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

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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.