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

Hoeboer, C.M.

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.