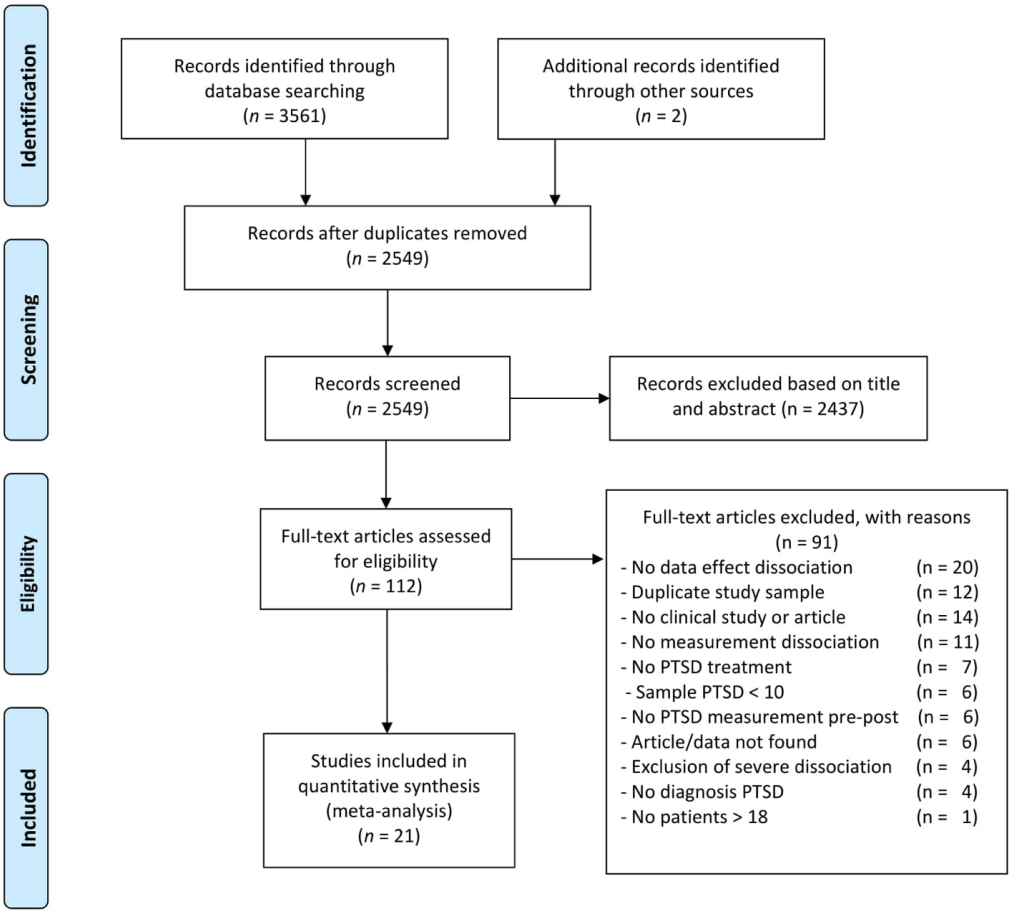


Figure 1. Flowchart of inclusion of studies.

Results

Selection and inclusion of studies

The systematic searches yielded a total of 3,563 papers (2,549 after removal of duplicates). Of these 2,549 papers, 2,437 were excluded based on title and abstract as they did not meet inclusion criteria. 112 full-text papers were retrieved of which 91 were excluded because they did not meet the inclusion criteria (see Figure 1 for details). The remaining 21 articles were included in this meta-analysis. Note that none of the included studies used severe levels of dissociation or diagnosis of dissociative (identity) disorder as exclusion criterion.

Characteristics of included studies

The 21 included studies contained a total of 1,714 patients from 9 RCTs and 12 uncontrolled clinical trials or treatment cohort studies. Table 1 shows the study characteristics and potential moderator variables (see supplement Table S2 for more study details).

Risk of bias score

The overall risk of bias of the included studies was modest (M = 6.6; SD = 2.94). Table 2 lists item and total scores for the risk of bias scores for each of the included studies. Agreement between two independent assessors regarding risk of bias of individual studies was high (Cohen's Kappa = .81, SE = .04, $p < .001$).

Effect of dissociation on PTSD treatment

Figure 2 depicts the main results of the meta-analysis. The pooled correlation between pre-treatment dissociation and decrease in PTSD symptoms during treatment was .04 (95% *CI:* -.04; .13, p =.32). The heterogeneity between studies was moderately high: I^2 = 68.90, $p < .001$. Visual inspection of the funnel plot did not indicate asymmetry in any direction (see Figure 3), which was confirmed by Kendall's tau based on the rank correlation (p = .46) and by Eggers' test (p = .25). The funnel plot shows two potential outliers: Harned et al. (2014) (positive effect of dissociation) and Abramowitz et al. (2016) (negative effect). The study sample of Harned et al. (2014) was very small and the drop-out was high. The study of Abramowitz et al. (2016) was an open study with a relatively small sample size. Therefore, both studies may have yielded an effect size that is not so reliable.

Table 1. Selected characteristics of studies examining the effect of dissociation on PTSD psychotherapy treatment outcome

Study	Treatments	Effect size	Female (%)	Age *M (SD)*	Measure PTSD; DSM	Measure dissociation	Moderators			
							Trauma focus	Design	Sample size	Bias score
Abramowitz et al. (2010)	Hypnotherapeutic olfactory conditioning	NR	0	41.2 (12.2)	IES-R; DSM-IV	DES	No	No RCT	36	11.0
Bae et al. (2016)	EMDR	1.27 Com.	59	34.9 (11.6)	CAPS; DSM-IV	CAPS subtype items + decreased awareness	Yes	No RCT	60	8.0
Cloitre et al. (2012)	Stair/NST; Support/NST; Stair/support	1.97 ITT	100	36.4 (9.40)	CAPS; DSM-IV	TSI-DIS averaged score	No	RCT	75	3.0
Gantt et al. (2007)[1]	Art, hypnosis, video therapy	NR	77	38 (14)	IES; DSM-IV	DES	No	No RCT	53	11.0
Haagen et al. (2018)	EMDR, NET, other interv.	.36 Com.	3.1	39.8 (10.1)	IES-R; DSM-IV	DES	No	No RCT	64	8.0
Hagenaars et al. (2010)	PE	3.07 Com.	83	35.75 (11.74)	CAPS; DSM-IV	DES	Yes	No RCT	36	4.0
Halvorsen et al. (2014)	NET + TAU	.95 Com.	31	35.55 (11.05)	CAPS; DSM-IV	CAPS subtype items	TAU: No NET: Yes	RCT	81	5.0
Harned et al. (2014)	DBT + DBT-PE	1.8 ITT	100	32.6 (12.0)	PSS; DSM-IV	DES	No	RCT	12	3.0
Kleindienst et al. (2016)	DBT-PTSD	NR	100	37.3 (10.5)	CAPS; DSM-IV	DES	No	RCT	24	4.5
Kratzer et al. (2018)	EMDR + em. reg. group	1.81 Com.	88	47.9 (10.5)	IES-R; DSM-IV	DES	No	No RCT	150	8.5
Lampe et al. (2014)[1]	PITT + psychodyn. Group	NR.	100	40.72 (10.0)	IES; DSM-IV	DES	No	No RCT	88	9.0
Lynch et al. (2008)[1]	NR	NR	83	36 (9.99)	PDS; DSM-IV	DES	No	No RCT	127	8.5
Murphy et al. (2015)	Group + indiv CBT	NR	1	NR	PSS; DSM-IV	DES	No	No RCT	244	11.0
Pabst et al.[1] (2014)	NET; TBE	.95 Com	100	29.91 (10.11)	PDS; DSM-IV	DES	TBE: No NET: Yes	RCT	36	3.0
Resick et al. (2012)	CPT; CPT-C; WA	1.68 ITT	100	35.4 (12.4)	CAPS; DSM-IV	TSI-DIS	Yes	RCT	117	3.0
Steele et al. (2018)	Treatment program	.70 Com.	29	42.94 (11.63)	Missisipi scale for PTSD	DES	No	No RCT	62	10.0
Steuwe et al. (2016)	NET + SIC	.70 ITT	90.9	34.9 (9.71)	PDS; DSM-IV	DES	No	No RCT	11	7.5
van Emmerik et al. (2008)[1]	CBT; SWT	.79 ITT	65	40.87 (11.97)	IES; DSM-IV	DES	Yes	RCT	50	6.5
Van Minnen et al. (2016)	PE; EMDR	1.67 Com.	54	41.2 (10.5)	CAPS; DSM-IV	CAPS subtype items	Yes	RCT	82	6.0
Wolf et al. (2016)	PE; PCT	NR	100	44.79 (9.44)	CAPS; DSM-IV	TSI subtype items averaged score	PCT: No PE: Yes	RCT	137	2.5
Zoet et al. (2018)	EMDR + PE + sport	2.03 Com.	70	38.16 (10.90)	CAPS; DSM-IV	CAPS subtype items	No	No RCT	169	5.0

Meth: methodological, Com: completely, PCT: present-centered therapy, CPT: cognitive processing therapy, CPT-C: cognitive therapy only, WA: written trauma accounts only, RCT: randomized controlled trial, EMDR: eye movement desensitization and reprocessing, Stair: skills

training in affective and interpersonal regulation, NST: narrative story telling, NET: narrative exposure therapy, PE: prolonged exposure, DBT; dialectical behaviour therapy, DBT-PTSD: dialectical behaviour therapy for PTSD, TBE: treatment by experts of borderline disorder, CBT: cognitive behavioural therapy, SWT: structured writing therapy, Av: Average, wk: weeks, CAPS: clinician-administered PTSD scale, IES: impact of events scale, PSS: PTSD symptom scale, PDS: post-traumatic stress diagnostic scale, TSI-DIS: trauma symptom inventory-dissociation, DES: dissociative experiences scale, DES-T: DES-taxon, FDS: German version of the dissociative experiences scale, ITT: intention to treat, Interv: interventions, Com: completers, Em. reg.: emotion regulation focused, PITT: Psychodynamic imaginative trauma therapy, psychodyn: psychodynamic, diss: dissociation, NR: not reported.

[1]Note: These studies provided additional data for a sub-sample of patients who met inclusion criteria of this meta-analysis so patient characteristics stated in this table are an estimation based on complete study sample

Table 2. Risk of bias scores of included studies with higher scores indicating a higher risk of bias.

	Item								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Total**
Abramowitz *et al.* (2010)	1 \ 1	1 \ 1	1 \ 1	1 \ 1	2 \ 2	2 \ 2	2 \ 2	1 \ 1	**11.0**
Bae *et al.* (2016)	1 \ 1	1 \ 1	0 \ 0	1 \ 1	0 \ 0	2 \ 2	2 \ 2	1 \ 1	**8.0**
Cloitre *et al.* (2012)	0 \ 0	0 \ 1	2 \ 2	0 \ 0	0 \ 0	0 \ 0	0 \ 0	0 \ 1	**3.0**
Gantt *et al.* (2007)	1 \ 1	1 \ 1	1 \ 1	1 \ 1	2 \ 2	2 \ 2	2 \ 2	1 \ 1	**11.0**
Haagen *et al.* (2018)	1 \ 1	1 \ 1	0 \ 0	1 \ 1	0 \ 0	2 \ 2	2 \ 2	1 \ 1	**8.0**
Hagenaars *et al.* (2010)	1 \ 1	1 \ 1	0 \ 0	1 \ 1	0 \ 0	0 \ 0	0 \ 0	1 \ 1	**4.0**
Halvorsen *et al.* (2014)	1 \ 1	1 \ 1	2 \ 1	0 \ 0	0 \ 0	0 \ 0	2 \ 2	0 \ 1	**5.0**
Harned *et al.* (2014)	1 \ 1	1 \ 1	1 \ 1	0 \ 0	0 \ 0	0 \ 0	0 \ 0	1 \ 1	**3.0**
Kleindienst *et al.* (2016)	1 \ 1	0 \ 0	0 \ 0	0 \0	2 \ 2	0 \ 0	2 \ 2	0 \ 1	**4.5**
Kratzer *et al.* (2018)	1 \ 1	1 \ 1	1 \ 1	1 \ 1	0 \ 0	2 \ 2	2 \ 1	1 \ 1	**8.5**
Lampe *et al.* (2014)	1 \ 1	1 \ 1	1 \ 1	1 \ 1	0 \ 0	2 \ 2	2 \ 2	1 \ 1	**9.0**
Lynch *et al.* (2008)	1 \ 1	1 \ 1	1 \ 1	1 \ 1	0 \ 0	2 \ 2	2 \ 1	1 \ 1	**8.5**
Murphy *et al.* (2015)	1 \ 1	1 \ 1	2 \ 2	2 \ 2	2 \ 2	0 \ 0	2 \ 2	1 \ 1	**11.0**
Pabst *et al.* (2014)	1 \ 1	1 \ 1	1 \ 1	1 \ 1	0 \ 0	2 \ 1	0 \ 0	0 \ 1	**3.0**
Resick *et al.* (2012)	0 \ 1	0 \ 0	2 \ 2	0 \ 0	0 \ 0	0 \ 0	0 \ 0	0 \ 1	**3.0**
Steele *et al.* (2018)	1 \ 1	1 \ 1	1 \ 1	1 \ 1	2 \ 2	2 \ 1	2 \ 1	1 \ 1	**10.0**
Steuwe *et al.* (2016)	1 \ 1	1 \ 1	1 \ 1	0 \ 0	0 \ 0	2 \ 2	2 \ 1	1 \ 1	**7.5**
Van Emmerik *et al.* (2008)	0 \ 0	1 \ 1	1 \ 1	0 \ 0	0 \ 0	2 \ 2	2 \ 2	0 \ 1	**6.5**
Van Minnen *et al.* (2016)	0 \ 1	0 \ 1	2 \ 2	0 \ 0	2 \ 2	0 \ 1	0 \ 0	0 \ 1	**6.0**
Wolf *et al.* (2016)	1 \ 1	1 \ 1	0 \ 0	0 \ 0	0 \ 0	0 \ 0	0 \ 0	0 \ 1	**2.5**
Zoet *et al.* (2018)	1 \ 1	1 \ 1	0 \ 0	0 \ 0	0 \ 0	0 \ 0	2 \ 2	1 \ 1	**5.0**

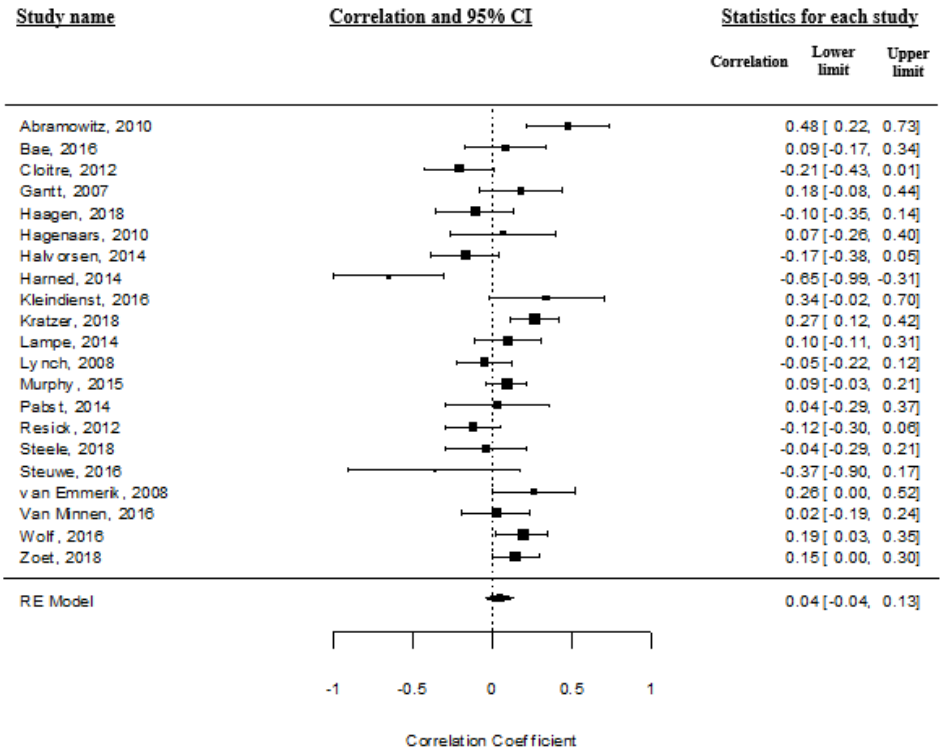


Figure 2. Pearson's Correlation coefficient (*r*) between baseline dissociation and change in PTSD symptoms from pre to post-treatment

Table 3. Effect of dissociation on improvement in PTSD symptoms and moderation analyses

	N	Pearson's r	95% CI	p
Overall outcome	21	.04	-.04; .13	.32
Moderation analyses				
Trauma-focused	8	.06	-.11; .22	.76[1]
Not trauma-focused/combination	16	.02	-.09; .14	
RCT	9	-.03	-.17; .11	.18[1]
No RCT	12	.10	-.02; .21	
Sample size	21	.001	-.001; .002	.38
Risk of bias score	21	.03	-.002; .06	.07

[1]p-value indicates whether effect size of subgroups differ significantly. A positive correlation (Pearson's correlation) indicates negative effect of dissociation on PTSD improvement.

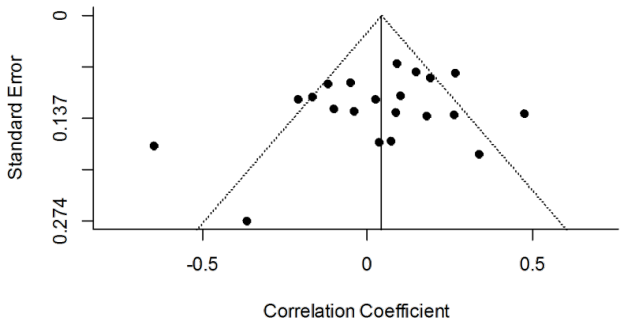


Figure 3. Funnel plot with Pearson's correlation coefficient between dissociation and change in PTSD symptoms from pre to post-treatment

Effect of potential moderators of the effect of dissociation on PTSD treatment outcome

Table 3 shows the results of the moderation analyses. We did not find that a higher risk of bias resulted in a larger effect of dissociation, although this effect was borderline significant (slope r =.03, CI: -.002; .06, p = .07). In addition, we found no difference in the effect of dissociation on the effectiveness of completely trauma-focused treatments compared to non-trauma-focused/multi-component treatments (p = .76). Similarly, we did not find that the effect of dissociation was different for randomized controlled trials compared to non-randomized studies (p = .18), nor did we find an effect of sample size (p =.38).

To explore the effect of risk of bias on the results, we performed a post-hoc analysis including only studies with a low-moderate risk of bias (i.e. risk of bias score ≤ 8 (n = 14)). The correlation between pre-treatment dissociation and decrease in PTSD symptoms during treatment for higher quality studies was -.01 (95% *CI*: -.13; .10, p =.80) and not different from the results derived over all studies.

Discussion

We found no evidence for a moderating effect of dissociation on psychotherapy outcome in patients with PTSD. Furthermore, differences between studies in the effect size of dissociation on treatment outcome were not explained by study characteristics. We conclude that comorbid dissociative symptoms do not reduce the effectiveness of psychotherapy in patients with PTSD. Although we did not specifically examine the dissociative subtype of PTSD, the present findings suggest that this subtype may not be associated with worse treatment outcomes as was suggested by the introduction of this subtype in the DSM-5.

Most included studies found non-significant effects of dissociation on the treatment outcome, which corresponds to the null finding of this meta-analysis. The results from the studies reported in this meta-analysis may differ from the conclusion from the individual papers. Some of these studies were hampered by methodological limitations, including incorrect moderation analyses. We assessed dissociation as treatment moderator. Some individual studies, however, did not test moderation, but reported the association between

dissociation and post-treatment PTSD severity. We were able to include a relatively large number of recently published clinical trials. The addition of the dissociative subtype to the DSM-5 seems to have increased awareness and research into dissociation. We found a moderately high heterogeneity among studies, indicating that the effect of dissociation varied due to systematic differences rather than chance. Despite this variation, the pooled effect size allows a uniform conclusion since the error bars (95% confidence intervals) of the effect sizes of most studies include the pooled effect size (Fletcher, 2007). Moreover, we did not find indications for publication bias.

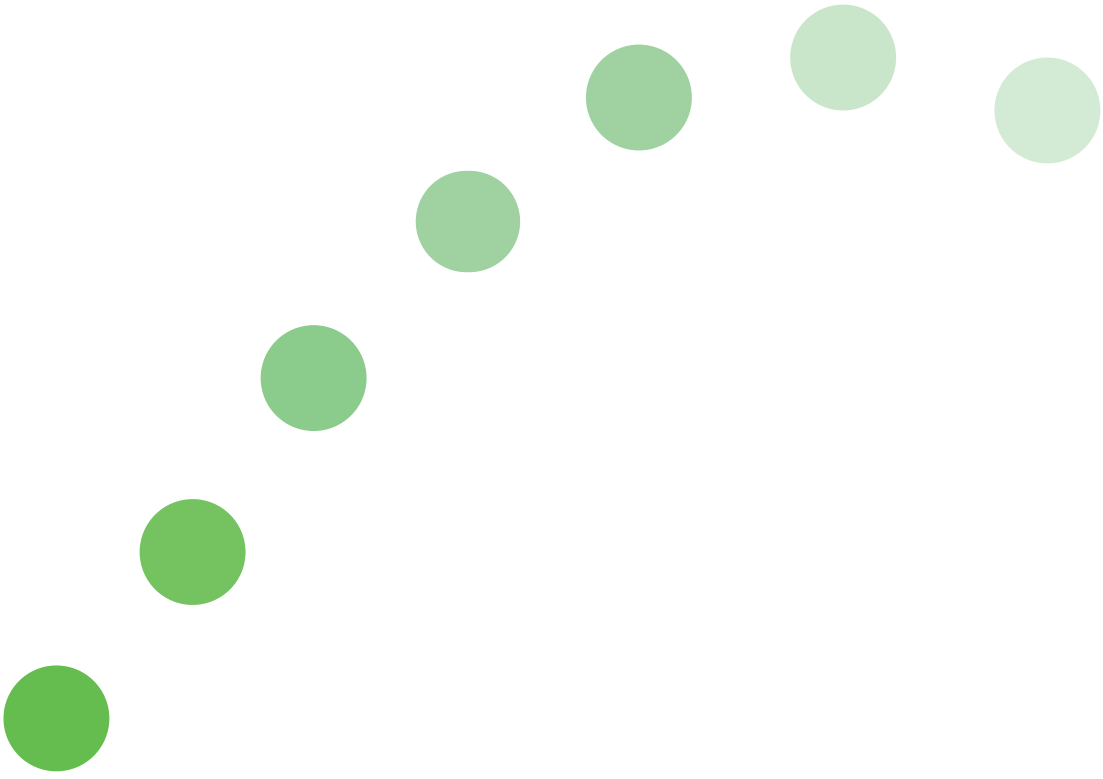
We examined whether the following study characteristics explained the heterogeneity between studies: type of treatment (exclusively trauma focus or not), risk of bias score, study design and sample size. We observed no effect of type of treatment, study-design and sample size. Only a borderline significant effect of bias score was observed. The effect of dissociation on treatment outcome tended to be smaller in the higher-quality studies. No less than one third of the studies (33%) had a low study quality score, however a post-hoc analysis including only those studies with a low or moderate risk of bias again revealed no moderating effect of dissociation. We conclude that this meta-analysis provides no evidence for the idea that dissociation specifically reduces the effectiveness of trauma-focused treatment in those suffering from PTSD.

This study has some limitations. Firstly, a meta-analysis can only be as convincing as the quality of the individual studies. In most studies, the effect size of dissociation is based on completer samples (n = 19), thereby limiting the conclusions to patients who complete treatment. However, all included studies which reported on the effect of dissociation on treatment drop-out found that dissociation was not related to higher treatment drop-out (Bae, Kim, & Park, 2016; Cloitre, Petkova, Wang, & Lu, 2012b; Hagenaars, van Minnen, & de Rooij, 2010; Halvorsen, Stenmark, Neuner, & Nordahl, 2014; Lynch et al., 2008; Murphy, Elklit, Murphy, Hyland, & Shevlin, 2017; van Minnen et al., 2016; Wolf, Lunney, & Schnurr, 2016). Cloitre and colleagues (2012) even found that patients with high dissociation were less likely to drop-out from treatment. We observed quite a few studies of less than optimal quality, however, results were independent of study quality. Because we included several non-controlled clinical trials or cohort studies, we evaluated whether the effect sizes of the included treatments were comparable to previous meta-analyses of psychotherapy for PTSD. The psychotherapies of the included studies showed large within-subject effect sizes from pre to post-treatment (Cohen's d or Hedges' g) for treatment completers (M = 1.42) and intention-to-treat samples (M = 1.39). These effect sizes are comparable to those found in meta-analyses investigating the effectiveness of psychotherapy for PTSD as such (and including only randomized clinical trials (Lee et al., 2016a)). General limitations of the current studies in patients with PTSD are a lack of long-term follow-up measurements and the use of exclusion criteria (e.g. suicidality, psychosis or substance abuse) which limits the generalizability of the results. We encourage future studies to use non-restrictive in- and exclusion criteria (Ronconi et al., 2014). Secondly, most (67% of) studies measured dissociation broadly with the dissociative experience scale (DES), which includes

depersonalisation, derealisation, amnesia and absorption. Only a few studies measured the dissociative subtype (depersonalisation and derealisation) specifically (*n* = 5). Furthermore, a recent study indicated that the broad and specific measures have a large overlap and high correlation (Swart, Wildschut, Draijer, Langeland, & Smit, 2019). Future studies could focus on other instruments with a different timing of dissociation, for example within session (state) dissociation (Kleindienst et al., 2016). Thirdly, we exclusively focused on the effect of only one moderator, that is dissociation, on treatment effects. This specific hypothesis was based on clinical experience and theoretical considerations. Possibly, a combination of patient characteristics (i.e. dissociation, depressive symptoms and functional impairment) is more predictive of treatment responsiveness (Deisenhofer et al., 2018). Future work may consider examining combinations of moderators to detect patients who do not (fully) recover with psychotherapy and to detect differential treatment responses (DeRubeis et al., 2014). However, the sample sizes will need to be substantial and the risk of spurious or population-specific findings increases if research is not hypothesis-driven. Finally, we did not have the power to evaluate how moderators of the effect of dissociation interact. This could provide more insight into the effect of dissociation under specific conditions (Li, Dusseldorp, & Meulman, 2017).

Conclusions

Despite these limitations, the strength of our meta-analysis is that it is the first to systematically review the effect of dissociation on psychotherapy outcome in patients with PTSD across different types of psychotherapies. Psychotherapy for PTSD is generally effective but there is room for improvement since about half of the patients still meet criteria for PTSD after treatment (Bradley et al., 2005). About half of the clinicians believe that any degree of dissociation is a contraindication for psychotherapeutic treatment of PTSD (Becker, Zayfert, & Anderson, 2004; Ronconi et al., 2014). Importantly, the results of our meta-analysis contrast this supposition. We found that pre-treatment dissociation did not reduce the effectiveness of psychotherapy in patients with PTSD.



Chapter 5

Does complex PTSD predict or moderate treatment outcomes of three variants of exposure therapy?

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Abstract

Background: One reason for the inclusion of Complex Posttraumatic Stress Disorder (CPTSD) in the 11th revision of the International Classification of Diseases (ICD-11) was its suspected relevance for treatment indications. We investigated whether CPTSD predicted and moderated treatment outcomes of Prolonged Exposure (PE), intensified PE (iPE) and Skills Training in Affective and Interpersonal Regulation followed by PE (STAIR+PE). We expected that CPTSD would predict worse treatment outcomes across treatments. Secondly, we expected that CPTSD would lead to better treatment effect in STAIR+PE compared to PE and iPE.

Methods: We analyzed 149 patients with childhood-abuse related PTSD from a randomized clinical trial. CPTSD diagnosis and symptom severity were measured with the International Trauma Questionnaire. The main outcome was change in clinician-assessed PTSD symptoms. Assessments took place at baseline, week 4, week 8, week 16 (post-treatment) and at a 6- and 12-month follow-up. Analyses were based on an intention-to-treat sample using mixed effect models.

Results: More than half (54%) of the patients met criteria for CPTSD at baseline. CPTSD was related to more severe PTSD symptoms and higher comorbidity at baseline. CPTSD neither predicted nor moderated treatment outcome.

Limitations: Inclusion was limited to patients with PTSD related to childhood abuse. Replication is needed in different samples.

Conclusions: CPTSD is associated with more severe PTSD and with higher comorbidity. CPTSD did not predict treatment outcome and did not indicate differential treatment outcome of STAIR+PE compared to PE and iPE.

Keywords: Complex PTSD, STAIR, prolonged exposure, predictor, moderator

Introduction

In the 11th revision of the International Classification of Diseases (ICD-11), Posttraumatic Stress Disorder (PTSD) was divided into two sibling diagnoses: PTSD and Complex PTSD (CPTSD; World Health Organization, 2018). The ICD-11 now recognizes a 'basic' form of PTSD with core features as well as a complex form of PTSD, that has disturbances in self-organization (DSO) alongside the core features (Maercker et al., 2013). DSO consists of emotion regulation difficulties, interpersonal problems and negative self-concept (World Health Organization, 2018). There is an ongoing debate on whether CPTSD pertains to a distinct group of patients (e.g., Brewin et al., 2017) or rather reflects more severe PTSD (e.g., Resick et al., 2012; Wolf et al., 2015). In the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) several CPTSD symptoms were added to the diagnostic criteria of PTSD, but a separate diagnosis of CPTSD was not included (Friedman, 2013).

Several terms have been used to describe the clinical picture of CPTSD, including 'disorders of extreme stress not otherwise specified' (DESNOS), 'posttraumatic personality disorder' and 'enduring personality change after catastrophic experience' (Classen, Pain, Field, & Woods, 2006; Wilson, Friedman, & Lindy, 2001; World Health Organization, 1992; Yehuda, 2002). All terms aim to describe patients who have been victim of severe, repeated and/or early traumatization (Brewin et al., 2017; Herman, 1992; World Health Organization, 2018; Yehuda, 2002). The experience of repeated, interpersonal trauma (particularly during childhood) interferes with emotional and cognitive development and may affect self-organization skills (Cloitre et al., 2009; Dvir et al., 2014; Lonergan, 2014).

An important reason to distinguish CPTSD as a separate diagnosis would be the relevance for treatment indications (Berliner et al., 2019; Brewin, 2019). For PTSD, trauma-focused treatments such as Prolonged Exposure (PE) are well established first-line interventions (Cusack et al., 2016; Watkins et al., 2018). However, it has been suggested that trauma-focused treatments may be less effective in patients with CPTSD (Berliner et al., 2019; Karatzias & Cloitre, 2019) because DSO symptoms may interfere with tolerating the distress of trauma-focused treatment (Cloitre et al., 2002). Patients with CPTSD may need a multi-modular treatment that targets both DSO and core PTSD symptoms (Cloitre, Karatzias, & Ford, 2020; Karatzias & Cloitre, 2019). Skills Training in Affective and Interpersonal Regulation followed by PE (STAIR+PE) is a multi-modular treatment for CPTSD (Cloitre et al., 2002; Cloitre et al., 2010). Symptoms related to DSO, such as emotion regulation and interpersonal dysfunction are addressed in the first phase (STAIR), followed by PE. Others, however, argue that patients with CPTSD respond well to trauma-focused treatment (De Jongh et al., 2016; Landy, Wagner, Brown-Bowers, & Monson, 2015; Resick et al., 2012). The empirical evidence on whether a CPTSD diagnosis predicts and/or moderates treatment outcome is limited. Three meta-analyses investigated the effectiveness of psychotherapy for patients with probable CPTSD based on the presence of DSO(-related) symptoms (Karatzias et al., 2019b); on the presence of DESNOS or co-morbid personality disorder (Dorrepaal et al., 2014); or the presence of complex interpersonal trauma (Mahoney, Karatzias, & Hutton, 2019). These meta-analyses show that patients with CPTSD symptomatology do benefit from

trauma-focused treatment, including group treatment, although their results may be less favorable than patients with 'simple' PTSD. The definitions of CPTSD in these meta-analyses were not identical, which is not surprising given the recency of the inclusion of CPTSD in the ICD-11. Moreover, these meta-analyses did not test the effect of CPTSD as predictor or moderator of treatment outcome.

Considering prediction, three studies tested whether symptom profiles of CPTSD or similar to CPTSD predict worse psychotherapy outcome. The first study found that meeting criteria for DESNOS was associated with less improvement of PTSD symptoms during an inpatient treatment program in patients with war trauma (Ford & Kidd, 1998). The second study found that 'simple' versus 'more complex' PTSD was not related to differences in treatment outcome of EMDR, PE or relaxation therapy (Taylor, Asmundson, & Carleton, 2006). The third study found no difference in benefit for those with CPTSD compared to non-CPTSD in an intensive trauma-focused treatment program (Voorendonk, De Jongh, Rozendaal, & Van Minnen, 2020). Given this limited evidence, we also searched for studies that investigated the predictive effect of the CPTSD dimensions. Interpersonal problems predicted poor treatment outcome in several studies (Ehlers et al., 2013; Sripada et al., 2019), but most of the studies found no evidence that interpersonal problems or emotion regulation difficulties predict treatment outcome (Cahill, Rauch, Hembree, & Foa, 2003; Hoeboer et al., 2020c; Rizvi, Vogt, & Resick, 2009; Tarrier, Sommerfield, Pilgrim, & Faragher, 2000; van Minnen, Arntz, & Keijsers, 2002).

Considering moderation, a *moderator* is a baseline variable which interacts with the effect of treatment condition on improvement over time and indicates for whom treatment A is likely to work better than treatment B – and vice versa (Hayes & Rockwood, 2017; Kraemer, 2016). A non-significant *predictor* variable may still be a relevant *moderator* (Kazdin, 2007; Kraemer, 2016). Hypothetically, a CPTSD diagnosis may be differentially related to outcome of treatments that specifically address DSO (i.e., STAIR) but not to treatments that do not (i.e., PE). No studies so far have investigated whether CPTSD moderates treatment outcome, but one study with 104 participants showed that a combination of several CPTSD-related dimensions (i.e., interpersonal problems, anger and regulation of negative mood) resulted in more beneficial outcomes of STAIR+PE compared to support+PE and STAIR+support (Cloitre et al., 2016). Interestingly, when these dimensions were modeled separately they did not moderate outcome.

The aim of the current study was to investigate whether CPTSD predicts and/or moderates treatment outcomes in patients with PTSD related to childhood abuse. We investigated the effect of 1) CPTSD diagnosis (yes versus no), based on the ICD-11 criteria and 2) DSO symptom severity (continuous measure). Firstly, we expected that both CPTSD diagnosis and higher DSO symptom severity predict worse treatment outcome (i.e. across conditions). Secondly, we hypothesized that CPTSD diagnosis and DSO symptom severity moderate treatment outcome. In particular, we expected that CPTSD and more higher DSO symptom severity would be related to better treatment effects in STAIR+PE in comparison to PE and intensive PE (iPE).

Method

Design

This study includes the sample of a randomized clinical trial investigating PTSD treatment for adults with childhood trauma: the IMPACT study (Oprel et al., 2018). The trial was approved by the Medical Ethics Committee of Leiden University Medical Center (NL57984.058.16). More detailed information about the design and main results of the study including baseline characteristics can be found elsewhere (Oprel et al., 2021)

Participants and procedure

The sample of the IMPACT study consists of adults with: at least moderately severe PTSD; related to multiple traumata including childhood sexual and/or physical abuse; committed by a primary caretaker or an authority figure. The sample included 149 patients randomized to PE, iPE or STAIR+PE. PTSD was diagnosed using the Clinician Administered PTSD Scale (CAPS-5). Patients had to be fluent in Dutch. Exclusion criteria included ongoing litigation concerning disability compensation or admission or stay in The Netherlands; pregnancy; severe non-suicidal self-injury or severe suicidal behavior in the past three months; severe disorder in the use of alcohol or drugs in past three months; cognitive impairment (IQ < 70); current engagement in psychological treatment and changes in psychotropic medication in past two months. No additional in- or exclusion criteria were used for the current study. The trial is registered at the clinical trials registry, number ISRCTN03194113.

Assessment schedule

Demographic information, and PTSD diagnosis and severity were assessed during the baseline assessment (T0). PTSD symptoms were assessed at baseline (T0), after 4 weeks (T1) after 8 weeks (T2), post-treatment after 16 weeks (T3) and at a 6-month (T4) and 12-month (T5) follow-up. The effect of CPTSD and DSO severity on PTSD symptom change during the treatment phase (from T0 to T3) is the main outcome of this study. The effect of CPTSD and DSO severity on the follow-up phase (T3-T5) is the secondary outcome. Note that any finding during this phase may be influenced by other sources than treatment condition since patients could seek further treatment after T4.

Treatment

PE was delivered in 16 weekly face-to-face sessions of 90 minutes. PE involved psychoeducation about PTSD, imaginal exposure and exposure in vivo (Foa et al., 2007). iPE was delivered three times a week for four weeks in face-to-face sessions of 90 minutes, followed by two sessions after one and two months (14 sessions total). Except for the time format, iPE was similar to the PE condition. STAIR+PE was delivered in 16 weekly face-to-face sessions. The first eight 60-minutes sessions consisted of STAIR and included psychoeducation and emotion regulation and interpersonal skills training. The subsequent 90-minutes sessions (i.e. session 9-16) consisted of PE. Treatment dropout was defined as stopping treatment prematurely after randomization. Overall dropout of the three

treatments was 24%. In PE, 29% of the patients dropped out, in iPE 27% and in STAIR+PE 18%.

Measures

The main outcome was change in clinician-rated PTSD symptom severity, measured with the CAPS-5 (Boeschoten et al., 2018). The CAPS-5 is a clinical interview that assesses DSM-5 PTSD diagnostic criteria and symptom severity with 20 items. Each item is scored on a five-point Likert scale (0-4). We used the total severity score which ranges between 0-80. The internal consistency of CAPS-5 total score was Cronbach's $\alpha = .88$ in a previous study studies (Weathers et al., 2018) and $\alpha = .75$ in the current study.

CPTSD diagnosis and symptom severity were determined using the updated version of the International Trauma Questionnaire ITQ (Cloitre et al., 2018). The ITQ is a self-report questionnaire that assesses PTSD symptoms with six items and Disturbance in Self Organization (DSO) with six items, using five-point Likert scales (0-4). Moreover, six items assess functional impairment associated with PTSD and DSO symptoms. PTSD symptoms consist of three two-item subscales: re-experiencing, avoidance and sense of threat. DSO symptoms also consist of three two-item subscales: affective dysregulation, negative self-concept and disturbances in relationships. For both subscales, an item score ≥ 2 is considered endorsement of a symptom. Diagnosis of CPTSD requires: 1) ≥ 1 symptom of each PTSD subscale; 2) ≥ 1 symptom of each DSO subscale; 3) endorsement of one item indicating functional impairment associated with PTSD and DSO symptoms. DSO severity can be assessed by summing the six DSO items with scores ranging from 0-24 (higher scores indicate greater severity). Internal consistency of this total score was high in the current sample (Cronbach's $\alpha = .81$).

Statistical analyses

We pre-registered a statistical analysis plan at the Center For Open Science (Hoeboer et al., 2020a). 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**).** We evaluated differences between demographic characteristics of patients with and without CPTSD diagnosis at baseline using t-tests and χ^2-tests of independence. 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 effect of time to account for the dependency in the data within persons (Hox, 2002; Kato et al., 2005). We modelled the linear effect of time with a piecewise growth model with two separate slopes: one for the treatment phase from baseline to post-treatment (T0-T3; main outcome) and one for the follow-up phase from post-treatment to 1-year follow-up (T3-T5; secondary outcome). We used a separate slope for the follow-up period to account for the differences in the effect of time during the treatment phase compared to the follow-up phase.

For the first hypothesis, we performed two independent linear mixed effect models. In the first model, CAPS-5 was the dependent variable and CPTSD diagnosis, the two time-slopes, and the interaction effects between the time-slopes and CPTSD diagnosis were

included as independent variables. In the second model, CAPS-5 was the dependent variable and DSO, the two time-slopes, and the interaction effects between the time-slopes and DSO were included as independent variables. For ease of interpretation, we mean-centered total symptom severity of DSO.

For the second hypothesis, we used the same models but added the following variables to the first model: condition (dummy coded), the interaction between the two time-slopes and condition, the interaction between CPTSD diagnosis and condition, and the three-way interactions between the two time slopes, condition and CPTSD diagnosis as independent variables. To the second model we added: condition, the interaction between the two time-slopes and condition, the interaction between DSO and condition, and the three-way interactions between the two time slopes, condition and DSO as independent variables. We used STAIR+PE as dummy-coded comparator in all moderation analyses, since we hypothesized that CPTSD would result in more beneficial effects of STAIR+PE compared to PE and iPE.

The assumptions of all analyses were met. We used semi-parametric bootstrapping to derive the estimated treatment trajectory with prediction intervals for patients with and without CPTSD based on 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). We evaluated effect sizes of the linear mixed effect models 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).

Sensitivity analyses

To assess the robustness of findings, we planned to conduct four sensitivity analyses. Firstly, to check whether results were influenced by differences in PTSD conceptualizations between the DSM-5 and ICD-11, we performed a sensitivity analysis with PTSD symptoms measured with the ITQ, following ICD-11 criteria, as outcome variable. Hence, the four models from the main analyses were repeated with ITQ PTSD subscale score (baseline to 1-year follow-up) as dependent variable. Secondly, to check whether results are influenced by patients who met DSM-5 PTSD criteria but who did not meet ICD-11 PTSD criteria, we performed a sensitivity analysis with a subset of patients who met ICD-11 PTSD criteria according to the ITQ. Thirdly, to check whether results were influenced by PTSD symptom severity, we performed a sensitivity analysis with baseline ITQ PTSD symptom severity as covariate in the four models from the main analyses. Fourthly, we checked whether results were influenced by baseline differences between patients with and without CPTSD by performing a sensitivity analysis with significant differences in baseline clinical/demographic characteristics between CPTSD and PTSD as covariates in the four models from the main analyses.

Results

Baseline differences

Table 1 lists the baseline characteristics for the total sample (*N* = 149) and the comparison of baseline characteristics for patients with (*n* = 80) and without (*n* = 69) CPTSD. Patients with CPTSD reported more childhood physical abuse, more frequently met criteria for current depression, psychotic disorder and personality disorder and suffered from more comorbid axis-1 diagnoses (in general) than patients without CPTSD.

Dropout

Patients with CPTSD did not show a higher dropout rate (24%) than patients without CPTSD (26%): $\chi^2(1) = .11$, $p = .74$. More severe DSO symptoms at baseline were not related to higher dropout rates: $b = -.008$, *Wald* $\chi^2(1) = .06$, $p = .82$.

Table 1. Baseline characteristics for the total sample and comparison of baseline characteristics for patients with and without CPTSD

	Total (*N* = 149)	PTSD (*n* = 69)	CPTSD (*n* = 80)	
Demographic characteristics, Mean (SD)				***t*-test versus χ2**
Age, y	36.86 (11.75)	36.07 (12.88)	37.55 (10.72)	$t(147) = .77$, $p = .45$
Duration of PTSD, y	15.06 (12.49)	14.19 (12.01)	15.83 (12.93)	$t(143) = .79$, $p = .43$
Mean number Axis-1 MINI diagnoses, excluding PTSD	3.12 (1.91)	2.16 (1.47)	3.95 (1.86)	$t(147) = 6.46$, $p < .001$
Demographic characteristics, No. (%)				
Gender (female)	114 (76.5)	54 (78.3)	60 (75.0)	$\chi^2(1) = .21$, $p = .64$
Marital status (married/cohabitating)	56 (37.6)	25 (36.2)	31 (38.8)	$\chi^2(1) = .10$, $p = .75$
Education (high)[1]	30 (20.1)	13 (18.8)	17 (21.3)	$\chi^2(1) = .13$, $p = .72$
Cultural background (non-Western)[2]	65 (43.3)	27 (39.1)	38 (47.5)	$\chi^2(1) = 1.06$, $p = .30$
Trauma category (single or multiple) DSM-5A criterion CAPS-5				
Childhood sexual abuse	108 (72.5)	47 (68.1)	61 (76.3)	$\chi^2(1) = 1.23$, $p = .27$
Childhood physical abuse	93 (62.4)	36 (52.2)	57 (71.3)	$\chi^2(1) = 5.75$, $p = .02$
Sexual abuse in adulthood	29 (19.5)	10 (14.5)	19 (23.8)	$\chi^2(1) = 2.03$, $p = .16$
Physical abuse in adulthood	42 (28.2)	16 (23.2)	26 (32.5)	$\chi^2(1) = 1.59$, $p = .21$
Axis-1 MINI diagnosis				
Current depression	85 (57.1)	30 (43.4)	55 (68.8)	$\chi^2(1) = 9.66$, $p = .002$
Severe suicidality past month	64 (43.0)	24 (34.8)	40 (50.0)	$\chi^2(1) = 3.50$, $p = .06$

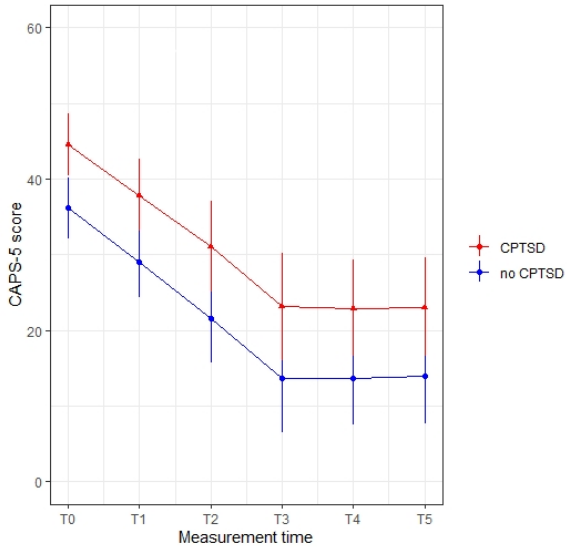
Current bipolar disorder (type1/2)	10 (6.7)	6 (8.7)	4 (5.0)	NA
Disorder alcohol/drug use past year	34 (22.8)	17 (24.6)	17 (21.3)	$\chi^2(1) = .24$, $p = .62$
Current psychotic disorder	19 (12.8)	4 (5.8)	15 (18.8)	$\chi^2(1) = 5.59$, $p = .02$
Any personality disorder diagnosis	90 (60.4)	33 (47.8)	57 (71.3)	$\chi^2(1) = 8.50$, $p = .004$

PTSD = Posttraumatic stress disorder, CPTSD = Complex PTSD, SD = standard deviation, y = year, N = sample size, No. = number, NA = not applicable, MINI = Mini-International Neuropsychiatric Interview, DSM-5 = Diagnostic and statistical manual of mental disorders version five, CAPS-5 = Clinician-administered PTSD scale for DSM-5. [1]high education = higher vocational education or university. [2]non-Western cultural background = at least one parent was not born in a Western country.

Predictor effects

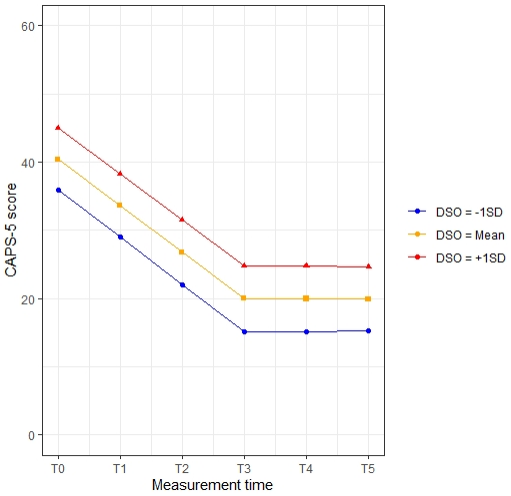
CPTSD was related to more severe PTSD symptoms at baseline: $b = 8.67$, $t(162) = 5.70$, $p < .001$ $d = .90$. Those who suffered from CPTSD ($M_{estimated} = 44.53$, $SE_{estimated} = 1.04$) had higher CAPS-5 baseline scores than those without CPTSD ($M_{estimated} = 35.87$, $SE_{estimated} = 1.52$). However, we did not find that CPTSD was a significant predictor of outcome during the treatment phase: $b = .38$, $t(132) = .40$, $p = .69$ or follow-up phase: $b = -.05$, $t(172) = -.04$, $p = .97$ (see Figure 1).

DSO severity was also related to higher CAPS-5 scores at baseline: $b = .81$, $t(162) = 5.99$, $p < .001$, $d = .94$, but it was no significant predictor of outcome during the treatment phase: $b = .02$, $t(133) = .26$, $p = .80$ or follow-up phase: $b = -.01$, $t(169) = -.14$, $p = .89$ (see Figure 2 for illustration).



CPTSD = Complex Posttraumatic stress disorder, ITQ = International Trauma Questionnaire, CAPS-5 = Clinician-Administered PTSD scale for DSM-5, T0 = baseline, T1 = 4 weeks, T2 = 8 weeks, T3 = 16 weeks, T4 = 6 month follow-up, T5 = 12 month follow-up.

Figure 1. Estimated treatment trajectory (baseline to 1-year follow-up) of patients with and without CPTSD based on the ITQ.



DSO = Disturbances in self-organization, SD = standard deviation, ITQ = International Trauma Questionnaire, CAPS-5 = Clinician Administered PTSD scale for DSM-5, T0 = baseline, T1 = 4 weeks, T2 = 8 weeks, T3 = 16 weeks, T4 = 6 month follow-up, T5 = 12 month follow-up.

Figure 2. Illustration of treatment trajectory (baseline to 1-year follow-up) of patients with average DSO, DSO one standard deviation below average and DSO one standard deviation above average measured with the ITQ. Estimations were based on probing of the interaction effect between DSO and Measurement time.

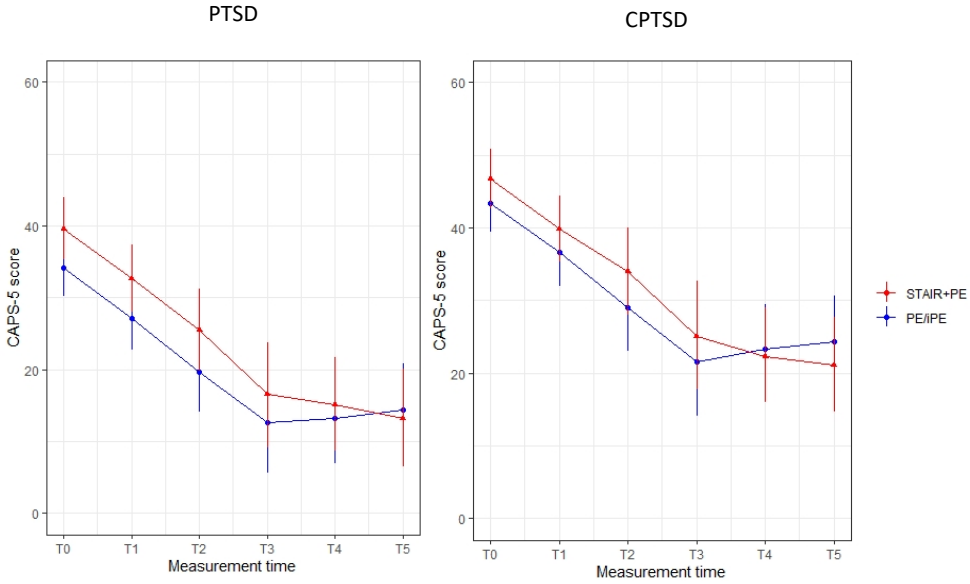
Moderator effects

We did not find that CPTSD diagnosis significantly moderated outcome (STAIR+PE versus PE/iPE) during the treatment phase: b = -.42, $t(133)$ = -.21, p = .83 or follow-up phase: b = 1.33, $t(188)$ = .54, p = .59. (see Figure 3).

We also did not find that DSO severity was a significant moderator of outcome (STAIR+PE versus PE/iPE) during the treatment phase: b = -.07, $t(135)$ = -.39, p = .70, or follow-up phase: b = .42, $t(193)$ = 1.85, p = .07. (see Figure 4 for illustration).

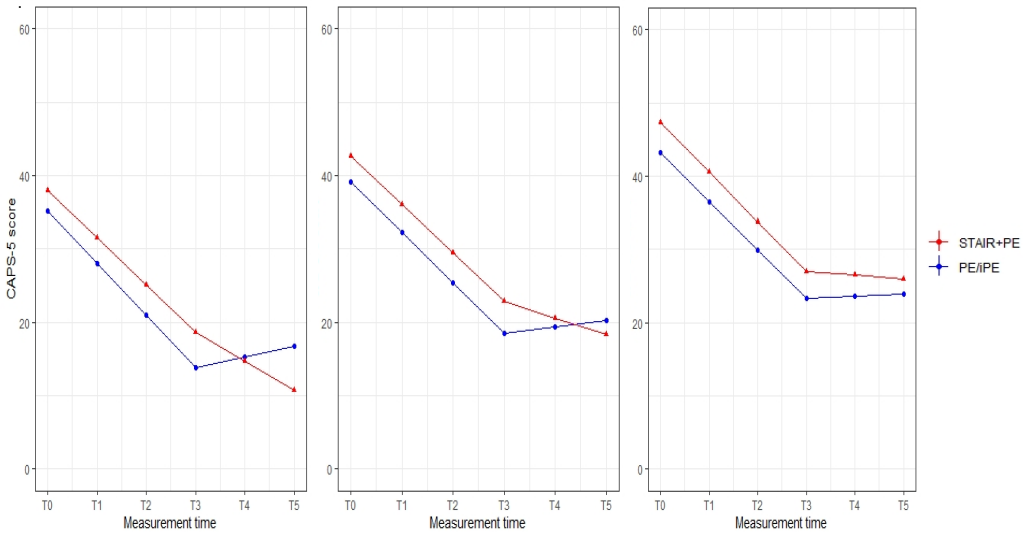
Sensitivity analyses

The results of the main analyses were replicated in the sensitivity analyses. In all sensitivity analyses, both CPTSD and DSO severity were significantly related to more severe PTSD symptoms at baseline, while we did not observe a significant prediction or moderation effect of CPTSD and DSO severity on the outcome during the treatment or follow-up phase.



STAIR+PE = Skills Training in Affective and Interpersonal Regulation followed by Prolonged Exposure, PE = Prolonged Exposure, iPE = intensified Prolonged Exposure, PTSD = Posttraumatic stress disorder, CPTSD = Complex PTSD, ITQ = International Trauma Questionnaire, CAPS-5 = Clinician Administered PTSD scale for DSM-5, T0 = baseline, T1 = 4 weeks, T2 = 8 weeks, T3 = 16 weeks, T4 = 6 month follow-up, T5 = 12 month follow-up

Figure 3. Estimated treatment trajectory of STAIR+PE and PE/iPE for patients with PTSD (left panel) versus CPTSD (right panel) based on the ITQ.



SD = standard deviation, STAIR+PE = Skills Training in Affective and Interpersonal Regulation followed by Prolonged Exposure, PE = Prolonged Exposure, iPE = intensified Prolonged Exposure, DSO = Disturbances in self-organization, ITQ = International Trauma Questionnaire, CAPS-5 = Clinician-Administered PTSD scale for DSM-5, T0 = baseline, T1 = 4 weeks, T2 = 8 weeks, T3 = 16 weeks, T4 = 6 month follow-up, T5 = 12 month follow-up.

Figure 4. Illustration of treatment trajectory (baseline to 1-year follow-up) of patients with average DSO (middle panel), DSO one standard deviation below average (left panel) and DSO one standard deviation above average (right panel) measured with the ITQ. Estimations were based on probing of the interaction effect between DSO, condition and measurement time.

Discussion

The aim of this study was to investigate whether CPTSD predicts or moderates trauma-focused treatment outcome in patients with PTSD related to child abuse. We found that patients with CPTSD had more severe PTSD symptoms and a higher rate of comorbid diagnoses at baseline. However, patients with CPTSD did not benefit significantly less from three variants of exposure therapy than patients without CPTSD. In particular, patients with CPTSD did not benefit significantly more from STAIR+PE than from PE or iPE than patients with non-complex PTSD. The same pattern of findings was observed with the severity of disturbances in self-organization (DSO) as predictor and moderator.

Before treatment, patients with CPTSD reported more severe PTSD symptoms, more childhood physical abuse, met more axis-1 diagnoses and more frequently met criteria for a personality disorder than patients with non-complex PTSD. This finding is in line with previous studies, that found that CPTSD is characterized by more comorbid diagnoses (Cloitre et al., 2019; Elklit, Hyland, & Shevlin, 2014; Karatzias et al., 2019a; Powers et al., 2017), by higher PTSD symptom severity (Powers et al., 2017) and by more severe impairment (Bondjers et al., 2019; Brewin et al., 2017; Cloitre et al., 2019; Karatzias & Cloitre, 2019). Consequently, we conclude that CPTSD is a more severe form of PTSD (or PTSD with more comorbidities).

Our hypothesis that CPTSD and more severe DSO would predict worse outcome of (variants of) exposure therapy was not supported. These results were replicated in the sensitivity analyses, suggesting that the results were robust and not influenced by differences in PTSD conceptualizations between the DSM-5 and ICD-11. Given that patients with CPTSD suffered from more severe PTSD symptoms at baseline and showed similar decrease in PTSD symptoms compared to patients without CPTSD, our results could imply that patients with CPTSD are in need of more treatment sessions to reach the same endstate functioning. This is specifically relevant for those who experienced large symptom reductions during treatment, but still suffered from elivated symptoms post-treatment, as initial symptom change is highly predictive of symptom change during treatment continuation (Sripada, Ready, Ganoczy, Astin, & Rauch, 2020). The finding that CPTSD is not a relevant predictor of treatment outcome is consistent with another recent study which found no difference in treatment response between patients with CPTSD and non-complex PTSD (Voorendonk et al., 2020). Future studies are needed to replicate these findings across study populations, treatment settings and different types of treatments.

Our hypothesis that CPTSD diagnosis and DSO severity score moderate treatment outcome was not supported. These results were replicated in sensitivity analyses. Our expectation that patients with CPTSD would benefit more from STAIR+PE than from PE/iPE was based on the fact that STAIR targets DSO symptoms directly during the first phase of treatment. Left untreated, DSO symptoms may negatively influence the effectiveness of PE, but our results indicate that this is not the case. As reported elsewhere, DSO dimensions improved over the course of treatment in all three conditions (Oprel et al., 2021). Other recent studies have also shown that PE reduces DSO symptoms (Jerud, Pruitt, Zoellner, & Feeny, 2016; Jerud et al., 2014; van Toorenburg et al., 2020). However, a combination of CPTSD-related constructs was related to differential treatment effects in a previous study; women with a high symptom load relative to emotion regulation strength benefitted the least from support plus exposure (eight sessions exposure) and benefitted most from STAIR plus exposure (Cloitre et al., 2016). Granted that PE sessions may positively affect DSO symptoms, these differential findings might be explained by the higher dosage of PE in the current study (14-16 sessions) in comparison to this work (8 sessions). In the absence of a prediction or moderation effect, the construct of CPTSD does not seem to refer to a distinct disorder.

Limitations and strengths

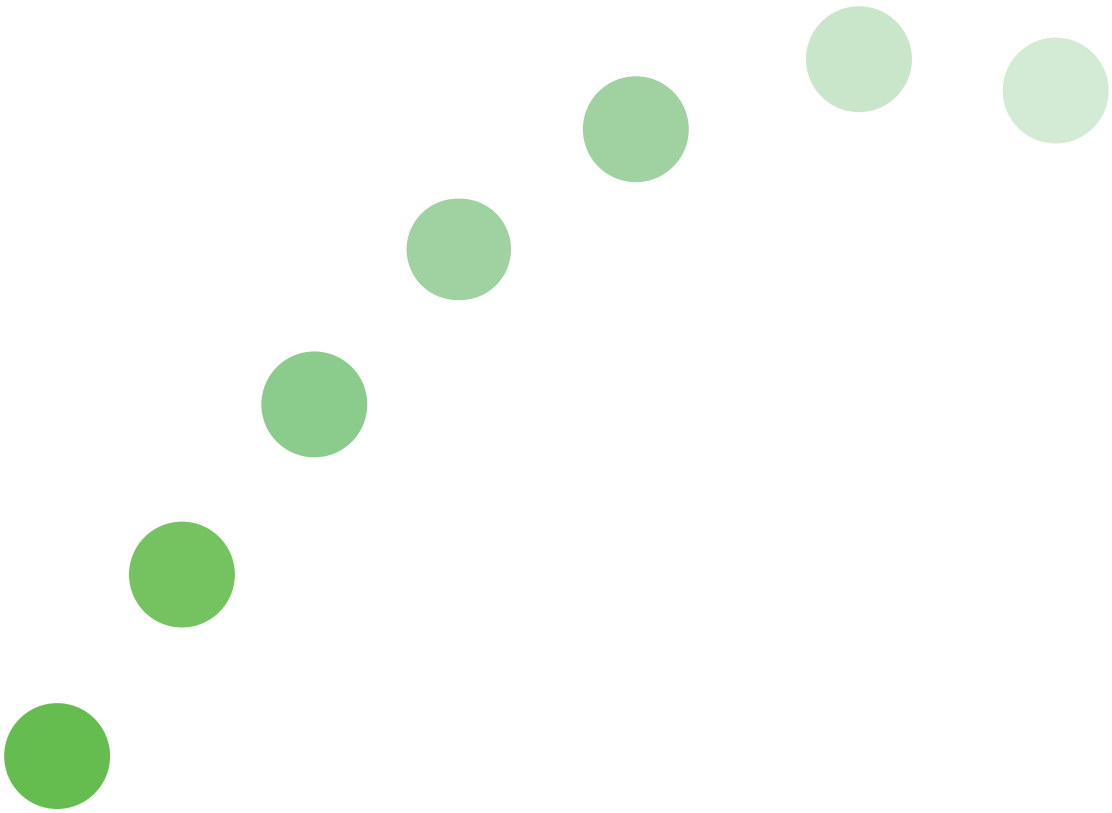
The present study has several limitations. Firstly, patients were included based on DSM-5 PTSD criteria, not on ICD-11. Applying ICD-11 criteria would have resulted in a slightly different sample (Hansen et al., 2017; Hyland et al., 2016; O'Donnell et al., 2014). We do not expect this difference to be clinically relevant. Secondly, all patients had a current diagnosis of PTSD based on the experience of childhood abuse. A little more than half of our population scored positive on CPTSD, which is high compared to other chronically traumatized samples (Barbieri et al., 2019; Grossman et al., 2019; Vallieres et al., 2018). CPTSD is also common in veterans (Folke, Nielsen, Andersen, Karatzias, & Karstoft, 2019; Letica-Crepulja et al., 2020; Murphy et al., 2020), genocide survivors (Grossman et al., 2019) and refugees (Barbieri et al., 2019; Vallieres et al., 2018) and their response to treatment may be different. Thirdly, we used the self-report version of the ITQ, which may differ from a clinician-administered version which is currently being developed (Cloitre, Roberts, Bisson, & Brewin, 2017). Clinician-administered questionnaires are the golden standard for diagnosing PTSD (Boeschoten et al., 2018), but first results indicate that the clinician-administered version of the ITQ leads to similar results as the self-report version (Bondjers et al., 2019).

The strengths of the current study include the large sample size and multiple measurements within persons, the long-term follow-up measurements and the assessment of both CPTSD and DSO symptom severity. Furthermore, the sensitivity analyses increase the robustness of findings.

Conclusions

Since this is the first study to assess the prediction and moderation effect of CPTSD, future studies are needed to replicate our findings across samples and treatments. If replicated,

these findings have important implications for clinical practice. Patients with CPTSD benefit from exposure therapies as well as patients with (non-complex) PTSD, implying that these treatments are indicated in patients with CPTSD related to childhood abuse. In other words, trauma-focused therapies should not be withheld from this patient population. Patients with CPTSD may benefit more from the implementation of existing treatments than from attempts to develop new treatments.



Chapter 6

Personalization of treatment for patients with childhood abuse-related posttraumatic stress disorder

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Abstract

Background: Differences in effectiveness among treatments for Posttraumatic Stress Disorder (PTSD) are typically small. Given the variation between patients in treatment response, personalization offers a new way to improve treatment outcome. The aim of this study was to identify predictors of psychotherapy outcome in PTSD and to combine these into a Personalized Advantage Index (PAI).

Methods: We used data from a recent randomized controlled trial comparing prolonged exposure (PE; *n* = 48), intensified PE (iPE; *n* = 51) and skills training (STAIR) followed by PE (*n* = 50) in 149 patients with Childhood Abuse-related PTSD (CA-PTSD). Outcome measures were clinician-assessed and self-reported PTSD symptoms. Predictors were identified in the exposure therapies (PE and iPE) and STAIR+PE separately using random forests and subsequent bootstrap procedure. Next, these predictors were used to calculate PAI and to determine optimal and suboptimal treatment in a leave-one-out cross-validation approach.

Results: More depressive symptoms, less social support, more axis-1 diagnoses and higher severity of childhood sexual abuse were predictors of worse treatment outcomes in PE and iPE. More emotion regulation difficulties, lower general health status and higher baseline PTSD symptoms were predictors of worse treatment outcomes in STAIR+PE. Randomization to optimal treatment based on these predictors resulted in more improvement than suboptimal treatment in clinician assessed (Cohens' *d* = .55) and self-reported PTSD symptoms (Cohens' *d* = .47).

Conclusion: Personalization based on PAI is a promising tool to improve therapy outcome in patients with CA-PTSD. Further studies are needed to replicate findings in prospective studies.

Keywords: Posttraumatic stress disorder, STAIR+PE, prolonged exposure therapy, personalized advantage index, predictors treatment outcome.

Introduction

Despite the well-established effectiveness of treatments for PTSD such as trauma-focused cognitive behavioral therapy (TF-CBT; Mavranezouli et al., 2020), meta-analyses showed that about half of the patients do not benefit (enough) from treatment or dropout prematurely (Bradley et al., 2005; Ehring et al., 2014; Lewis et al., 2020; Watkins et al., 2018). For the past decades, research has focused on developing new treatments (e.g., Wilson, Becker, & Tinker, 1995) or adapting already existing ones (e.g., Cloitre et al., 2002; Hendriks et al., 2018). This has led to new effective treatments, but failed to improve treatment outcome (Mavranezouli et al., 2020; Zhou et al., 2020). Given these alternative treatment options, *personalization* offers a new approach towards improving PTSD treatment outcome. The basic idea is that patients might respond differently to two distinct treatments. Hence, investigating which patients are most likely to benefit from one treatment compared to another may improve individual patient outcomes (Seidler & Wagner, 2006). Clinicians already use personalization to some degree on an intuitive level since treatments indications are often based on patient characteristics (e.g., Becker et al., 2004). However, intuition is prone to biases and this approach is unsystematic and not evidence-based (Perlis, 2016; Waller, 2009). In contrast, personalization based on statistical algorithms might result in systematic and empirically derived treatment recommendations.

Treatment personalization of PTSD has received little attention compared to other fields (e.g. medicine). There have been three studies that investigated treatment personalization in patients with PTSD. Two studies used a Personalized advantage Index (PAI) which indicates relative preference for one treatment compared to another based on a combination of predictors or moderators of treatment outcome (Deisenhofer et al., 2018; Keefe et al., 2018). Both studies found that the PAI approach led to relevant treatment recommendations with medium effect sizes. Deisenhofer et al. (2018) compared trauma-focused cognitive behavioral therapy (TF-CBT) with eye movement desensitization and reprocessing (EMDR) and used depressive symptoms as outcome. They found that age, employment status, gender, and functional impairment were predictors of outcome in TF-CBT and baseline depressive symptoms and prescribed antidepressant medication were predictors of outcome in EMDR. Keefe et al. (2018) compared Prolonged Exposure (PE) with Cognitive Processing Therapy (CPT) and used drop-out as outcome. They assessed moderators of treatment outcome rather than predictors in the two treatment separately and found that childhood physical abuse, current relationship conflict, anger and being a racial minority moderated treatment outcome. The third study used generated modifiers (Petkova, Park, Ciarleglio, Ogden, & Tarpey, 2020), a composite moderator indicating differential treatment outcome in a support condition followed by PE (support+PE), skills training (STAIR) and skills training followed by exposure (STAIR+PE) in patients with Childhood Abuse-related PTSD (CA-PTSD; Cloitre et al., 2016). They used clinician-assessed PTSD symptoms as outcome. They found that the combination of symptom burden and emotion regulation might be relevant for personalization, but did not evaluate whether this led to relevant treatment recommendations (Cloitre et al., 2016).

To summarize, personalization offers a promising approach for PTSD treatment, but so far no study evaluated its relevance for treatment recommendations using PTSD symptoms as outcome while this is the primary focus of treatment. Furthermore, most studies only assessed a limited number of potential predictors, which does not capture the heterogeneous symptom representation of patients with PTSD. In the current study, we aimed to develop and evaluate treatment personalization in patients with CA-PTSD using PAI based on a broad range of patient characteristics including both self-reported and clinician assessed characteristics. We used a sample of 149 patients randomized to an exposure only condition (PE and intensified PE (iPE)) or STAIR+PE. Our first aim was to identify which patient characteristics were predictors of treatment outcome in the exposure only conditions (PE and iPE) and STAIR+PE separately. Our second aim was to calculate the PAI based on these predictors and evaluate whether optimal treatment according to the PAI resulted in better treatment outcome compared to suboptimal treatment.

Methods

This study used the data of a randomized controlled trial investigating three psychotherapies of CA-PTSD (Oprel et al.; Oprel et al., 2018). A total of 149 patients were recruited in two outpatient mental health services in The Hague and Rotterdam, the Netherlands. These patients were randomized to PE (*n* = 48), intensified PE (*n* = 51) or STAIR+PE (*n* = 50).

Participants

Inclusion criteria of the original study sample included: age between 18 and 65 years; PTSD diagnosis according to the DSM-5 established with the Clinician Administered PTSD Scale for DSM-5 (CAPS-5; Boeschoten et al., 2018); at least moderate severity of PTSD symptoms (CAPS-5 score ≥ 26) and a specific memory of the traumatic event. Exclusion criteria included: ongoing compensation case or legal procedures about admission or stay in The Netherlands; pregnancy; severe non-suicidal self-injury, which required hospitalization during the past three months; severe suicidal behavior in the past three months; severe disorder in the use of alcohol or drugs in the past three months; cognitive impairment (estimated IQ < 70); changes in psychotropic medication in the two months prior to inclusion; and engagement in any current psychological treatment. See Table 1 for sample characteristics. The trial was approved by the Medical Ethics Committee of Leiden University Medical Center (NL57984.058.16).

Procedures

Written informed consent was obtained from all participants before the baseline assessment when patients received all relevant information and decided to participate. Patients were randomized in a 1:1:1 ratio to PE, iPE and STAIR+PE. Predictors were assessed during the baseline assessment (T0). PTSD symptoms were assessed at baseline (T0), after four weeks (T1), eight weeks (T2) and post-treatment after 16 weeks (T3). Clinical interviews were carried out by independent interviewers who were blind to the treatment condition of patients. The authors assert that all procedures contributing to this work comply 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.

Treatment

PE included 16 weekly sessions of 90 minutes and consisted of a combination of imaginal exposure and exposure in vivo (Foa et al., 2007). iPE included 12 sessions, three times a week (4 weeks total), followed by two booster sessions after one and two months respectively. Treatment protocols of PE and iPE were identical. STAIR+PE included 16 weekly sessions of which the first half consisted of 60 minutes STAIR and the second half consisted of 90 minutes PE. STAIR sessions included skills training in emotion regulation and interpersonal functioning. PE sessions were similar to the PE and iPE conditions.

Measures

Outcome measures

PTSD symptom severity measured with the CAPS-5 (Weathers et al., 2013a) was the primary outcome of this study. The CAPS-5 includes 20 items on a 5-point Likert-scale resulting in a total score between 0 and 80 (Cronbach's α current study = .75).

Self-reported PTSD symptom severity measured with the PTSD checklist for DSM-5 (PCL-5; Blevins et al., 2015) was the secondary outcome of this study. The PCL-5 includes 20 items on a 5-point Likert-scale resulting in a total score between 0 and 80 (Cronbach's α current study = .89).

Predictor variables

Patient expectancies

Patients' expectancies of the treatments were indicated by two predictors: total score of the Expectancy of burden (Cronbach's α current study = .91) and Credibility questionnaire (Cronbach's α current study = .90) as used in previous studies (e.g., de Bont et al., 2013). See Table 1 for additional information about predictors.

Demographics

Demographic predictors included age, gender, cultural background education and employment.

Social support

Social support was indicated by the total score of the social support survey from the Medical Outcome Study (MOS; Kempen, 1992; Cronbach's α current study = .97).

Trauma background

We included four subscale scores of the Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998) as indicators of childhood trauma background: childhood emotional abuse (Cronbach's α current study = .86), emotional neglect (Cronbach's α current study = .86), physical abuse (Cronbach's α current study = .88) and sexual abuse (Cronbach's α current study = .88).

Table 1. Descriptive information about potential predictors for exposure therapies and STAIR+PE.

Predictors[1]	Possible range of predictor scores min-max	Exposure therapies (*n* = 99) Mean (SD) or %	STAIR+PE (*n* = 50) Mean (SD) or %
Patient expectancies			
Expected burden	0-10	5.98 (2.56)	6.73 (2.37)
Credibility	0-10	6.75 (1.89)	6.72 (1.74)
Demographics			
Age, y		36.76 (11.47)	37.07 (12.39)
Gender, female		75.76	78.00
Cultural background, western		39.39	52.00
Education, high		21.21	18.00
Employment, yes		40.40	34.00
Social support			
MOS total score	1-5	3.41 (1.10)	3.32 (1.04)
Trauma background			
CTQ childhood emotional abuse	5-25	17.06 (6.04)	17.54 (6.21)
CTQ childhood emotional neglect	5-25	17.74 (5.08)	19.84 (5.38)
CTQ childhood physical abuse	5-25	13.09 (6.97)	14.42 (6.36)
CTQ childhood sexual abuse	5-25	15.48 (7.12)	15.62 (7.68)
General health status			
EQ-5D-5L general health status	0-100	55.56 (26.31)	58.18 (20.03)
Self-reported psychiatric symptoms			
BDI total score	0-63	33.63 (10.06)	34.88 (11.15)
PTCI total score	33-231	133.26 (36.40)	149.64 (31.64)
IIP total score	0-4	1.65 (.62)	1.70 (.50)
RSES total score	0-30	12.52 (5.84)	11.32 (6.14)
DERS total score	36-180	115.63 (21.27)	117.46 (20.46)
SDQ-5 total score	5-25	6.78 (2.93)	7.64 (3.11)
Psychotropic medication		49.49	44.00
Clinician-assessed psychiatric symptoms and disorders			
Any SCID-2 personality disorder		59.60	62.00
DSP-I total score	0-36	1.78 (3.20)	3.22 (5.65)
Axis-1 MINI diagnoses, excluding PTSD		2.99	3.38
CAPS-5 baseline total score	0-80	40.28 (8.73)	43.56 (10.46)

STAIR+PE = Skills Training in Affective and Interpersonal Regulation + Prolonged Exposure, Min: minimum, max: maximum, CAPS-5: Clinician Adminstered PTSD Scale, SCID II: Structured Clinical Interview for DSM-IV axis-II personality disorders, DSP-I: Dissociatief Subtype van PTSS interview, CTQ: Childhood Trauma Questionnaire, DERS: Difficulties in Emotion Regulation Scale, BDI: Beck Depression Inventory-II, PTCI: The posttraumatic cognitions inventory, SDQ-5: Somatoform Dissociation Questionnaire-5, IIP: Inventory of Interpersonal Problems, MOS: Medical Outcomes Study, RSES: Rosenberg Self-Esteem Scale, EQ-5D-5L: EuroQoL 5 Dimensions 5 Levels, SD = standard deviation, y = year, n = sample size, MINI = Mini-International Neuropsychiatric Interview.

[1]Higher scores on predictors indicate higher symptom severity. Exceptions: for social support higher scores indicate more social support, for EQ-5D-5L general health status higher scores indicate better health status and for the CTQ higher scores indicate more severe childhood maltreatment.

General health status

General health status was measured with the visual analogue scale of the EuroQoL 5 Dimensions 5 Levels (EQ-5D-5L; Brooks, 1996; Le et al., 2013)

Self-reported psychiatric symptoms

Depressive symptoms were indicated by the Beck Depression Inventory (BDI; Beck et al., 1996; Cronbach's α current study = .87). Posttraumatic cognitions were indicated by the Posttraumatic Cognitions Inventory (PTCI; Foa et al., 1999; Cronbach's α current study = .94). Interpersonal problems were indicated by the Inventory of Interpersonal Problems (IIP; Barkham et al., 1996; Cronbach's α current study = .87). Self-esteem was indicated by the Rosenberg Self-esteem Scale (RSES; Schmitt & Allik, 2005; Cronbach's α current study = .87). Emotion regulation difficulties were indicated by the Difficulties in Emotion Regulation Scale (DERS; Lee et al., 2016b; Cronbach's α current study = .90). Somatoform dissociation was indicated by the screener version of the Somatoform Dissociation Questionnaire (SDQ-5; Nijenhuis, Spinhoven, VanDyck, VanderHart, & Vanderlinden, 1996; Cronbach's α current study = .71). The use of psychotropic medication was determined using a self-report question.

Clinician-assessed psychiatric symptoms and disorders

Meeting criteria for at least one personality disorders was assessed with the clinical interview for DSM-IV personality disorders (SCID-2; Weertman et al., 2003). Number of DSM-IV defined Axis-1 disorders (excluding PTSD) was assessed with the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). Dissociation was indicated by Dissociative subtype of PTSD Interview (DSP-I; Eidhof et al., 2019; Cronbach's α current study = .78). PTSD symptom severity at baseline was assessed with the CAPS-5.

Statistical analysis

Outcome

Estimated change in CAPS-5 and PCL-5 scores from baseline to post-treatment in the exposure conditions (n = 99) and STAIR+PE (n = 50) were outcome variables in the analyses with higher scores indicating larger symptom decrease. They were separately estimated by subtracting the predicted post-treatment score from the baseline score per individual using all available measurements per outcome from baseline to post-treatment in a linear mixed effect model with R package lme4 (Bates et al., 2015). This model included random intercepts and random slopes. This method provides a more reliable indicator of treatment outcome compared to only using observed post-treatment scores (Raudenbush & Bryk, 2002)

Initial predictor selection with Boruta

Predictors of treatment outcome for the exposure conditions (PE and iPE) and STAIR+PE were selected separately out of the total number of potential predictors (k = 24) using R package Boruta (Kursa & Rudnicki, 2010). The Boruta algorithm determines the relevance of

predictors by comparing their performance with 'shadow' predictors, which are created by randomly shuffling the values of the original predictors. A random forest classifier is performed by developing multiple trees on different bagging samples of the dataset. Importance of shadow and original variables is calculated with Z-scores by dividing the average loss of accuracy of classification caused by random permutations of the variable between samples by its standard deviation. The original variable is a relevant predictor during a round when it's Z-score is higher than the maximum shadow variable's Z-score. This is stored as a hit in a vector. When the number of hits from a predictor is significantly higher or lower than the best shadow variable, the variable is deemed important or unimportant respectively. Unimportant variables are deleted from the dataset. The procedure repeats for maximum 1000 iterations or until all variables are categorized.

Further predictor selection using bootstrap procedure

After identifying predictors of treatment outcome with the Boruta algorithm, we performed a bootstrapped model using R package bootStepAIC (Rizopoulos, 2009) and selected the variables of the model with the best model fit. Since the aim of Boruta is to identify all variables which have *any* relevance under some circumstances, further selection ensured that we did not overfit the data. Furthermore, since the PAI is calculated using a linear combination of variables, the bootstrapped AIC approach ensured that we included the best combination of variables to predict outcome in a linear manner.

Personalized advantage index

With the final set of predictors, we calculated the predicted outcome of all patients using a regression model with a leave-one-out cross-validation approach (predicted outcome per patient was based on a training set including all other patients). Treatment outcome of the treatment that patients did not receive was predicted by the model based on the patients of the other condition (so every patient had two predictions in total: one for exposure therapies and one for STAIR+PE). PAI was calculated by subtracting predicted outcome in the STAIR+PE condition from predicted outcome in exposure conditions and indicated relative advantage of exposure conditions over STAIR+PE. When patients had been randomized to their recommended treatment, we defined them as having received optimal treatment versus suboptimal, when they had been randomized to their non-recommended treatment.

Results

The average estimated change in CAPS-5 scores from baseline to post-treatment was not different in the exposure conditions (M = 21.38; SD = 7.90) compared to STAIR+PE (M = 20.13; SD = 6.75), while estimated change in PCL-5 scores from baseline to post-treatment was significantly larger in the exposure conditions (M = 25.82; SD = 10.14) compared to STAIR+PE (M = 20.16; SD = 9.29).

Variable selection for exposure therapies and STAIR+PE

Figure 1 depict the results of Boruta for exposure conditions and STAIR+PE. Variables dropped in the subsequent bootstrap procedure can be found in the Appendix. For the

CAPS-5, in the final model for the exposure conditions, higher BDI scores, higher CTQ childhood sexual abuse scores, lower MOS scores and more Axis-1 MINI diagnoses were related to worse treatment outcome (see Table 2.a). In the final model of the STAIR+PE condition, higher DERS score, higher CAPS-5 baseline score and lower EQ-5D-5L general health status were related to worse treatment outcome (see Table 2.a).

For the PCL-5, in the final model of the exposure conditions, higher BDI scores and lower MOS scores were related to worse treatment outcome (Table 2.b). In the final model of the STAIR+PE condition, lower EQ-5D-5L general health status and higher DERS scores were related to worse treatment outcome (Table 2.b).

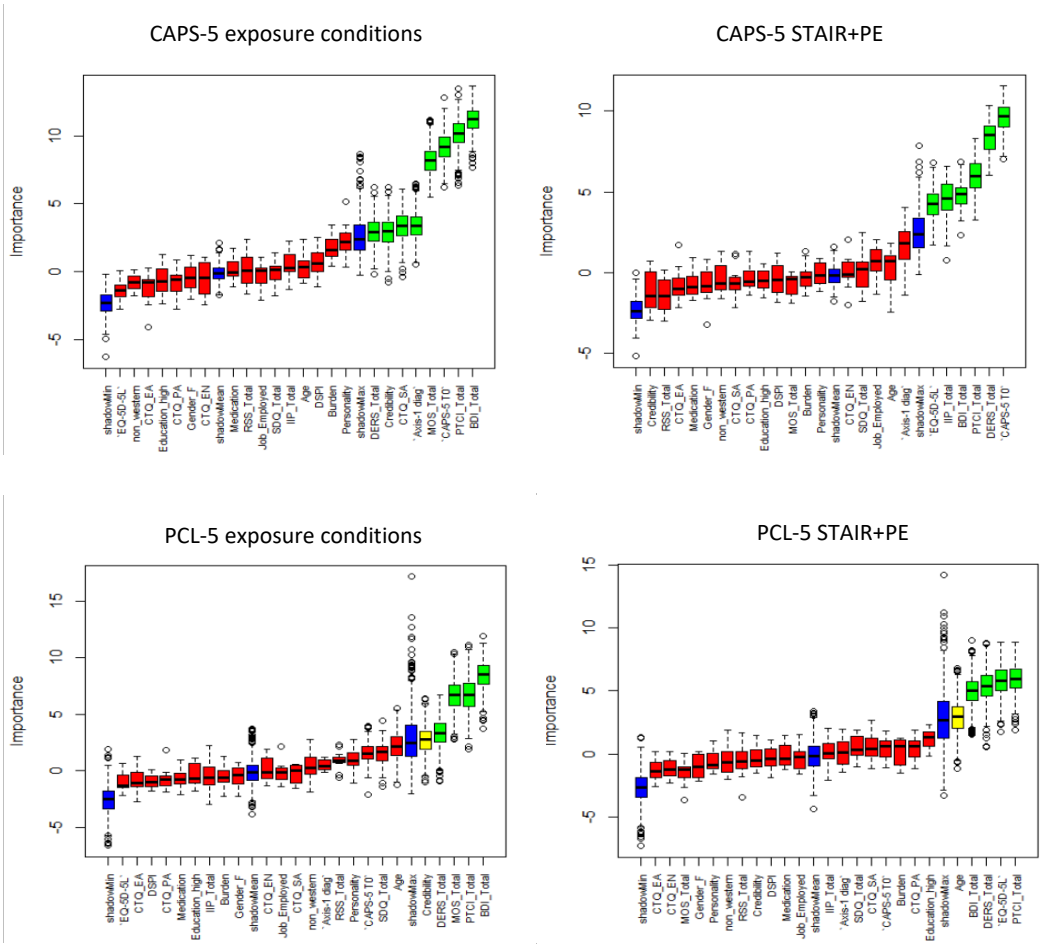

Figure 1. Results of Boruta algorithm for predictor selection with estimated change in CAPS-5 score from pre to post-treatment for exposure conditions (upper left) and STAIR+PE (upper right panel) and estimated change in PCL-5 score for exposure conditions (bottom left) and STAIR+E (bottom right). Relevant predictors are indicated in green, tentative in yellow, irrelevant predictors in red and shadow variables (minimum, mean, maximum) in blue.

Table 2.a Final prediction models of exposure therapies and STAIR+PE with estimated change in CAPS-5 score baseline to post-treatment as outcome variable.

Exposure therapies	Estimate	Std. Error	*t*-value	*p*
BDI	-.24	.07	-3.40	< .001
MOS	2.23	.62	3.63	< .001
Axis-1 MINI diagnoses	-.89	.37	-2.42	.02
CTQ sexual abuse	-.18	.09	-2.04	.04
STAIR+PE				
EQ-5D-5L	.07	.04	1.97	.05
DERS	-.10	.04	-2.54	.01
CAPS-5 baseline	-.26	.08	-3.19	.003

Note that prediction models of all individuals differed slightly due to the cross-validation approach.

Table 2.b Final prediction models of exposure therapies and STAIR+PE with estimated change in PCL-5 score baseline to post-treatment as outcome variable.

Exposure therapies	Estimate	Std. Error	*t*-value	*p*
BDI	-.26	.10	-2.65	.01
MOS	2.59	.89	2.90	.005
STAIR+PE				
EQ-5D-5L	.11	.06	1.78	.08
DERS	-.16	.06	-2.75	.009

Note that prediction models of all individuals differed slightly due to the cross-validation approach.

STAIR+PE = Skills Training in Affective and Interpersonal Regulation + Prolonged Exposure, CAPS-5: Clinician Adminstered PTSD Scale, CTQ: Childhood Trauma Questionnaire, DERS: Difficulties in Emotion Regulation Scale, BDI: Beck Depression Inventory-II, MOS: Medical Outcomes Study, EQ-5D-5L: EuroQoL 5 Dimensions 5 Levels, MINI = Mini-International Neuropsychiatric Interview.

Personalized advantage index

The PAI was calculated based on the final models using leave-one-out cross-validation. For the CAPS-5, the average error of the predictions (difference between predicted score based on final models and estimated outcome) was 5.09 (*SD* = 7.57) in the exposure conditions and 4.06 (*SD* = 7.25) in the STAIR+PE conditions. Half of the patients (*n* = 75; 50%) were randomized to their optimal treatment, while *n* = 74 (50%) were not. Patients randomized to their optimal treatment improved more on the CAPS-5 from baseline to post-treatment ($M_{\text{improvement}}$ = 22.96; $SD_{\text{improvement}}$ = 6.99), compared to patients randomized to their suboptimal treatment ($M_{\text{improvement}}$ = 18.94; $SD_{\text{improvement}}$ = 7.57; $F(1,147) = 11.36$, $p < .001$). The standardized mean difference between optimal and suboptimal treatments corresponded to a medium effect size (Cohen's *d* = .55 [.23, .88]). For the PCL-5, the average error of the predictions was 7.09 (*SD* = 6.16) in the exposure conditions and 7.24 (*SD* = 4.74) in the STAIR+PE condition. Based on the PCL data, a little more than over half of the patients (*n* = 94; 63%) were randomized to their optimal treatment, while *n* = 55 (37%) were not.

Patients randomized to their optimal treatment improved more on the PCL-5 ($M_{improvement}$ = 25.65; $SD_{improvement}$ = 10.04) compared to patients randomized to their suboptimal treatment ($M_{improvement}$ = 20.96; $SD_{improvement}$ = 9.84; $F(1,147) = 7.67$, $p = .006$). The standardized mean difference between optimal and suboptimal treatments corresponded to a medium effect size (Cohen's $d = .47$ [.13, .81]). Figure 2 depicts the distribution of estimated change in PCL-5 and CAPS-5 scores from baseline to post-treatment for patients randomized to their optimal versus suboptimal treatment.

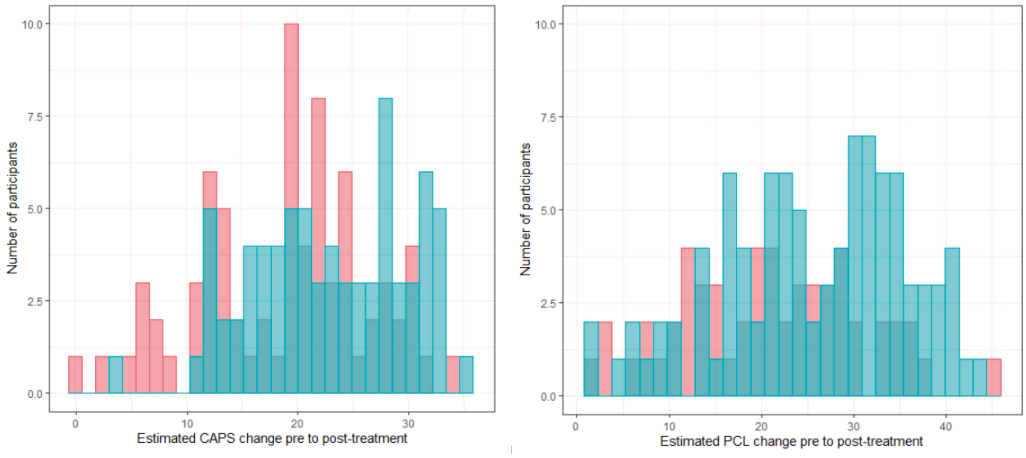

Figure 2. Estimated change in CAPS-5 (left) and PCL-5 (right) scores from baseline to post-treatment for patients randomized in their optimal (blue) and suboptimal (red) treatment condition.

Discussion

This study aimed to identify characteristics of patients with CA-PTSD which predicted treatment outcome in exposure conditions and STAIR+PE, and to evaluate the relevance of the PAI for differential treatment outcome based on the combination of these predictors. Predictors were different in the two conditions, which implies that personalized treatment recommendations have clinical potential. We found that more severe depressive symptoms and less social support were related to worse treatment outcome in the exposure conditions for both clinician-assessed and self-reported PTSD symptoms. For clinician-assessed PTSD symptoms, we also found that more axis-1 diagnoses and more severe childhood sexual abuse were related to worse treatment outcome. For the STAIR+PE condition, we found that more severe emotion regulation difficulties and lower general health status were related to worse treatment outcome for clinician-assessed and self-reported PTSD symptoms. For clinician-assessed PTSD symptoms, we also found that more severe baseline PTSD symptoms were related to worse treatment outcome. Patients randomized to their optimal treatment based on the PAI improved significantly more with medium effect sizes in clinician assessed and self-reported PTSD symptoms compared to patients randomized to their suboptimal

treatment. About half of the patients were randomized to their suboptimal treatment, implying that these patients could have benefitted from randomization based on baseline predictors.

Clinical predictors identified in the current study correspond well to the type of predictors found in previous personalization studies in patients with PTSD. Symptom burden, emotion regulation and social support are consistent indicators for personalization (Cloitre et al., 2016; Deisenhofer et al., 2018; Keefe et al., 2018). In contrast to previous studies, we did not identify demographics that predicted treatment outcome (Deisenhofer et al.; Keefe et al., 2018). This may be related to the larger number of clinical predictor candidates in our study which may be more important for treatment outcome than demographics. Predictors of the exposure conditions correspond to previously identified predictors of PTSD treatment in general. There is considerable evidence for the relationship between more severe depressive symptoms and worse treatment outcome and between less social support and worse treatment outcome of PTSD treatment (Barawi et al., 2020; Dewar et al., 2020). Predictors of STAIR+PE have not been frequently investigated, but the finding that more emotion regulation difficulties predicted worse treatment outcome in this condition seems to contradict a previous study which found that more emotion regulation difficulties relative to symptom burden was related to better outcome in STAIR+PE compared to PE (Cloitre et al., 2016). Since that study used a method which combined several moderators using a different comparator condition than our study (support+PE), results are difficult to compare. However, our finding is notable since STAIR+PE was specifically designed for patients with severe emotion regulation difficulties who might not be able to tolerate and benefit from PE (Cloitre et al., 2002). We found the opposite: more severe emotion regulation difficulties were related to *worse* outcomes in STAIR+PE specifically. Furthermore, many predictors often indicated as relevant for PTSD treatment outcome such as dissociation and personality disorders did not predict worse treatment outcomes for exposure conditions and STAIR+PE. This suggests that only a few predictors might have to be taken into account for relevant personalization recommendations.

Strengths and limitations

Strengths of the current study include the repeated measures of clinician-assessed and self-reported PTSD symptoms, the broad range of predictor candidates including patient expectancies and the robust predictor selection process and use of cross-validation techniques (James, Witten, Hastie, & Tibshirani, 2013). Notably, although we investigated a broad range of characteristics for personalization, the predictors were predominantly self-report questionnaires and similar to previous studies which focused on a limited set of predictors. Moreover, most predictors were consistent for self-reported and clinician-assessed PTSD symptoms, which implies that predictors are robust and not questionnaire specific.

An important limitation of the current study is the sample size, which did not allow for evaluation of the model using a 5-10 fold cross-validation or an holdout sample - a

statistically independent validation sample (see for example: Delgadillo & Duhne, 2020). A recent study showed that the evaluation in a holdout sample might lead to somewhat less optimistic results than the more traditional evaluation within one sample (Schwartz et al., 2020). Since there has been no external validation of personalization models in patients with PTSD yet, future personalization studies should focus on evaluating previously found models in independent samples. Additionally, the PAI was based on the linear combination of predictors in the current study. Some of the predictors identified in the Boruta algorithm but dropped during the bootstrap procedure (e.g. posttraumatic cognitions) might be relevant for treatment outcome in a non-linear manner. Future studies might evaluate how these predictors are related to treatment outcome.

Conclusions

The current study identified predictors of exposure therapies and STAIR+PE and showed that a combination of these predictors is relevant for differential treatment outcomes of patients with CA-PTSD. Future studies could evaluate previously found prediction models in independent samples and perform prospective studies in which patients are randomized based on personalized predictions or routine care (Delgadillo & Lutz, 2020). Notably, a first prospective randomized controlled trial found that treatment strategy recommendations improved treatment outcomes when therapists followed the recommended feedback (Lutz et al., 2021). If personalized predictions lead to significantly better treatment outcomes than routine care, the personalized predictions can be implemented into clinical practice using a system such as the Trier Treatment Navigator and to keep updating the predictions based on previous patients to further improve the prediction models (Lutz, Rubel, Schwartz, Schilling, & Deisenhofer, 2019). In conclusion, this study shows that tailored treatment indications based on a combination of predictors is a promising way to improve treatment outcome for patients with PTSD.

Chapter 7

Temporal relationship between change in subjective distress and PTSD symptom decrease during prolonged exposure therapy for posttraumatic stress disorder

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Abstract

Objective: There is growing evidence that change in distress is an indicator of change during Prolonged Exposure (PE) for posttraumatic stress disorder (PTSD). However, temporal sequencing studies investigating whether change in distress precedes PTSD symptom decline are lacking. These studies are essential since the timeline between indicators of change and treatment outcome is a key assumption for mediation. The aim of the present study was to assess the temporal relationship between within- and between-session change in subjective distress and PTSD symptom decrease.

Method: We analyzed session data from 86 patients with PTSD. Data were analyzed using dynamic panel models. We distinguished temporal effects (within-persons) from averaged effects (between-persons).

Results: Results regarding the temporal effect showed that within-session change in subjective distress preceded PTSD symptom improvement while the reversed effect was absent. Averaged within-session change in subjective distress was also related to PTSD symptom improvement. Results regarding the temporal effect of between-session change in subjective distress showed that it did not precede PTSD symptom improvement. Averaged between-session change in subjective distress was related to PTSD symptom improvement.

Conclusions: This study provides evidence for within- but not between-session change in subjective distress as indicator of change during PE. We also found that the way of modeling potential indicators of change affects results and implications. We recommend future studies to analyze mediators during treatment using temporal rather than averaged effects.

Keywords: PTSD, prolonged exposure, working mechanism, change in distress, temporal sequencing, dynamic panel model

Introduction

Prolonged Exposure (PE) is a widely researched and effective psychotherapy for Posttraumatic Stress Disorder (PTSD), but remission rates leave ample room for improvement (Lee et al., 2016a; Mavranezouli et al., 2020; Watts et al., 2013). Investigating indicators of mechanisms of change, i.e. processes responsible for symptom change, will lead to a better understanding of the theoretical underpinnings of PE and may provide directions for further improvements (Kazdin, 2007; Kindt, 2014). Emotional Processing Theory (EPT) has long been the dominant theory on PE's mechanisms of change (Foa & Kozak, 1986). In short, EPT proposes that prolonged exposure to fear-evoking stimuli leads to emotional processing which in turn leads to symptom alleviation. Emotional processing is not directly measurable (Foa & McLean, 2016), but within-session change in subjective distress and between-session change in subjective distress are suggested to be indicators of change as they indicate emotional processing taking place (Foa & Kozak, 1986; Foa & McLean, 2016).

A large body of work supports the proposition that between-session change in subjective distress[2] is related to positive treatment outcome in patients with PTSD (e.g., Cooper et al., 2017a; see Table 1 for overview), although this work has also been criticized (e.g., Craske et al., 2008). Reasons for this criticism include limited use of complete session data - either by averaging session data or only considering the first and last sessions - and the categorization of outcome in (responder) categories which do not allow for a direct evaluation of the relationship between the indicators of change and outcome (Craske, et al., 2008). Moreover, given that many previous studies had small samples to begin with (see Table 1), results may be unreliable. Most studies found no evidence that within-session change in subjective distress and symptom improvement are related. But note, that these studies suffered from the same limitations as studies into between-session change in subjective distress. Importantly, nearly all of the previous studies considered the *averaged* effect of change in subjective distress (across individuals), referring to the relationship between averaged change in subjective distress across all sessions and treatment outcome. The *temporal effect* of change in subjective distress, referring to the relationship between change in subjective distress at timepoint X and outcome at timepoint X+1 within a person, has rarely been investigated (see Table 1). Temporal effects, however, are much more likely to reflect indicators of change than averaged effects, so the omission of temporal effects is problematic (Falkenstrom, Solomonov, & Rubel, 2020; Kazdin, 2007).

Establishing a timeline between an indicator of change and symptom change is in fact a crucial *prerequisite* for establishing mediation (Hayes, 2013; Kazdin, 2007; Kumpula et al., 2017) and the direction of the relationship between change in subjective distress and symptom change is as yet unclear. Previous results showing that averaged between-session change in subjective distress and symptom change are related may refer to three different

[2] Note that in previous work, the terms *habituation* or *extinction* have been interchangeably used to describe subjective change in distress levels during exposure sessions, while these terms actually refer to theoretically distinct mechanisms. To avoid theoretical confusion , we use the descriptive term change in subjective distress throughout this manuscript

associations: between-session change in subjective distress *precedes* symptom improvement, *co-occurs* with symptom improvement or *follows* symptom improvement. Only the first is relevant from the perspective of mechanisms of change. Secondly, temporal relations are clinically relevant as they provide information about change processes on an individual level. In contrast, averaged effects may be influenced by (unchangeable) covariates at the individual level and are therefore less informative for change processes. For example, patients with high intelligence might have more between-session change in subjective distress and more symptom improvement while these are temporally unrelated to each other. Thirdly, using temporal data has statistical advantages as it results in more power than averaged data and takes covariates at the person level into account. When averaged relationships are generalized to temporal relationships, these covariates may result in biased conclusions (Hamaker, 2012). For example, on average, a higher number of PE sessions might be related to worse treatment outcomes (between-persons). However, this might be due to covariates at the person level, e.g., persons who respond well may finish treatment early. If this averaged result is generalized to a temporal effect one might falsely conclude that providing more PE sessions to a patient leads to poorer treatment outcome.

Almost all studies on the effect of change in subjective distress as indicator of change during PE have used averaged-person data, raising doubts about the conclusions. The only exception is a study about the effect of within-session change in subjective distress on symptom change during D-cycloserine- versus placebo-enhanced PE (de Kleine, Smits, Hendriks, Becker, & van Minnen, 2015). This study is one of only two studies (de Kleine, Hendriks, Becker, Broekman, & van Minnen, 2017; de Kleine et al., 2015) that found a significant relationship between within-session change in subjective distress and PTSD symptom improvement. This raises the question whether earlier null-findings on the effect of within-session change in subjective distress on symptom change might be explained by the data-analytic strategy. Ideally, a study using temporal data would also report on averaged-person relationships as 'control analysis', as this allows a better comparison to previous findings in this field.

The aim of the current study was to investigate whether within- and between-session change in subjective distress is related to PTSD symptom improvement using temporal data. We studied the timeline between change in subjective distress and symptom improvement using dynamic panel models. These models allow for distinguishing temporal effects from averaged effects without violating assumptions (a problem with mixed-model analyses; see Allison, Williams, & Moral-Benito, 2017; Hamaker & Muthen, 2019; Leszczensky & Wolbring, 2019). Based on the premises of EPT, we expected change in subjective distress, both within- and between-sessions to predict next session change in PTSD symptoms. To test temporality, we reversed predictors and outcome, and expected that PTSD symptoms would not – or to a lesser extent – predict subsequent changes in subjective distress within- or between-sessions. To allow comparison with previous studies, we also assessed the averaged-person effect of change in subjective distress within- and between-sessions to elucidate whether

the use of temporal data leads to different results than the use of averaged data. Based on previous findings (Cooper et al., 2017a), we expected averaged change in subjective distress between-sessions, but not within-sessions, to predict PTSD symptom decrease.

Table 1. Evidence for the effect of within- and between-session change in distress as mediators of prolonged exposure

Study	Year	Sample size	Mechanism of change	Within person data mechanism	Within person data outcome	Within-session	Between-session
Norr et al.	2019	108	Within and Between	Not used	Not used	-	+/-
Reger et al.	2019	96	Between	Used	Not used	NA	+
Rauch et al.	2018	97	Within and Between	Used	Not used	-	+
Hendriks et al.	2018	69	Within and Between	Not used	Not used	-	+
Badour et al.	2017	46	Within and Between	Not used	Not used	-	+
De Kleine et al.	2017	50	Within and Between	Not used	Not used	+	+
Wisco et al.	2016	22	Between	Used	Not used	NA	+
Harned et al.	2015	16	Within and Between	Not used	Not used	-	+
Nacasch et al.	2015	39	Within and Between	Not used	Not used	-	+
Sripada et al.	2015	12	Within and Between	Used	Not used	-	+
De Kleine et al.	2015	67	Within and Between	Used[1]	Used[1]	+	+
Bluett et al.	2014	88	Between	Not used	Not used	NA	+
Gallagher et al.	2012	88	Between	Not used	Not used	NA	+
Van Minnen et al.	2006	92	Within and Between	Not used	Not used	-	+
Rauch et al.	2004	69	Between	Not used	Not used	NA	+
Van Minnen et al.	2002	34	Within and Between	Not used	Not used	-	+

[1]Used for within-session but not for between-session change in distress

NA = Not applicable; + = significant finding; - = non-significant finding; +/- = mixed finding

Method

Participants

We used the data from the IMPACT study (Oprel et al., 2018), a multicenter randomized controlled trial comparing PE with intensified PE (iPE) and phase-based treatment

compromising Skills Training in Affective and Interpersonal Regulation followed by PE (STAIR+PE). The trial is registered at the clinical trials registry, number NCT03194113. All participants (1) met DSM-5 diagnosis of PTSD established with the Clinician Administered PTSD Scale (CAPS-5) with moderate-severe PTSD-symptoms (CAPS-5 score ≥ 26) following repeated interpersonal childhood physical/sexual abuse by a primary caretaker or an authority figure and had at least one specific memory of the traumatic event (Boeschoten et al., 2015), (2) were between 18 and 65 years old and (3) spoke Dutch. Participants were excluded when they (1) were involved in a compensation case or legal procedures concerning admission or stay in The Netherlands, (2) were pregnant, (3) engaged in severe non-suicidal self-injury (NSSI) which required hospitalization during the past three months, (4) engaged in severe suicidal behavior defined by either 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) had a severe disorder in the use of alcohol or drugs in the last three months according to the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998), (6) suffered from cognitive impairment (estimated IQ < 70), (7) changed psychotropic medication in the two months prior to inclusion or (8) engaged in any current psychological treatment. Informed consent was obtained prior to randomization from all participants. For this article, we included participants from the exposure only conditions[3]: PE (n = 48) and iPE (n = 51). Patients also had to complete at least two PE sessions with measurements of subjective distress levels and PTSD symptoms, such that a timeline could be established (n_{PE} = 44, n_{iPE} = 42). Most patients were female (79%) and patients had an age between 20 and 60 years old (M = 36.8, SD = 11.5). Almost half (40%) of the patients had a non-western cultural background, 20 percent of the patients were highly educated (i.e. higher vocational education or university), 43 percent of the patients were employed and 51 percent of the patients used psychotropic medication. Patients suffered on average from 3.0 comorbid axis-1 diagnoses (*SD* = 1.9) in addition to the PTSD diagnosis and 47 percent of the patients suffered from severe suicidality according to the MINI (Sheehan et al., 1998). Moreover, 62 percent of the patients met criteria for a personality disorder according to the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-2; Weertman et al., 2003). We refer to the design paper for detailed information about the design, recruitment, participants, procedure or therapy (Oprel et al., 2018) and to the main outcome paper for detailed information about the study sample (Oprel et al., 2021). The study was approved by the Medical Ethical Committee of Leiden University Medical Center (NL57984.058.16).

Procedure

After enrollment, patients were randomized to PE, iPE and STAIR+PE (1:1:1 ratio) by an independent researcher based on a computerized randomization sequence of permutated blocks of six participants stratified by gender. Prolonged exposure (PE) was delivered in 16

[3]The STAIR+PE condition is excluded because it is based on the notion that skills training in the first phase of treatment will increase the tolerability of PE and therefore influences the proposed working mechanism of PE. This precludes conclusions about the working mechanism of PE.

weekly sessions of 90 minutes. Intensive prolonged exposure (iPE) was delivered in 14 sessions of 90 minutes starting with three weekly sessions for four weeks followed by two sessions after one and two months. For practical reasons, iPE was alternately provided by two therapists. The treatment manual of PE and iPE was identical and largely based on the protocol by Foa et al. (2007). The exposure sessions involved psychoeducation in the first session and 60 minutes imaginal exposure and exposure in vivo from the second session onwards. During imaginal exposure, patients were instructed to repeatedly and vividly recount the most disturbing traumatic memories. During exposure in vivo, patients repeatedly approached trauma-related stimuli. Between sessions, patients listened to recordings of the imaginal exposure and performed in-vivo homework assignments. For this paper, data from session 15 and 16 of the PE condition were omitted, because these sessions did not include sufficient observations. The exposure sessions involved psychoeducation in the first session, 60 minutes of imaginal exposure in the second session and 60 minutes of the imaginal exposure and within-session exposure in vivo from the third session onwards. observations for the temporal models (only 18 patients [21%] completed session 15 and 15 patients [17%] completed session 16).

Measures

Weekly changes in PTSD symptoms were assessed during every session of PE and during session 1, 4, 7, 10, 12, 13, and 14 of iPE. Subjective distress levels were assessed during in-session exposure, every session from the second session onwards.

Table 2. Descriptive information about mechanisms of change and outcome as a function of session

	PCL-5			Within-session change in distress			Between-session change in distress		
Session	N	M	SD	N	M	SD	N	M	SD
1	85	54.29	12.72						
2	43	55.93	12.59	86	25.48	23.82			
3	44	54.25	15.74	85	24.94	26.54	85	7.01	14.90
4	83	50.61	15.32	83	22.35	21.00	82	1.77	15.64
5	42	46.95	17.87	79	23.99	21.72	79	5.72	14.74
6	40	46.10	18.42	73	21.63	20.73	74	3.95	21.51
7	73	42.93	18.83	73	20.41	18.76	72	-0.10	16.90
8	35	38.03	21.71	69	18.96	17.63	68	2.81	17.77
9	33	34.94	21.17	64	18.91	19.51	66	2.18	16.28
10	66	36.50	20.42	64	21.20	21.67	63	-0.05	14.96
11	27	32.93	23.60	63	19.52	17.89	62	4.21	19.30
12	62	32.08	20.07	60	19.67	21.30	59	5.24	17.42
13	62	30.35	20.95	56	15.02	16.58	55	6.69	23.53
14	55	30.80	23.10	46	15.07	19.22	48	5.44	21.97

PCL-5 = PTSD checklist for DSM-5

PTSD symptoms

The primary outcome of this study was self-reported PTSD symptom severity measured with the weekly version of the PTSD checklist for DSM-5: PCL-5 (Blevins et al., 2015) . The PCL-5 consists of 20 items scored on a five-point Likert scale, ranging from 0 (not at all) to 4 (extremely), with total scores ranging from 0-80. The PCL-5 demonstrated high internal consistency in previous studies, high test-retest reliability and convergent and divergent validity with other measures (Blevins et al., 2015; Van Praag, Fardzadeh, Covic, Maas, & von Steinbuchel, 2020) and showed substantial agreement with a clinical interview for assessing PTSD in a Dutch population (van der Meer, Bakker, Schrieken, Hoofwijk, & Olff, 2017). The PCL-5 demonstrated high internal consistency in previous studies (Cronbach's α = .94; Blevins et al., 2015). In the current sample, the PCL-5 had a high internal consistency at the first session (Cronbach's α = .89). For the standard PE condition, data was available for 44 patients who completed on average 12.07 sessions (range 3-16, total sum of sessions = 531). The PCL-5 was assessed at the start of every session and completed in 98.5% of the sessions (n = 523). For the iPE condition, data was available for 42 patients who completed on average 12.83 sessions (range 4-14, total sum of sessions = 539). The PCL-5 was assessed at the start of session 1,4,7,10,12,13 and 14 (total sum of sessions with PCL-5 = 265) and completed in 97.7% of the sessions (n = 259).

Change in subjective distress within and between sessions

During the 60 minutes of imaginal exposure of PE (every session except the first session), participants' subjective distress was assessed with subjective units of distress (SUDs). Every 10 minutes, the participants rated their subjective distress on a scale from 0 (no distress) to 100 (maximum distress). The SUD peak was indicated by the highest subjective distress score within a session and SUD end was indicated by the last observed subjective distress score within a session. In line with EPT (Foa & McLean, 2016) and previous work (Harned et al., 2015; Hendriks et al., 2018; Nacasch et al., 2015), change in subjective distress within-session was indicated by the difference between the SUD peak and SUD end of a session. Change in subjective distress between sessions was indicated by the change in SUD peak ratings over two subsequent sessions. In 21 sessions (2.1% of the total exposure sessions) the therapist or patient refrained from performing any exposure in-session, so there was no SUDs data available for those sessions. Of all sessions wherein exposure took place for PE (n = 474), SUDs data were available for 96.0% (n=455) of the sessions. Of all sessions wherein exposure took place for iPE (n = 489), SUD data were available for 97.8% of the sessions (n= 478). For the temporal analyses, we used the data per session for within- and between-session change in subjective distress. For the averaged analyses, data of within- and between-session change in subjective distress was averaged over all sessions per person.

Statistical analyses

The data analysis plan was pre-registered at OSF (Center for Open Science; Hoeboer et al., 2020b). We used dynamic panel models based on maximum likelihood estimation (Allison et al., 2017) following recent recommendations for models with lagged dependent variables

(Falkenstrom et al., 2020; Xu, DeShon, & Dishop, 2019). Models were fitted using structural equation models (SEM) with R package Lavaan and dpm (Rosseel, 2012). In these models, results are corrected for stable, unobserved heterogeneity between persons and reverse causation (Allison et al., 2017). We corrected for the autoregressive effect of the outcome variable (the effect of the outcome at time point X-1 on the same outcome at time point X) and used cross-lagged effects of predictors (the effect of the predictor at time point X-1 on outcome at time point X). We used fixed effect models which included a random intercept that was allowed to correlate with predictors, thereby correcting for the effect of clustering without violating the assumption of independent errors. Missing data was handled using full information maximum likelihood (FIML). The temporal relationship between mediators and outcome is by default estimated with the fixed effect model of the dynamic panel model. We included bootstrapped standard errors in all analyses to account for violations to the normal distribution of the data. This was especially relevant for the analyses with change in subjective distress as dependent variable. The assumptions of all models were met.

Temporal analyses

In the first analysis, we assessed a dynamic panel model with the PCL-5 scores as dependent variable and with the autoregressive effect of the PCL-5 and cross-lagged *within*-session change in subjective distress as independent variables. For example, PCL-5 scores in session 4 were predicted by PCL-5 scores in session 3 and within-session change in subjective distress (SUD_{peak} -SUD_{end}) during session 3. In the iPE condition, participants had multiple sessions per week, while the PCL-5 was administered once per week. Therefore, only the SUDs data that was directly linked to PCL-5 assessment was used from this condition (e.g. session 3 included no PCL-5 score so within-session change in subjective distress from session 2 was not used).

In the second analysis, we assessed a dynamic panel model with PCL-5 scores as dependent variable and with the autoregressive effect of the PCL-5 and cross-lagged *between*-session change in subjective distress as independent variables. To illustrate, PCL-5 scores at session 4 were predicted by PCL-5 scores at session 3 and the change in peak distress between session 2 and 3 ($SUD_{peak\ session2} - SUD_{peak\ session3}$).

As the two exposure conditions differed in their delivery format (weekly vs. intensive) and the delivery format might affect change mechanisms, we ran two additional analyses to investigate the effect of condition on the relationship between change in distress and PCL-5 outcomes. These analyses were carried out using the same model as for the primary analyses, but additionally included condition (PE versus iPE) and the interaction effect between condition and mediators. If condition proved to affect outcomes, analyses were carried out per condition.

To test temporality, we next ran dynamic panel models testing effects in the opposite direction. In the third analysis, we included *within*-session change in subjective distress as dependent variable and the autoregressive effect of *within*-session change in subjective distress and cross-lagged change in PCL-5 scores as independent variables. In the fourth analysis, we included *between*-session change in subjective distress as dependent variable

and the autoregressive effect of *between*-session change in subjective distress and cross-lagged change in PCL-5 scores as independent variables.

Averaged analyses

To test whether using temporal data would lead to different results than using averaged-person data, we performed two analyses with averaged-person effects. The averaged-person effect was estimated using a fixed-effect model including person-averaged mediators. In the first analysis, we assessed a dynamic panel model with PCL-5 scores as dependent variable and with the autoregressive effect of PCL-5 scores and averaged change in subjective distress within-sessions as independent variables. In other words, we assessed the effect of the *average* change in subjective distress on PTSD symptom change over the course of treatment. In the second analysis, we assessed a dynamic panel model with PCL-5 score as dependent variable and with the autoregressive effect of PCL-5 scores and averaged change in subjective distress between sessions as independent variables.

Results

Fifty-five (64%) of the 86 patients who were included in this study completed fourteen sessions. The PCL-5 scores decreased during the course of treatment, from on average 54.24 (*SD* = 12.72) in the first session to on average 30.80 (*SD* = 23.10) in session fourteen. Within-session change in subjective distress showed a large variation between patients and was larger at the start of treatment ($M_{\text{session 2}}$ = 25.48; $SD_{\text{session 2}}$ = 23.82) compared to the end of treatment ($M_{\text{session 14}}$ = 15.07; $SD_{\text{session 14}}$ = 19.22). Between-session change in subjective distress also showed a large variation between patients without clear pattern over the course of treatment ($M_{session\ 3}$ = 7.01; $SD_{\text{session 3}}$ = 14.90 to $M_{session\ 14}$ = 5.44; $SD_{\text{session 14}}$ = 21.97; see Table 2 for more details).

Temporal analyses

We found that within-session change in subjective distress was significantly related to lower PTSD symptoms in the next session (i.e. the temporal effect): *b* = -.04, *SE* = .02, *z* = -2.17, *p* = .03, Cohen's *d* = .48, while correcting for the autoregressive effect of PTSD symptoms (see Table 3). This effect was not different for iPE compared to PE (*b* = .01, *SE* = .05, *z* = .27, *p* = .79). The reversed temporal effect of PTSD symptom change on next session's within-session change in subjective distress was not significant: *b* = -.08, *SE* = .09, *z* = -.85, *p* = .40, while correcting for the autoregressive effect of within-session change in subjective distress.

Table 3. Temporal effect of within-session change in subjective distress on next session's PTSD symptoms and reversed effect of PTSD symptom change on next session's within-session change in subjective distress

Temporal effects	Estimate	SE	*z*-value	*p*-value
Lagged within-session change in subjective distress	-.04	.02	-2.17	.03
Autoregressive effect PCL-5 score	.70	.06	12.37	< .001
Reversed effects				
Lagged change in PCL-5 score	-.08	.09	-.85	.40
Autoregressive effect within-session change in subjective distress	.11	.07	1.75	.08

PTSD = Posttraumatic Stress Disorder; PCL-5 = PTSD checklist for DSM-5

We found that between-session change in subjective distress was not significantly related to lower PTSD symptoms in the next session (i.e. the temporal effect): b = .003, SE = .02, z = .17, p = .86, while correcting for the autoregressive effect of PTSD symptoms (see Table 4). This effect was not different for iPE compared to PE (b = -.03, SE = .04, z = -.73, p = .47). The reversed temporal effect of PTSD symptom change on between-session change in subjective distress in the next session was also not significant b = .05, SE = .12, z = .39, p = .70, while correcting for the autoregressive effect of between-session change in subjective distress.

Table 4. Temporal effect of between-session change in subjective distress on next session's PTSD symptoms and reversed effect of PTSD symptom change on next session's between-session change in subjective distress

Temporal effects	Estimate	SE	*z*-value	*p*-value
Lagged between-session change in subjective distress	.003	.02	.17	.86
Autoregressive effect PCL-5 score	.66	.09	7.78	< .001
Reversed effects				
Lagged change in PCL-5 score	.05	.12	.39	.70
Autoregressive effect between-session change in subjective distress	-.41	.06	-7.56	< .001

PTSD = Posttraumatic Stress Disorder; PCL-5 = PTSD checklist for DSM-5

Averaged analyses

Averaged within-session (b = -.16, SE = .05, z = -3.06, p = .002, Cohen's d = .70) and between-session (b = -.53, SE = .20, z = -2.71, p = .007, Cohen's d = .61) change in subjective distress were both related to lower PTSD symptoms over the course of treatment while correcting for the autoregressive effect of PTSD symptoms.

Discussion

The main goal of this study was to test the effect of change in subjective distress during prolonged exposure (PE) therapy on PTSD symptom improvement using temporal analyses. The results indicated that within- and not between-session change in subjective distress preceded symptom improvement. These findings stand in contrast to the commonly expressed finding that between- and not within-session change in subjective distress is related to better treatment response (e.g., Asnaani, McLean, & Foa, 2016; Brown, Zandberg, & Foa, 2019; Cooper et al., 2017a; Foa & McLean, 2016). Importantly, in the current work we used a new-analytic framework (Allison et al., 2017) and distinguished temporal from averaged effects (Falkenstrom et al., 2020; Hamaker, 2012; Hamaker & Muthen, 2019) which probably explains the divergent findings.

Our first hypothesis, that within-session change in subjective distress would predict change in PTSD symptoms to the next session, was confirmed. Crucially, we did not find the reversed effect. Our findings thus point to within-session change in subjective distress as an indicator of change during PE, as it precedes and predicts symptom improvement (Kazdin, 2007). This finding is in line with EPT, but stands in contrast with most previous studies that examined the effect of within-session subjective change in distress on PE outcome (see Table 1). Notably, these studies used data-analytic strategies which only considered averaged effects. The only other study using temporal data for both within-session change in subjective distress and PTSD symptom change during PE found similar results (de Kleine et al., 2015). Our findings imply that within-session reduction of subjective distress precedes PTSD symptom change during PE. This is of clinical relevance, as in-session indices of change can guide clinicians in their implementation of PE.

In contrast to our expectations, we found that *averaged* within-session change in subjective distress was also related to change in PTSD symptoms. This is remarkable as the data-analytic strategy for this analysis was in line with earlier work, yet leading to a different outcome. Our finding implies that those with, on average, more within-session change in subjective distress showed more change in PTSD symptoms. One important factor that might explain our divergent findings is a difference in statistical power. Notably, about half of the previous studies that assessed within-session change in distress included small sample sizes with less than 40 patients (Harned et al., 2015; Jaycox et al., 1998; Nacasch et al., 2015; Sripada & Rauch, 2015; van Minnen & Hagenaars, 2002). Moreover, these studies mostly defined outcome as a pre-post difference rather than utilizing the repeated measurements per patient (resulting in far less power; e.g., Morgan & Case, 2013), Therefore, these studies lacked adequate power resulting in increased false positive and false negative findings (see for rationale: Button et al., 2013). In line, a recent meta-analysis on change in subjective distress on symptom improvement during PE concluded that there was insufficient power to establish the effect of within-session change in subjective distress on outcome (Rupp, Doebler, Ehring, & Vossbeck-Elsebusch, 2017).

Our second hypothesis, that between-session change in subjective distress predicts change in PTSD symptoms in the next session, was not confirmed, nor did we find the

reversed effect. This finding contradicts previous studies that consistently found between-session change in subjective distress to be related to PTSD symptom change (see Table 1). However, this difference might be explained by our different data-analytic method. Previous studies did not use temporal analyses but assessed averaged effects. Indeed, in line with previous work, we found that averaged between-session change in subjective distress predicted change in PTSD symptoms. As these analyses omit the temporal relationship between indicators of change and outcome, this relationship might be driven by a third factor related to both the indicator of change and outcome (i.e., personal characteristics such as learning ability) or time-congruency of both factors. The latter would imply that between-session change in distress might be a *proxy* of treatment response, rather than an indicator of change (Cooper et al., 2017a). To conclude, our results indicate that between-session reduction in distress does not precede PTSD symptom decline. These results are supported by previous work that showed that patients without between-session change in distress also improved over the course of treatment (e.g., Bluett et al., 2014).

This is the first temporal sequencing study about within- and between-session change in subjective distress as indicators of change during PE. Although temporal precedence is a key assumption which is often overlooked when studying change processes (Kazdin, 2007), it does not in itself suggest a mechanistic relationship. To establish mechanisms of change additional evidence is required such as experimental evidence of cause (see Tryon, 2018). Note that our results also do not imply that within-session reduction of subjective distress is the only indicator of change during PE, as it is likely that multiple change mechanisms explain treatment outcome (Kredlow, de Voogd, & Phelps, 2020; Vervliet, Craske, & Hermans, 2013). Based on novel insights from emotional learning research, the inhibitory learning theory (ILT; Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014) postulates that the learning and retrieval of inhibitory non-threat associations is crucially important for successful treatment outcome. Both EPT and ILT are rooted in extinction theory and partially overlap in theoretical mechanisms (Cooper et al., 2017a), but the theories differ with respect to their view on distress reduction as an index of meaningful change. In short, ILT proposes that distress reduction may be a by-product of inhibitory learning. ILT proposes new indices of meaningful change during exposure therapy such as expectancy violation or enhanced tolerance of distress (Bluett et al., 2014; Craske et al., 2008; Knowles & Olatunji, 2019; Sripada, Rauch, & Liberzon, 2016). Future studies might test whether these indices also precede and fuel PTSD symptom decrease, and how they relate to distress reduction. Moreover, EPT also proposes other indices of emotional processing such as emotional engagement. Strong empirical evidence for the relevance of emotional engagement is lacking (Cooper et al., 2017a), but so are temporal studies assessing its relevance. Thus, future studies might also examine such indices with temporal models.

An already previously established indicator of change during PE is the reduction of maladaptive trauma-related cognitions (Cooper et al., 2017a). In studies focusing on trauma-related cognitions (e.g. “the world is dangerous” or “I have no future”), mixed-effect models including temporal data have already been successfully used to establish the timeline

between these cognitions and PTSD symptom improvement (Cooper, Zoellner, Roy-Byrne, Mavissakalian, & Feeny, 2017c; Kumpula et al., 2017; Zalta et al., 2014). Changes in trauma-related cognitions were found to be related to symptom improvement during PE and to precede symptom improvement. Our current findings add to these findings as within-session change in subjective distress also predicted and preceded symptom improvement during PE. An important next step is to test several indicators of change simultaneously in one model, to better understand how they (interactively) lead to symptom PTSD change. In light of the recent developments in the availability of statistical algorithms to adequately model temporal data and lagged effects (e.g. using dynamic panel models; Rosseel, 2012), we also urge future studies into mechanisms of change to take temporality into account and distinguish averaged relationships (between-persons) from temporal relationships (within-persons). Note that already collected data might also be re-analyzed using temporal sequencing models to improve understanding about within- and between-session change in subjective distress as indicators of change during PE. Future studies might also consider the use of experience sample and ecological momentary assessments to establish a timeline between indicators of change and symptom change more precisely (see for example: Padovano & Miranda, 2018).

The current study has several limitations. Firstly, the intensified PE condition in our study did not have session data available for every exposure session and included only fourteen PE sessions. This resulted in less temporal precision in this condition, less data and consequently less power. Secondly, the panel data in our study was unbalanced due to missing data which is inherent to clinical trials but reduces statistical power (Moral-Benito, Allison, & Williams, 2019). This was especially problematic for session 15 and 16 of the PE condition which were therefore omitted for the analyses. Related to this, the current sample size did not allow for assessing multiple indicators of change in one dynamic panel model. Future studies may consider including other relevant predictors of symptom improvement in dynamic panel models such as homework adherence (Cooper et al., 2017b). Finally, the assessment method of change in distress in the current study (subjective self-reportage) differs from methods used in controlled laboratory research on underlying mechanisms of fear extinction which commonly include physiological indicators of distress (Carpenter, Pinaire, & Hofmann, 2019). Physiological measures of distress might, therefore, be an important additional indicator of change in distress and have already been shown to relate to treatment response in previous research (Wangelin & Tuerk, 2015).

To conclude, we found that within, but not between-session change in subjective distress predicted next session's change in PTSD symptoms using temporal data. Against contemporary belief, these results indicate that within-session change in subjective distress is an indicator of change during PE. This suggests that within-session change in subjective distress could be used to monitor treatment progress. Since this is the first study to investigate temporal relationships between change in subjective distress and PTSD symptom change, more research is needed to replicate these findings.

Chapter 8

Summary and discussion

Prolonged Exposure (PE) is an established and effective guideline treatment for posttraumatic stress disorder (PTSD) and has been studied in many samples across different types of traumatic events and backgrounds. Nevertheless, a considerable number of patients drop out from treatment or do not (completely) recover from PTSD during PE. This raises the question whether treatment effectiveness may be improved by adapting PE. Moreover, treatment outcomes may be improved by better treatment allocation (i.e. for which patients is PE effective and for which patients not) and better understanding of the active ingredients of PE (i.e. how does PE result in a symptom decrease). More specifically, it has been suggested that several populations are at risk for suboptimal treatment outcomes. These include patients who developed PTSD related to childhood abuse (CA-PTSD), patients with prominent dissociative symptoms alongside PTSD and patients with Complex PTSD (CPTSD). Empirical evidence to substantiate these claims is imperative for better treatment indications. Additionally, treatment outcomes may be improved by allocation of patients to their best fitting treatment. This may be done by calculating the relative benefit of PE compared to alternative treatments for individual patients based on a combination of predictors of treatment outcome. Finally, although many studies into mediators of PE have been published, temporality is often ignored as well as a focus on within-person relationships (effect of change in mediator in a session and outcome in the next session within a person) while both are crucial for understanding how PE works.

The main aim of this dissertation was to improve treatment outcomes for patients with CA-PTSD. In order to achieve this aim, we designed the IMPACT study, comparing standard PE with two innovations: intensified PE (iPE) and skills training in affective and interpersonal regulation followed by PE (STAIR+PE). We studied the overall effectiveness and investigated for whom and how these treatments work. In this chapter, we summarize and discuss the results of studies included in this dissertation and reflect on their implications and limitations. Thereafter, we provide a general discussion and conclusion about the improvement of PTSD treatment outcome for patients with CA-PTSD.

Summary of main findings

Chapter 3: Main outcomes of the IMPACT study

In Chapter 3, we presented the main outcomes of the IMPACT study. We randomly assigned 149 patients to PE (*n* = 48), iPE (*n* = 51) and STAIR+PE (*n* = 50). Both PE, iPE and STAIR+PE led to large improvements in PTSD symptoms from baseline to 1-year follow-up. In contrast to our expectations, STAIR+PE and iPE did not lead to more improvements in self-reported and clinician-assessed PTSD symptoms than PE. iPE led to faster improvements in self-reported PTSD symptoms compared to PE and STAIR+PE and to faster improvements in clinician-assessed PTSD symptoms compared to STAIR+PE but not compared to PE. Moreover, STAIR+PE did not result in more improvements in commonly defined comorbid problems with emotion regulation, interpersonal problems and self-esteem from baseline to 1-year follow-up compared to PE and iPE. iPE and STAIR+PE also did not result in lower dropout rates than PE. Hence, we conclude that iPE and STAIR+PE did not improve overall outcomes

of PE, although iPE led to faster symptom improvements. The treatments were all effective in reducing PTSD and PTSD-related symptomatology.

The main aim of the IMPACT study was to improve treatment outcomes of PE for patients with CA-PTSD. Overall, we found large effect sizes of the three treatments on PTSD symptoms and related symptomatology. Hence, patients with CA-PTSD can be effectively treated with any of these three treatments. We also found that iPE led to fast symptom improvement within four weeks, so quick symptom relief can be established with intensified treatment in this population. However, the treatment innovations did not improve overall outcomes of PE. Importantly, we found that PE was very effective in patients with CA-PTSD in contrast to our expectation that this population would need different treatment options (Oprel et al., 2018). Previous studies have shown that PE is underutilized and that comorbid problems especially in combination with childhood trauma history might lead therapists to refrain from providing PE (Becker et al., 2004; van Minnen et al., 2010). A recent qualitative study about the use of trauma-focused treatment in patients with CA-PTSD also concluded that therapists might sometimes avoid the use of a trauma-focused treatment such as PE in patients with CA-PTSD because of the notion that these patients might not be able to tolerate this treatment (de Haan et al., 2021). This same notion was one of the reasons to conduct this study, but we found that patients with CA-PTSD benefitted well from PE and were able to tolerate the treatment. Even more, patients with CA-PTSD were well able to tolerate an intensive form of PE and benefitted even faster with this form of treatment compared to standard PE and skills training followed by PE. The key towards improving treatment outcomes of patients with CA-PTSD in clinical practice might, therefore, be to increase the utilization of PE for this population. Hence, it is imperative that future studies focus on effective dissemination and implementation of PE.

Although the current study included a fairly large sample for a clinical trial in patients with CA-PTSD (a meta-analysis in CA-PTSD included 16 studies with an average sample size of 78 patients and only two of these studies included a sample size larger than ours; Ehring et al., 2014), we were not powered to detect very small differences between treatments. Given the current results, one might wonder whether replication in a larger sample might show that one of the three treatments is somewhat more effective than the others. Although a larger sample size has many advantages (e.g., for prediction, moderation and mediation studies; Gold et al., 2017), the clinical benefit of focusing on small differences between treatments is debatable (Bhardwaj, Camacho, Derrow, Fleischer, & Feldmann, 2004; Markowitz, 2016). Rather than focusing on these small differences between treatments on a group level, it may be more interesting to focus on the almost 50% of the patients who did not lose their PTSD diagnosis after treatment and about a quarter of the patients who did not respond to the treatment at all. How may treatment outcome be improved for *these* patients? Possibly, characteristics such as dissociative symptoms, or meeting criteria for Complex PTSD (CPTSD) predict who is unlikely to benefit from treatment. We also consider the fact that patients may not have been randomized to their 'best fitting' treatment. In other words, some patients may be more likely to benefit from PE, while others are more

likely to benefit from STAIR+PE. If we are better able to predict treatment outcome on an individual level, better treatment allocation might further improve treatment outcomes. Finally, we also focus on the treatment process itself. Changing treatment content or augmenting effective elements may improve treatment outcome. In the next chapters, we will address these approaches and their potential for enhancing treatment outcome.

Chapter 4: Meta-analysis about the influence of dissociation on psychotherapy outcome in PTSD

Chapter 4 described a meta-analysis which summarizes the impact of dissociative symptoms on the effectiveness of psychotherapy for patients with PTSD. The meta-analysis included 21 studies with a total of 1714 patients. We extracted the correlation coefficient between baseline dissociative symptoms and change in PTSD symptoms from baseline to post-treatment from each study. Moreover, we extracted some study characteristics which may be related to the influence of dissociation on treatment outcome: trauma focus of the treatment, design of the study (randomized controlled trial; yes or no), sample size and risk of bias. We found no evidence that dissociative symptoms influenced the effectiveness of psychotherapy in patients with PTSD. We also found no evidence for publication bias. There were some differences among studies in the effect of dissociation on treatment effectiveness, but we did not identify study characteristics related to the effect of dissociation. We conclude that dissociative symptoms did not reduce effectiveness of psychotherapy in patients with PTSD.

Given the large number of clinical trials of PTSD, it would have been interesting to perform an individual patient data meta-analysis which allows for standardized, intention-to-treat analyses across studies (Riley, Lambert, & Abo-Zaid, 2010). This would have allowed for testing the linearity of the relationship between dissociative symptoms and treatment outcome, which has been debated in previous research (Bryant, 2007). However, the process of collecting data from individual studies is time consuming and sharing data is not yet common for every researcher. During our study, we received data from fewer than half of the contacted researchers for our meta-analysis while we sent numerous reminders.

What do these results imply for clinical practice? The absence of an impact of baseline dissociation on the effectiveness of psychotherapy for PTSD implies that patients who suffer from PTSD and dissociative symptoms can - and should - receive evidence-based psychotherapy such as PE for their PTSD symptoms. A previous survey study showed that about half of the therapists consider dissociative symptoms a contraindication for the use of PE (Becker et al., 2004). It is crucial for future studies to evaluate whether this is still the case and if so, to study reasons for this and to educate therapists about the non-existing relationship between dissociative symptoms pre-treatment and treatment effectiveness.

For now, we only focused on dissociative symptoms measured pre-treatment, but we do not know how dissociative symptoms occurring during the sessions influence treatment outcome. Hypothetically, dissociative symptoms during a therapy session could reduce emotional engagement (thought crucial for effective trauma processing, EPT; Foa & Kozak,

1986) and this could subsequently reduce symptom improvement. Indeed, one small study found that dissociative symptoms during treatment predicted treatment outcome while pre-treatment dissociative symptoms did not (Kleindienst et al., 2016). This study also assessed whether conceptualization of dissociation (baseline versus during treatment) was relevant for predicting treatment outcome by comparing the proportion of explained variance by trait and state dissociation but did not find a significant difference between the two conceptualizations. Future studies are encouraged to assess the impact of dissociative symptoms during trauma-focused treatment sessions in an adequately powered sample.

Chapter 5: Complex PTSD as predictor and moderator of treatment outcome

In chapter 5, we presented the results of a study into the relevance of Complex PTSD (CPTSD) as predictor and moderator of treatment outcome of PE, iPE and STAIR+PE. We hypothesized that CPTSD would predict worse treatment outcome across the three treatments and that CPTSD would lead to better effects in STAIR+PE compared to PE and iPE, because patients with CPTSD may not be able to tolerate PE while the STAIR phase of STAIR+PE addresses these CPTSD symptoms before the PE phase (Cloitre et al., 2002). We assessed the relevance of the CPTSD diagnosis and severity of CPTSD symptoms, i.e., emotion regulation difficulties, interpersonal problems and low self-esteem, and used clinician-assessed PTSD symptoms as main outcome (CAPS-5). We found that many patients in our sample met criteria for the CPTSD diagnosis (54%) and that CPTSD was related to comorbidity and more severe PTSD symptoms at baseline. Notably, CPTSD did not predict nor moderate treatment outcome. Results were similar in sensitivity analyses with PTSD symptoms according to the ICD-11 as outcome, in a subsample of patients who met diagnosis of PTSD according to the ICD-11 and in analyses with ICD-11 PTSD severity and other significant baseline differences between PTSD and CPTSD patients included as covariates. Hence, we concluded that CPTSD is related to more severe symptoms at baseline, but that CPTSD is no predictor or moderator of treatment outcome. This implies that patients with CPTSD can be effectively treated with the three variants of exposure therapy in this study.

In Chapter 5, we focused on the relevance of CPTSD for treatment indications. Given the consistent finding that many baseline patient characteristics do not consistently determine treatment outcome and do not contraindicate the use of trauma-focused treatment (e.g., Hoeboer et al., 2020c; van den Berg et al., 2015; van Minnen et al., 2012; van Toorenburg et al., 2020), it may be worthwhile to investigate continued treatment of those who still meet PTSD criteria *after* trauma-focused treatment. Since patients with CPTSD start and end treatment with more PTSD symptoms than patients with PTSD, this is especially relevant for these patients. Although some studies on the effectiveness of a second treatment for non-responders have been carried out, these studies rarely investigated the effectiveness of a consecutive or prolonged treatment directly after the first in the same trial but rather included a sample of treatment-resistant PTSD patients based on retrospective self-reports (Fonzo, Federchenco, & Lara, 2020; Starke & Stein, 2017). Furthermore, the definition of treatment-resistance varied among studies (Sippel,

Holtzheimer, Friedman, & Schnurr, 2018). Including a treatment resistant PTSD sample based on retrospective reporting about the content and results of the first treatment has limitations since it is difficult to ensure that the first treatment was performed adequately (including dosage, duration, content). A standardized clinical interview developed to assess treatment-resistance can help to overcome these difficulties (Dunlop, Kaye, Youngner, & Rothbaum, 2014). Also note that studies based on such samples are unable to answer many questions relevant for clinical practice (e.g., should the same therapist continue treatment after lack of response or could another therapist lead to better results?). Therefore, future clinical trials may include multiple phases: a first phase of trauma-focused treatment followed by a second phase for those who still meet PTSD criteria. This second phase may include treatment continuation for those who already show some response in the first phase (see: Sripada et al., 2020), but also a shift to another evidence-based psychotherapy (with or without therapist shift). Note that the sequence of interventions is also relevant to investigate (Van Minnen, Voorendonk, Rozendaal, & de Jongh, 2020).

Chapter 6: Personalization of treatment based on a combination of predictors of treatment outcome

Chapter 6 included the results of a personalization study of the treatment for patients with CA-PTSD. The aim of the study was twofold. Firstly, we aimed to identify relevant predictors of treatment outcome in PE and iPE and STAIR+PE. Secondly, we aimed to combine these predictors into a personalized advantage index (PAI) and to evaluate its relevance for differential treatment outcome. Outcomes of this study were clinician-assessed (CAPS) and self-reported (PCL-5) PTSD symptom severity. We used random forests followed by a bootstrap procedure to identify predictors and we used leave-one-out cross-validation to determine the relevance of the PAI. We found that more depressive symptoms, less social support, more axis-1 diagnoses and higher severity of childhood sexual abuse were predictors of worse treatment outcomes in PE and iPE. More emotion regulation difficulties, lower general health status and higher baseline PTSD symptoms were predictors of worse treatment outcomes in STAIR+PE. If patients were allocated to their retrospectively identified optimal treatment based on these predictors, their improvement was larger than in the suboptimal treatment, with a medium effect size. Hence, personalization is a promising technique to improve treatment outcome by matching patients to their optimal treatment.

Although the results were promising, the current dataset did not allow for a holdout validation set (see for example: Schwartz et al., 2021), which allows for more reliable validation of the PAI algorithm compared to cross validation approaches. This is especially relevant as we identified predictors in the same dataset in which we assessed the benefit of allocation based on these predictors in a PAI algorithm (Kriegeskorte, Simmons, Bellgowan, & Baker, 2009; Lorenzo-Luaces, Peipert, Romero, Rutter, & Rodriguez-Quintana, 2020). Consequently, the statistical model used to provide the PAI has to be validated in future studies. Also note that it is unclear how well results from one sample and treatment center

generalize to other samples and treatment centers. Therefore, in addition to a holdout set (which is generated with the same recruitment procedure as the original dataset) it is important to validate results in a new study with another recruitment procedure.

Ultimately, the effects of treatment indications on treatment outcome based on a statistical algorithm need to be compared to routine clinical care. Most likely, clinicians intuitively use some form of treatment personalization (e.g., Bruijniks, Franx, & Huibers, 2018), and it needs to be established whether the statistical algorithm is superior to this intuitive allocation process. Based on the current work, this is worthwhile to investigate as the statistical algorithm showed potential for predicting differential treatment outcomes while some of the often intuitive predictors of (differential) treatment outcome for therapists such as dissociative symptoms and Complex PTSD (Becker et al., 2004; Cook, Dinnen, Simiola, Thompson, & Schnurr, 2014; van Minnen et al., 2010) were not related to (differential) treatment outcomes in our studies (see Chapter 4 and Chapter 5). In order to establish the benefit of personalization compared to routine clinical practice, prospective studies are required in which patients are randomized to treatments based on a PAI algorithm or routine practice. Currently, two prospective trials are carried out in patients with anxiety and depression (Delgadillo, 2018; Lutz, Zimmermann, Muller, Deisenhofer, & Rubel, 2017). In these studies, a condition with personalized treatment recommendations indicating the optimal treatment for a patient based on a statistical algorithm is compared with a control condition without these personalized treatment recommendations. In PTSD, several personalization studies have now been published (Cloitre et al., 2016; Deisenhofer et al., 2018; Keefe et al., 2018), so we expect that prospective trails in PTSD patients will soon be carried out.

Chapter 7: Temporal relationship between change in subjective distress and PTSD symptom decrease during prolonged exposure therapy for posttraumatic stress disorder

In chapter 7, we described the results of a mediation study using temporal sequencing to establish the timeline between change in subjective distress – a proposed mediator of PE – and symptom change. The aim of this study was to get better insights in the mechanisms of change of PE. In order to achieve this, we 1) investigated the temporal relationship between change in subjective distress and symptom change and 2) distinguished within from between-person effects in this relationship. Only within-person effects are likely to reflect (indices of) mechanisms of change (Falkenstrom et al., 2020). We assessed subjective change in distress within sessions (change in distress from peak to the end of a session) and subjective change in distress between sessions (change in distress from the peak of one session to the peak of the next session). We hypothesized that both subjective change in distress within and between sessions would temporally precede symptom improvement while we did not expect the reversed effect of symptom improvement on change in subjective distress. We also hypothesized that averaged between-, but not within-, session change in subjective distress would be related to symptom improvement over the course of treatment.

We found that within-session change in subjective distress preceded and predicted symptom improvement in the temporal analyses, while between-session change in subjective distress did not. This implies that within-session change in subjective distress is important to track during PE sessions. Interestingly, we also found an averaged effect of within-session and between-session change in subjective distress on symptom improvement over the course of treatment. Thus, between-session change in subjective distress explains variance between, but not within, persons and is therefore unlikely to mediate symptom improvement. Instead, person characteristics may lead to both between-session change in subjective distress *and* symptom improvement. Alternatively, between-session change in subjective distress might be a proxy of symptom improvement, so both occur at the same time thereby explaining the absence of any temporal relationships (Cooper et al., 2017a).

Change in distress was proposed as indicator of change during PE a few decades ago (Foa & Kozak, 1986) and many studies have been carried out to assess its relevance (Badour et al., 2017; Bluett et al., 2014; de Kleine et al., 2017; de Kleine et al., 2015; Gallagher & Resick, 2012; Harned et al., 2015; Hendriks et al., 2018; Jaycox et al., 1998; Nacasch et al., 2015; Norr et al., 2019; Pitman et al., 1996; Rauch et al., 2018; Reger et al., 2019; Sripada & Rauch, 2015; van Minnen & Foa, 2006; van Minnen & Hagenaars, 2002; Wisco et al., 2016). However, some of the key criteria of mediators proposed by Kazdin (2007) have not yet been investigated in this field, such as temporality and causality. Therefore, we focused on the temporal relationship between change in distress and symptom change during PE. Although this addresses an important omission in the literature, more studies are needed to provide more definitive answers about the indicators of change during PE. For example, recent insights in emotional learning research indicate that emotional processing as key mechanism of change of PE might not only refer to a change in existing associations in the fear network, but also include a more active process involving learning and retrieval of novel inhibitory non-threat associations (Craske et al., 2008; Craske et al., 2014). To reflect this active learning component, novel indicators of change are introduced such as expectancy violation. Temporal studies investigating expectancy violation and PTSD symptom change might unravel whether expectancy violation also precedes PTSD symptom improvement. Importantly, we do not yet know how indicators of mechanisms of change relate to each other since they are all investigated in separate studies. For example within-session change in subjective distress and expectancy violation might both be indicators of change during PE explaining another part of treatment outcome independent of each other (so called parallel mediators), but within-session change in subjective distress may also lead to expectancy violation which in turn leads to symptom improvement or vice versa (serial mediators; Hayes, 2013). Within-session change in distress might also be the result of expectancy violation without explaining treatment outcome on itself or vice versa. In other words, when testing multiple potential mediators some might turn out to be a proxy for other mediators and become redundant. Hence, an important next step for future studies is to test multiple mediators in one model using temporal analyses.

General discussion

How promising are the results of the IMPACT study?

In the IMPACT study, we found that the three variants of exposure therapy resulted in large improvements in PTSD symptoms and other comorbid problems in patients with PTSD related to childhood trauma (see Chapter 3). During the course of the trial only a few adverse events occurred mostly unrelated to the treatment which indicates that this patient population is well able to tolerate exposure therapy even in an intensified form. These results are promising as it has been argued that patients with PTSD resulting from childhood trauma (CA-PTSD) might not be able to tolerate exposure therapy (Cloitre et al., 2002) or might be at risk for suboptimal treatment outcomes (e.g., Karatzias et al., 2019b). Does this mean that the results are promising for all patients with CA-PTSD? Although the effect of the three therapies on PTSD symptoms was large (Cohen's *d* > 1.6), many patients (52%) had an unfavorable outcome: they did not respond to treatment (~30%), did not lose their PTSD diagnosis (~40%) and/or dropped out prematurely (~25%). How do these results compare to similar therapies for (CA-)PTSD?

First, let us discuss the effect size. Note that we could only report uncontrolled (within-group) effect sizes as we compared three active treatments for PTSD without control condition. The effect sizes of the therapies in the current study for PTSD symptoms (Cohen's *d* > 1.6; Hedges *G* = 1.59) were relatively large compared to uncontrolled (within-group) effect sizes of psychotherapy for PTSD in patients with CA-PTSD (Hedges G = 1.24; Ehring et al., 2014) and comparable to PE in PTSD in general (Cohen's *d* = 1.57; Bradley et al., 2005). Hence, the effects of the three variants of exposure therapy on PTSD symptoms in the IMPACT study are comparable to treatment effect in PTSD in general, and thus do not suggest hampered effectiveness for those suffering from PTSD following childhood trauma specifically.

Secondly, let us consider the incomplete response to treatment. Both the percentage of patients who did not respond to treatment (~30%) or did not lose their PTSD diagnosis in the IMPACT study (~40%) is comparable to PTSD in general where previous meta-analyses showed that about 37% of the patients did not respond to treatment (Loerinc et al., 2015) and 44-47% of the patients did not lose their PTSD diagnosis (Bradley et al., 2005; Springer, Levy, & Tolin, 2018). These results do not suggest reduced treatment response or loss of diagnosis in CA-PTSD. If anything, patients in our trial have responded to a greater degree to treatment than patients in previous PTSD trials. However, the finding that about half of the patients did not lose their PTSD diagnosis is still worrying and indicates that further improvement of the treatment for these patients is worthwhile to investigate.

Thirdly, let us elaborate on the dropout rates. Reducing drop-out was one of the motivating forces for setting up the IMPACT trial since a meta-analyses indicated that dropout rates in patients with CA-PTSD are relatively high (24%; Ehring et al., 2014) compared to PTSD in general (18%; Lewis et al., 2020). Our results show a dropout rate of 25% from the three variants of exposure therapy. This is similar to dropout rates in CA-PTSD

in previous studies (Ehring et al., 2014), but relatively high compared to PTSD in general (Lewis et al., 2020). Hence, the treatment innovations did not improve the relatively high dropout rates in patients with CA-PTSD. Is dropout, however, always an unfavorable outcome? It is commonly believed that patients terminate treatment prematurely because it is ineffective, too burdensome or emotionally demanding and that dropout is therefore a negative outcome (Najavits, 2015; Schottenbauer, Glass, Arnkoff, Tendick, & Gray, 2008; Szafranski, Smith, Gros, & Resick, 2017). However, a recent study indicated that many patients who drop out actually *improved* (Szafranski et al., 2017). In our study, we found that from the total dropouts (37 patients), six patients dropped out before the start of treatment, eight patients dropped out for practical reasons such as moving to another house or starting a new job and five patients dropped out due to improvements. Only eight patients dropped out due to burden of the treatment or lack of improvements and for ten patients dropout reasons were unknown. Therefore, dropout was not necessarily an adverse outcome for about half of the patients in our trial. It would be interesting to compare this with previous studies, but definition of dropout differs substantially between studies and reasons for dropout are often not reported (Lewis et al., 2020). We encourage future studies to document reasons for dropout to facilitate a more meaningful comparison between studies.

To summarize, the results of the IMPACT study were promising in the sense that the three treatments led to large improvements in PTSD symptoms and comorbid problems while adverse events were rare and incomplete response was comparable to previous studies in PTSD in general.

Dropout rates from the three treatments in the IMPACT study were relatively high but not necessarily a negative outcome. Hence, these three forms of exposure therapy are effective treatment options for patients with CA-PTSD. Since the treatments were not effective for all patients, further attempts to improve treatment outcome for those who do not benefit from treatment are important.

Choosing the right track

We could not confirm the (differential) effect of Complex PTSD and dissociation on treatment outcomes, despite their prominence in clinical and diagnostic manuals (Berliner et al., 2019; Brewin, 2019; Friedman, 2013). This raises the question of what empirical evidence formed the basis for these new constructs. In the case of Complex PTSD and the dissociative subtype, evidence primarily included neurobiological studies about differences in brain activation, studies showing that these constructs were related to a more severe clinical condition (e.g., high comorbidity and impairment) and studies showing that these constructs are related to specific symptom profiles (e.g., latent class analyses). For both constructs, there was also a clear reasoning explicating how they could be relevant for treatment indications. Patients suffering from dissociative symptoms have problems with overmodulation of affect which reduces emotional engagement, one of the proposed change mechanisms of PE (Lanius et al., 2010). Patients with Complex PTSD suffer from emotion regulation difficulties and therefore might not be able to tolerate PE (Cloitre et al.,

2002). But do differences in brain activation, comorbidity, impairment and symptom profiles necessarily lead to differences in treatment effectiveness? Current evidence suggests that this is not the case (Barawi et al., 2020; Dewar et al., 2020). Up until now, there is almost no evidence for the relevance of brain activation and impairment for treatment outcome in terms of PTSD symptoms (see for exception: Fonzo et al., 2017). For comorbidity, current evidence suggests that *some* comorbid conditions might be relevant for treatment outcome such as depression (Barawi et al., 2020; Dewar et al., 2020), while many comorbid disorders (e.g. personality disorders) are not investigated or not related to treatment outcome (Dewar et al., 2020). There is also mixed evidence for the relevance of specific symptom profiles or more severe PTSD symptoms at baseline (Barawi et al., 2020; Dewar et al., 2020). Hence, there seems to be a gap between on the one hand theory and evidence about the manifestation of new types of pathology and on the other hand evidence about the relevance of these constructs for treatment outcome. This gap can become problematic for both research and clinical practice. Researchers may decide to use these constructs as exclusion criteria for clinical trials testing PTSD treatment because of their alleged effect on treatment outcome, thereby limiting generalization to this population without empirical basis (see for example of dissociation: Greenwald, McClintock, & Bailey, 2013). Clinicians may believe that these constructs are contraindications for the use of first line psychotherapy, thereby denying these patients effective treatment (Becker et al., 2004; Cook et al., 2014; van Minnen et al., 2010).

Can a data-driven, personalized, approach narrow this gap between manifestation of (sub)types of pathology and their relevance for treatment outcome? Rather than first developing a theory about the way novel types of pathology may affect treatment indications, we may start (data-driven) by investigating how a combination of patient characteristics predicts or moderates treatment outcomes. On the one hand, personalization is often referred to as a revolution with the potential to finally improve treatment outcomes (e.g., Hollon, Cohen, Singla, & Andrews, 2019). Personalization has been extensively studied in the field of medicine for more than two decades (Welch & Kawamoto, 2013) and resulted in new clinical decision support tools (Jameson & Longo, 2015; Welch & Kawamoto, 2013; Ziegler, Koch, Krockenberger, & Grosshennig, 2012). On the other hand, current personalization literature has limitations and there are many omissions in our knowledge about the potential of personalization (see for overview: Lorenzo-Luaces et al., 2020). For example, recent attempts to replicate personalization algorithms in new independent datasets found no statistical difference between optimal versus suboptimal treatment in depressed patients (Van Bronswijk et al., 2021). In the field of medicine, challenges are similar including a lack of prospective studies (Goetz & Schork, 2018; Welch & Kawamoto, 2013; Ziegler et al., 2012) and implementation challenges (e.g., Jameson & Longo, 2015; Rodon et al., 2015). In some way, in the field of psychology the challenge might be even more complex since in addition to the variation between patients, we also have to deal with variation between therapists, for example in experience and attitudes towards the treatment (e.g., Lingiardi, Muzi, Tanzilli, & Carone, 2018; Lorenzo-Luaces et al., 2020; Lutz et

al., 2021). In fact, a recent prospective RCT found no differences between a treatment as usual condition and condition with personalized treatment recommendations, based on initial impairment and chronicity, previous treatments and treatment expectancy. Of interest, they also found that therapists often did not adhere to the personalized treatment recommendations. Only when the therapists followed the personalized recommendations, this condition led to better outcomes (Lutz et al., 2021). In this study, therapists received feedback on treatment recommendations at the start of treatment and treatment adaptations for patients at risk for nonresponse based on statistical algorithms. Lutz and colleagues found that therapists attitude and confidence in the feedback system predicted treatment outcome. Hence, therapists' factors are important to take into account for future research and implementation of personalization algorithms. To conclude, a data-driven approach may be able to narrow the gap between manifestation of (sub)types of pathology and their relevance for treatment outcome, but its relevance for therapists in clinical practice is not established yet. Prospective studies, replication studies and implementation studies are first needed to demonstrate that a data-driven approach is superior to clinical decision making and feasible to implement in clinical practice.

Given these different sources of information for treatment outcome of psychotherapy, future studies might consider combining these for better predictions (e.g., Zilcha-Mano & Errazuriz, 2017). For example, personalization algorithms may provide initial treatment recommendations based on baseline patient and therapist characteristics. Thereafter, patients may follow a few (pilot) sessions with measurements of indicators of change, therapist characteristics and patient reported outcome. The combination of all this data is likely to result in better predictions of treatment outcome compared to only using baseline data. Early treatment responses have been found to be a reliable indicator of later treatment success (Beard & Delgadillo, 2019). When this indeed is confirmed, a next step could be to study whether early recommendations with respect to treatment continuation (for example, changing therapist or treatment) may improve treatment outcome. This data-informed feedback might help to improve treatment effects and allow for early changes in the treatment process.

Since more research is needed for treatment indications based on a data-driven approach, therapists cannot use this information yet in clinical practice. We propose that for now, it is important for clinicians to primarily rely on empirical evidence from prediction and moderation studies as basis for conclusions about treatment indications (Kraemer, 2016). Note that preferably a meta-analysis summarizing evidence from prediction and moderation studies should be used for definite conclusions since solely relying on single studies will probably lead to an overestimation of the relevance of predictors and moderators due to publication bias (Thornton & Lee, 2000). Previous survey studies showed that many therapists have beliefs about potential contraindications for treatment without empirical evidence to substantiate these beliefs (Becker et al., 2004; Cook et al., 2014; de Haan et al., 2021; van Minnen et al., 2010). These beliefs can be harmful when they lead to undertreatment of (a group of) patients. For researchers, these therapists' beliefs are a great

source of inspiration for research into predictors and moderators. Although therapists' beliefs about potential contraindications for treatment should not be a basis for clinical decisions on itself, they should be the basis for research which can support clinical decision-making.

Recommendations for future research

In the treatment of anxiety and mood disorders, within-treatment variation of responsiveness tends to be much larger than the difference in effectiveness between treatments. In fact, after decades of research and numerous clinical trials, outcomes of PE have not been improved by novel treatments (Mavranezouli et al., 2020) or with variants of existing treatments (Zhou et al., 2020). Should we rethink the way we attempt to improve treatment outcomes? Let us first address the risks of continuing to improve treatment outcomes the same way we did in the past decades. Apart from the enormous efforts of developing new treatments and performing clinical trials, patients often have to endure a passive control condition which might be considered unethical with so many effective treatments around (Devilly & McFarlane, 2009; Gold et al., 2017). For example, 43 clinical trials investigating psychotherapy in PTSD randomized in total 1312 patients to a waitlist condition (Mavranezouli et al., 2020). This continues to be a problem as more than 70% of the most recently included studies in the meta-analysis of Mavranezouli et al. (2020), published in 2017 and 2018, included a waitlist or attention placebo control condition. Although patients might improve somewhat during a waitlist condition, the effect size is typically four times smaller than an active treatment (Hedges G = .34 for waitlist and 1.5 for active treatment; Devilly & McFarlane, 2009). Moreover, trials often neglect other outcomes than the primary question: does treatment A outperform treatment B? Two recent reviews identified about 125 randomized controlled trials investigating psychotherapy in PTSD while only *fifteen* of them reported on at least one predictor of treatment outcome (Barawi et al., 2020; Dewar et al., 2020). Trials are also rarely powered for and focused on anything else than the difference between two treatments (Kraemer, 2016). We found that about half of studies into change in subjective distress as mechanisms of change of PE included very small sample sizes of less than 40 patients (see Chapter 7) and many of the (limited number of) predictor and moderator studies were underpowered (Barawi et al., 2020; Dewar et al., 2020). Hence, we miss a lot of information about predictors, moderators and mediators of treatment and much of the available information is based on studies with methodological limitations.

What can we do differently in the future? Firstly, we could start by using data which is already collected to answer our research questions. We may, for example, consider using novel data-analytic method such as dynamic panel models to re-analyze session data from previous studies and thereby investigate how working mechanisms are temporally related to outcome without collecting new data. When we understand better how treatments actually work, i.e. what drives subsequent symptom change, we might be able to better track patient progress in an early stage and potentially improve treatment outcomes by enhancing its effective elements (Kazdin, 2007). We may also use the wealth of data from ~125 RCTs to

systematically summarize the effect of predictors and moderators in an individual patient data meta-analysis (which in turn might be used for personalization algorithms; Abo-Zaid, Sauerbrei, & Riley, 2012; Fisher, Carpenter, Morris, Freeman, & Tierney, 2017; Weitz, Kleiboer, Van Straten, Hollon, & Cuijpers, 2017). This approach may improve the generalizability of personalization algorithms and has more power to detect predictors and moderators as the pooled coefficient from a meta-analysis is based on many studies instead of only one. The heterogeneity (i.e., variability) in the correlation coefficients between predictors/moderators and outcome from individual studies found in a meta-analysis might also provide some directions about the use of the coefficient in an algorithm as a small heterogeneity implies that the coefficient is stable across samples. Finally, we may focus more on data from clinical practice: what are perceived barriers and facilitators by therapists for the use of exposure therapy in patients with PTSD at this moment? How can we overcome these and how can researchers support in this? For example, if we empirically test patient characteristics that are perceived as barriers for exposure therapy, we will always find relevant results as we can either find that a patient characteristic is indeed related to worse treatment outcomes which might help to tailor treatment indications or we might find that a patient characteristic is not related to worse treatment outcomes which facilitates the use of exposure therapy. When we finally understand better for whom and how current treatments work, we may actually succeed in improving treatment outcomes (Kraemer, 2016).

General conclusion

In this dissertation, we aimed to improve treatment outcomes for patients with CA-PTSD by comparing PE with two innovations (STAIR+PE and iPE) and by investigating for whom and how these treatments work. Our results were promising, since the three treatments were effective in reducing PTSD symptoms and comorbid symptomatology. Not all patients benefitted equally from the treatments, but this was comparable to previous research in PTSD. The present results have important clinical implications. The first and foremost conclusion is that patients with CA-PTSD can be effectively treated in a short time span of 14-16 sessions. Secondly, Complex PTSD and dissociative symptoms alongside PTSD are no reason to withhold evidence-based trauma-focused treatment. Thirdly, a personalized advantage index based on a combination of predictors, may lead to differential treatment indications. However, this technique needs further validation. Fourthly, we found that it is crucial to use temporal models and to distinguish temporal from averaged relationships when investigating mechanisms of change. Using this technique, we found that within-session change in subjective distress precedes and predicts PTSD symptom improvement and therefore is important to track during PE. We conclude that exposure – in any form – is an effective treatment for patients with CA-PTSD.

Chapter 9

Nederlandse samenvatting

Posttraumatische-stressstoornis

Mensen die een traumatische gebeurtenis meemaken, zoals een beroving of verkrachting, kunnen hier last van blijven houden en een posttraumatische-stressstoornis (PTSS) ontwikkelen. Zij hebben last van terugkerende, opdringende intrusies over de gebeurtenis, vermijden gedachtes en gevoelens gerelateerd aan de gebeurtenis, hebben een negatieve stemming en negatieve cognities en ervaren verhoogde spanning en prikkelbaarheid. Volwassenen kunnen ook PTSS ontwikkelen ten gevolge van fysiek of seksueel misbruik in de kindertijd. Deze volwassenen hebben naast PTSS vaak ook bijkomende klachten zoals moeite met het omgaan met emoties, interpersoonlijke problemen en een laag zelfbeeld. Dit maakt de lijdensdruk groot en onderstreept het belang om de klachten effectief te behandelen.

Behandeling van PTSS ten gevolge van fysiek of seksueel misbruik in de kindertijd

Exposuretherapie is een effectieve behandelvorm voor PTSS. Tijdens deze therapie worden patiënten herhaald, systematisch en gecontroleerd blootgesteld aan herinneringen aan de traumatische gebeurtenissen. Zo leren patiënten dat het nu veilig is om terug te denken aan de traumatische gebeurtenissen en dat ze de negatieve emoties die daarbij horen ook aankunnen. Dit leidt gedurende de behandeling tot een afname in PTSS klachten.

Helaas herstelt niet iedereen voldoende met exposuretherapie. Daarnaast stoppen veel mensen vroegtijdig met therapie. Sommige onderzoekers zijn ervan overtuigd dat dit specifiek speelt bij patiënten met PTSS gerelateerd aan fysiek of seksueel misbruik in de kindertijd, omdat de exposuretherapie te zwaar voor hen zou zijn. Door de bijkomende klachten, zoals moeilijk om kunnen gaan met emoties, zouden ze de exposuretherapie emotioneel niet goed kunnen verdragen. Daarom is er voor deze patiënten een nieuwe, gefaseerde exposure behandeling ontwikkeld. In deze gefaseerde behandeling starten patiënten met een vaardigheidstraining om aan de bijkomende klachten te werken voordat ze starten met de exposuretherapie in de tweede fase van de behandeling. Het idee van deze behandeling is dat patiënten na de vaardigheidstraining minder last hebben van de bijkomende klachten en de exposuretherapie goed aan kunnen. Dit zou ervoor zorgen dat ze optimaal kunnen profiteren van de behandeling.

Andere onderzoekers zijn van mening dat er weinig bewijs is dat patiënten met PTSS, gerelateerd aan fysiek of seksueel misbruik in de kindertijd, niet direct kunnen starten met exposuretherapie. Zij suggereren onderzoek naar een andere behandelinnovatie die veelbelovende resultaten heeft laten zien in de behandeling van PTSS na verschillende soorten trauma: intensieve exposuretherapie. Bij deze vorm van therapie krijgen patiënten meerdere sessies per week. Wanneer de sessies kort na elkaar plaatsvinden zou het kunnen dat minder mensen vroegtijdig stoppen, doordat er minder tijd is om op te zien tegen de volgende sessie. Daarnaast zou intensieve therapie ook tot snelle klachtenverbetering kunnen leiden en daarmee snel de lijdensdruk kunnen verlichten.

Ondanks de verschillende zienswijzen over de behandeling van PTSS gerelateerd aan fysiek of seksueel misbruik in de kindertijd, bestaat er over sommige punten ook overeenstemming tussen onderzoekers: er is tot nu toe te weinig onderzoek naar deze groep

patiënten gedaan en in de klinische praktijk wordt bij deze doelgroep te weinig exposuretherapie gebruikt. Kortom, het is belangrijk om de effectiviteit van deze behandeling bij deze patiënten te onderzoeken en te evalueren of de behandelinnovaties, intensieve en gefaseerde therapie, de behandelresultaten van reguliere exposuretherapie kunnen verbeteren in deze doelgroep.

IMPACT-studie

De IMPACT-studie is opgezet om te onderzoeken of intensieve en gefaseerde exposuretherapie de behandelresultaten van reguliere exposuretherapie verbeteren bij patiënten met PTSS gerelateerd aan fysiek of seksueel misbruik in de kindertijd. De hoofduitkomst van de studie is PTSS symptomen, gemeten met een klinisch interview. Secundaire uitkomsten zijn zelfgerapporteerde PTSS symptomen, moeite met het omgaan met emoties, interpersoonlijke problemen en zelfbeeld. We kijken ook naar het aantal mensen dat vroegtijdig stopt met behandeling.

In alle drie de varianten van exposure therapie in deze studie worden patiënten blootgesteld aan de traumatische herinneringen en gestimuleerd hun vermijdingsgedrag te doorbreken. Patiënten luisteren thuis naar opnames van de sessies en oefenen zelf met het doorbreken van vermijdingsgedrag. In de eerste variant, de reguliere exposure conditie, bestaat de therapie uit 16 wekelijkse exposure sessies. De tweede variant, de intensieve exposure conditie, bestaat uit drie sessies per week gedurende vier weken (12 sessies in totaal) gevolgd door twee boostersessies. De derde variant, de gefaseerde exposure conditie, bestaat uit 16 wekelijkse sessies opgedeeld in twee fases. In de eerste fase van 8 weken krijgen mensen een vaardigheidstraining en in de tweede fase van 8 weken krijgen ze exposuretherapie.

Naast de hoofduitkomsten van de IMPACT-studie onderzoeken we ook *voor wie* en *hoe* de behandeling werkt. We weten uit vorige onderzoeken dat exposuretherapie bij ongeveer de helft van de patiënten onvoldoende werkt. Door beter te weten wie deze patiënten zijn kunnen we in de toekomst gericht onderzoek doen om behandeluitkomsten in deze groep te verbeteren. Patiënten verschillen op veel manieren van elkaar: de ernst van de PTSS klachten, de aanwezigheid van andere psychische klachten naast de PTSS, het gebruik van medicatie, het soort trauma dat ze hebben meegemaakt, enzovoorts. Van sommige van deze patiëntkenmerken wordt gedacht dat zij van invloed kunnen zijn op de effectiviteit van exposure therapie. Bijvoorbeeld, het lijden aan dissociatieve symptomen naast de PTSS klachten. Mensen die last hebben van dissociatieve symptomen ervaren een disconnectie met hun eigen lichaam of de wereld om hen heen. Dit zou een probleem kunnen zijn tijdens de exposuretherapie doordat patiënten minder angst zouden kunnen ervaren tijdens de behandelsessies, terwijl activatie van angst nodig is om te profiteren van de behandeling. Een ander voorbeeld is het lijden aan zogenaamde “complexe PTSS”. Er is recent een nieuwe diagnose “complexe PTSS” toegevoegd in de 11e editie van *the International Classification of Diseases* (ICD-11) specifiek voor patiënten die moeite hebben met het omgaan met emoties en die interpersoonlijke problemen en een laag zelfbeeld hebben,

naast de PTSS symptomen. Mensen met complexe PTSS zouden minder baat kunnen hebben van reguliere exposuretherapie en mogelijk juist specifiek kunnen profiteren van de gefaseerde exposure therapie, aangezien de eerste fase in deze therapie gericht is op de complexe PTSS klachten.

Verder onderzoeken we ook data gedreven voor wie welke behandeling de meeste kans heeft om tot een klachtenvermindering te leiden, ook wel personalisatie genoemd. Het idee hierachter is dat patiënten verschillend kunnen reageren op verschillende behandelingen en dat dit te voorspellen zou kunnen zijn op basis van een combinatie van patiëntkenmerken. We bekijken specifiek voor wie reguliere en intensieve exposure therapie en voor wie gefaseerde exposure therapie de meeste kans heeft om te werken. Om tot een combinatie van patiëntkenmerken te komen identificeren we eerst voorspellers van behandeluitkomsten in de reguliere en intensieve exposure condities en in de gefaseerde conditie door middel van machine learning technieken. Vervolgens bekijken we retrospectief of patiënten op basis van deze voorspellers zijn ingedeeld in de optimale conditie of in de suboptimale conditie en of deze indeling samenhangt met de behandeluitkomsten.

Tenslotte onderzoeken we het werkingsmechanisme van exposuretherapie. Als we beter weten wat de effectieve elementen zijn van exposuretherapie kan deze kennis worden gebruikt om de behandeling verder te verbeteren, door deze elementen te vergroten. Ook zouden ze gebruikt kunnen worden om tijdens de behandeling in de gaten te houden wie er 'on track' is. Er is al veel onderzoek gedaan naar het belang van spanningsreductie tijdens de behandelsessies. Het idee hierachter is dat een vermindering van spanning een voorteken van verbetering is: spanningsafname tijdens de behandelsessies zou een aanwijzing zijn dat de traumatische gebeurtenissen succesvol worden verwerkt. Vorige onderzoeken hebben niet onderzocht of een vermindering in spanning *voorafgaat* aan een vermindering in PTSS symptomen, ook wel de temporele relatie genoemd. Om zicht te krijgen op werkingsmechanismen tijdens exposuretherapie is het onderzoeken van temporele relaties van groot belang. Als de effecten van exposuretherapie (gedeeltelijk) gedreven worden door spanningsafname tijdens therapiesessies, zou de afname in spanning logischerwijs vooraf moeten gaan aan de afname van PTSS symptomen.

Het proefschrift

In **hoofdstuk 2** beschrijven we het design van de IMPACT-studie. **Hoofdstuk 3** bevat de hoofdresultaten van de IMPACT-studie. **Hoofdstuk 4** bestaat uit een meta-analyse over het effect van dissociatie op de behandeluitkomsten en **hoofdstuk 5** beschrijft het effect van complexe PTSS op de behandeluitkomsten. In **hoofdstuk 6** onderzoeken we personalisatie van PTSS behandeling door middel van het combineren van verschillende patiëntkenmerken en in **hoofdstuk 7** beschrijven we de temporele relatie tussen spanningsreductie en een verandering in PTSS symptomen. In **hoofdstuk 8** bediscussiëren we de hoofdstukken uit dit proefschrift.

IMPACT hoofdresultaten

In hoofdstuk 3 onderzochten we of intensieve en gefaseerde therapie de behandeluitkomsten van reguliere exposuretherapie bij patiënten met PTSS, gerelateerd aan fysiek of seksueel misbruik in de kindertijd, verbeteren. We hebben 149 patiënten gerandomiseerd naar reguliere exposuretherapie (*n* = 48), intensieve exposuretherapie (*n* = 51) en gefaseerde exposuretherapie (*n* = 50). Alle drie de vormen van exposuretherapie leidden tot een grote verbetering in PTSS symptomen. Intensieve en gefaseerde therapie leidden niet tot een *grotere* verbetering in PTSS symptomen of minder uitval uit de behandeling dan reguliere exposuretherapie. Intensieve therapie leidde tot een snellere afname in PTSS symptomen gemeten met een klinisch interview in vergelijking met gefaseerde therapie, maar niet in vergelijking met reguliere exposuretherapie. Intensieve therapie leidde wel tot een snellere afname van zelf gerapporteerde PTSS symptomen in vergelijking met gefaseerde therapie en reguliere exposuretherapie. Tenslotte vonden we dat gefaseerde exposuretherapie niet tot meer verbetering leidde dan de andere twee therapievormen in het omgaan met emoties, interpersoonlijke vaardigheden en zelfbeeld. Kortom, de twee innovaties zijn geen verbetering gebleken van exposuretherapie maar alle drie de therapievormen waren effectief voor deze doelgroep.

Dissociatie heeft geen invloed op de behandeleffectiviteit

In hoofdstuk 4 beschrijven we de resultaten van een meta-analyse over de invloed van dissociatieve symptomen op de effectiviteit van psychotherapie voor patiënten met PTSS. We hebben 21 studies met 1714 patiënten in deze meta-analyse geïncludeerd. We vonden geen relatie tussen de ernst van dissociatieve symptomen voorafgaand aan de behandeling en de behandeleffectiviteit. We concluderen dat er geen bewijs is dat dissociatieve symptomen voorafgaand aan de behandeling gerelateerd zijn aan de effectiviteit van psychotherapie voor PTSS.

Complexe PTSS heeft geen invloed op de behandeleffectiviteit

In hoofdstuk 5 presenteren we de resultaten van onze studie naar de invloed van complexe PTSS op de behandeleffectiviteit. Daarnaast onderzochten we of complexe PTSS gerelateerd was aan een beter behandeleffect in de gefaseerde exposurebehandeling in vergelijking met de reguliere en intensieve exposurebehandelingen. We vonden dat ruim de helft van de IMPACT-deelnemers voldeed aan de diagnose complexe PTSS voorafgaand aan de behandeling. We vonden niet dat complexe PTSS gerelateerd was aan slechtere behandelresultaten. Ook vonden we niet dat patiënten met complexe PTSS meer profiteerden van gefaseerde exposurebehandeling in vergelijking met de reguliere en intensieve exposurebehandelingen. Dit betekent dat ook patiënten met complexe PTSS effectief behandeld kunnen worden met de drie vormen van exposuretherapie.

Personalisatie van de behandeling van PTSS

Hoofdstuk 6 beschrijft de uitkomsten van onze studie naar de relatie tussen een combinatie van patiëntkenmerken en differentiële behandeluitkomsten van de reguliere en intensieve

exposure condities en de gefaseerde exposure conditie. Ons doel was allereerst om voorspellers te identificeren van slechtere behandeluitkomsten in de reguliere en intensieve exposurecondities en gefaseerde exposureconditie door middel van machine learning technieken. Ons tweede doel was om deze voorspellers te combineren en te onderzoeken of een combinatie van voorspellers relevant zou kunnen zijn voor differentiële behandeluitkomsten. We vonden dat vier variabelen gerelateerd waren aan slechtere behandeluitkomsten in de reguliere en intensieve exposurecondities: meer depressieve symptomen, minder sociale support, meer as-1 stoornissen en frequenter seksueel misbruik in de jeugd. Daarnaast vonden we dat drie variabelen gerelateerd waren aan slechtere behandeluitkomsten in de gefaseerde exposureconditie: meer emotieregulatie problemen, slechtere algemene gezondheidsstatus en meer PTSS symptomen. De patiënten die gerandomiseerd waren in de conditie die op basis van deze voorspellers hun voorkeursconditie was, verbeterden aanzienlijk meer dan patiënten die waren ingedeeld in hun suboptimale behandelconditie. Personalisatie op basis van patiëntkenmerken lijkt behandeluitkomsten te kunnen verbeteren. Er is echter nog geen prospectief vervolgonderzoek gedaan met dezelfde voorspellers in een nieuwe populatie. De repliceerbaarheid van deze bevindingen is dus onbekend.

Temporele relatie tussen spanningsreductie tijdens de behandeling en verbetering in PTSS symptomen

Om beter te begrijpen *hoe* exposuretherapie tot verbetering in PTSS symptomen leidt, onderzochten we in hoofdstuk 7 de temporele relatie tussen spanningsreductie tijdens de behandelsessies en verandering in PTSS symptomen. We bekeken de spanningsreductie binnen een sessie (van de piek naar het einde van de sessie) en tussen twee sessies (van de piek van de ene sessie naar de piek van de volgende sessie). Daarbij bekeken we de relatie tussen spanningsreductie en verandering in PTSS symptomen op twee verschillende manieren: 1) *binnen* een individuele patiënt: de relatie tussen spanningsafname bij patiënt A en afname in PTSS symptomen bij patiënt A een week later; en ter vergelijking met vorige studies ook 2) *tussen* verschillende patiënten: de relatie tussen gemiddelde spanningsafname bij patiënt A t/m Z en hun gemiddelde afname in PTSS symptomen. De relatie tussen spanningsreductie en PTSS symptomen *binnen* een individuele patiënt is hierbij cruciaal: Als de effecten van exposuretherapie gedreven worden door een spanningsafname tijdens therapiesessies, zou deze spanningsafname vooraf moeten gaan aan de afname van PTSS symptomen.

Allereerst, wanneer we keken naar de relatie binnen een patiënt, vonden we dat een spanningsreductie binnen een sessie, maar niet tussen twee sessies, gerelateerd was aan een verandering in PTSS symptomen in de daaropvolgende sessie. Wanneer we keken naar de relatie tussen patiënten, vonden we dat zowel gemiddelde spanningsreductie binnen een sessie als tussen twee sessies gerelateerd was aan de afname in PTSS symptomen. Dit wijst erop dat een afname in spanning tijdens een sessie, maar niet tussen sessies, relevant kan zijn om te begrijpen hoe de behandeling werkt en een indicator kan zijn dat iemand gaat

profiteren van behandeling. Om beter inzicht te krijgen in werkingsmechanismen van exposuretherapie is het van belang dat in toekomstig onderzoek gekeken wordt naar temporele relaties tussen een werkingsmechanisme en symptoomverandering binnen een patiënt.

Discussie van de resultaten

Hoe veelbelovend zijn de resultaten van de IMPACT-studie?

We vonden in de IMPACT-studie dat alle drie de vormen van exposuretherapie effectief waren voor patiënten met PTSS gerelateerd aan fysiek of seksueel misbruik in de kindertijd. Dit is een hoopvol resultaat, omdat er weinig bekend is over het effect van exposuretherapie voor deze doelgroep en het de vraag was of deze doelgroep de behandeling emotioneel wel aan zou kunnen. Betekent dit dat iedereen beter werd? Alhoewel de behandelingen gemiddeld genomen tot een grote verbetering in PTSS symptomen leidden werd niet iedereen beter. Ongeveer de helft van de patiënten profiteerde niet optimaal van behandeling: ze hadden überhaupt geen positief effect van de behandeling (~30%), verloren niet hun PTSS diagnose na behandeling (~40%) en/of stopte vroegtijdig met de behandeling (~25%). Hoe veelbelovend zijn dan eigenlijk de resultaten van de IMPACT-studie in vergelijking met andere studies naar PTSS gerelateerd aan fysiek of seksueel misbruik in de kindertijd of naar PTSS na elk type trauma? Het aantal mensen dat geen positief effect had van de behandeling of hun PTSS diagnose niet verloor is vergelijkbaar met vorige onderzoeken naar PTSS na elk type trauma. De uitval uit behandeling is echter iets hoger bij de IMPACT-studie in vergelijking met studies bij patiënten met PTSS na elk type trauma. Dit percentage is wel weer vergelijkbaar met vorige studies bij patiënten met PTSS gerelateerd aan fysiek of seksueel misbruik in de kindertijd. Kortom, er lijkt toch een relatief hoge uitval uit behandeling te zijn bij patiënten met PTSS gerelateerd aan fysiek of seksueel misbruik in de kindertijd, wat niet is verbeterd in de twee innovaties uit de IMPACT-studie. Maar, is uitval uit de behandeling wel altijd een negatieve behandeluitkomst? Wanneer we naar de redenen kijken waarom mensen vroegtijdig stoppen met therapie in de IMPACT-studie, zien we dat sommige mensen al stoppen voordat de therapie is begonnen, anderen stoppen omdat hun klachten juist zijn verbeterd met de therapie en ze geen meerwaarde meer zagen van de therapie en er waren ook mensen die stopten vanwege praktische redenen zoals een verhuizing. Eigenlijk stopte maar een klein deel (*n* = 8; 5%) van de patiënten in onze studie omdat de behandeling te zwaar was. We concluderen daarom dat het belangrijk is om de redenen van vroegtijdig stoppen met therapie te onderzoeken om te achterhalen of dit een probleem is dat te maken heeft met de behandeling.

Kortom, de resultaten van de IMPACT-studie zijn veelbelovend in de zin dat de behandelingen tot grote klachtenverbetering leidden bij patiënten met PTSS, zelfs met comorbide symptomen. En dat niet optimaal profiteren van de behandeling vergelijkbaar was met vorige onderzoeken naar PTSS na elk type trauma. Er stopten wel relatief veel mensen vroegtijdig met de behandeling in de IMPACT-studie maar dit bleek vaak niet per definitie een negatieve behandeluitkomst te zijn. We concluderen dat deze drie vormen van

exposuretherapie effectieve behandelingen zijn voor PTSS gerelateerd aan fysiek of seksueel misbruik in de kindertijd. Aangezien niet iedereen van de behandelingen profiteerde, is het belangrijk verder te onderzoeken hoe we de behandeling voor deze mensen kunnen verbeteren.

Choosing the right track

We vonden geen negatieve invloed van dissociatieve symptomen en complexe PTSS op de behandeluitkomsten, terwijl dit nu juist een van de redenen was om deze constructen toe te voegen in de diagnostische handboeken. Deze tegenstelling kan problematisch zijn zowel voor onderzoek als voor de klinische praktijk. In onderzoek worden deze constructen soms gebruikt als exclusiecriterium vanwege hun mogelijke invloed op de behandeluitkomsten wat leidt tot een beperkte generaliseerbaarheid van de resultaten naar patiënten die last hebben van deze klachten. Ook clinici kunnen ervan overtuigd zijn dat deze constructen contra-indicaties zijn voor het gebruik van psychotherapie en daarmee deze patiënten effectieve behandeling onthouden.

Een manier om dit probleem te voorkomen is door data gedreven te starten en eerst te kijken hoe een combinatie van patiëntkenmerken samenhangt met behandeluitkomsten. Alhoewel dit een veelbelovende aanpak is, moet nog veel onderzoek gedaan worden voordat dit toe te passen is in de klinische praktijk. Resultaten van vorige data gedreven studies moeten gerepliceerd worden en we hebben prospectieve onderzoeken nodig die een data-gedreven toewijzing aan behandelingen vergelijken met toewijzing zoals dit nu gebeurt in de huidige klinische praktijk.

Voor nu is onze aanbeveling voor de klinische praktijk om empirische studies naar voorspellers van (differentiële) behandeluitkomsten te gebruiken voor beslissingen over behandelindicaties. Bij voorkeur zouden hierbij resultaten van meta-analyses moeten worden gebruikt, omdat die de meest betrouwbare informatie geven. Vorige studies hebben laten zien dat veel clinici ideeën hebben over patiëntkenmerken die een contra-indicatie zijn voor psychotherapie. Dit is problematisch als het leidt tot onderbehandeling van patiënten. Deze ideeën kunnen echter wel een belangrijke inspiratiebron zijn voor onderzoek wat op haar beurt weer helpend kan zijn voor verbetering van behandelindicaties.

Aanbevelingen voor toekomstig onderzoek

Het is de afgelopen decennia niet gelukt om de uitkomsten van exposuretherapie voor PTSS te verbeteren terwijl er veel nieuwe behandelingen zijn ontwikkeld. De vraag is daarom of het ontwikkelen van nieuwe behandelingen nog wel zinvol is. Daarnaast wordt een nieuwe behandeling vaak vergeleken met een passieve wachtlijstconditie wat ethische consequenties heeft: een patiënt wordt (tijdelijk) effectieve behandeling onthouden. Veel studies focussen ook op een vergelijking tussen de effectiviteit van behandelingen terwijl er maar weinig informatie is over voorspellers en werkingsmechanismes van behandelingen.

Wat kunnen we anders doen in toekomstig onderzoek? Allereerst kunnen we nieuwe innovatieve statistische methoden gebruiken om vragen te beantwoorden met behulp van

data van eerdere studies. We zouden ook data van eerdere studies kunnen gebruiken om voorspellers van (differentiële) behandeluitkomsten samen te vatten in meta-analyses. Tenslotte zouden we onderzoek kunnen doen in samenwerking met de klinische praktijk: Wat wordt door therapeuten als barrière gezien bij het geven van exposuretherapie voor PTSS? Hoe kunnen we hier als onderzoekers bij ondersteunen?

Conclusie

In dit proefschrift was ons hoofddoel om de behandeluitkomsten van patiënten met PTSS gerelateerd aan fysiek of seksueel misbruik in de kindertijd te verbeteren door standaard exposure te vergelijken met twee innovaties: intensieve exposure en gefaseerde exposure therapie. Daarnaast wilden we onderzoeken voor wie en hoe de behandelingen werken. Onze resultaten zijn veelbelovend aangezien alle drie de behandelingen effectief waren voor PTSS symptomen en bijkomende klachten. De belangrijkste klinische implicatie is daarom ook dat patiënten met PTSS gerelateerd aan fysiek of seksueel misbruik in de kindertijd effectief en snel behandeld kunnen worden in 14-16 sessies. Daarnaast zijn dissociatieve symptomen of een complexe PTSS geen reden om mensen behandeling te ontzeggen. We vonden dat een combinatie van patiëntkenmerken veelbelovend is om differentiële behandeluitkomsten te voorspellen, maar deze uitkomsten hebben wel nog verdere validatie nodig. Tenslotte vonden we dat het belangrijk is om de temporele relatie te onderzoeken van werkingsmechanismes van therapie en onderscheid te maken tussen de temporele relatie binnen en tussen patiënten. We vonden dat spanningsreductie tijdens een sessie gerelateerd is aan daaropvolgende afname van PTSS symptomen terwijl dit niet het geval is voor spanningsreductie tussen twee sessies. We concluderen dat exposuretherapie – in elke vorm- een effectieve behandeling is voor patiënten met PTSS gerelateerd aan fysiek of seksueel misbruik in de kindertijd.

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Curriculum Vitae

Chris Hoeboer was born on the 17th of April 1993 in Katwijk. He completed his secondary education at the Stedelijk Gymnasium in Leiden in 2011. Chris obtained his Bachelor's degree in Psychology at Leiden University in 2014 and completed the Honours Programme of Social and Behavioural science. He graduated from the Research Master Clinical and Health Psychology (cum laude) at Leiden University in 2017 and completed the International Leiden Leadership Programme. In 2017, Chris started his PhD project at Leiden University and PsyQ The Hague about 'Improving treatment for patients with childhood abuse related posttraumatic stress disorder'. Chris received training from the Dutch-Flemish post-graduate school for Experimental Psychopathology and the Graduate School of Social and Behavioural Sciences of Leiden University. During his PhD, Chris trained and supervised students in clinical interviews, supervised students with their master theses and supervised clinical psychologists in training for their research project as part of their post-master study. Chris was also member of the communication committee, chairman of Special interest group 'Young Minds' and board member responsible for research of the Dutch Association for Psychotrauma. In the third year of his PhD, Chris received the KNAW Van der Gaag grant which allowed him to write his paper about personalization of PTSD treatment together with the research group from professor Lutz. Since the fourth year of his PhD, Chris has been working part-time as postdoctoral researcher at the AmsterdamUMC location AMC on several projects related to interpersonal partner violence, impact of COVID-19 on mental health and social safety, prevalence rates of PTSD and (cross-cultural) questionnaire/screener validations.

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