From Department of Clinical Neuroscience
Karolinska Institutet, Stockholm, Sweden

NOVEL INTERVENTION APPROACHES AFTER RECENT EXPOSURE TO TRAUMA

Maria Bragesjö

Karolinska Institutet

Stockholm 2021

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2021

ISBN 978-91-8016-251-7

NOVEL INTERVENTION APPROACHES AFTER RECENT EXPOSURE TO TRAUMA
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Maria Bragesjö

The thesis will be defended in public at Andreas Vesalius, Berzelius väg 3, 171 65 Solna, 4th of June 2021.

Principal Supervisor:
Associate Professor Erik Andersson
Karolinska Institutet
Department of Clinical Neuroscience
Division of Psychology

Co-supervisor:
Associate Professor Filip Arnberg
Uppsala University
Department of Neuroscience
National Centre for Disaster Psychiatry

Opponent:
Professor Richard Bryant
University of New South Wales
School of Psychology

Examination Board:
Professor Maria Tillfors
Karlstad University
Department of Social and Psychological Studies

Associate Professor Gertrud Hafstad
Norwegian Centre for Violence and Traumatic Stress Studies

Associate Professor Johanna Ekdahl
Mid Sweden University
Department of Psychology

To Klara and Julia. You are the light in my life.

SVENSK SAMMANFATTNING

Bakgrund: Risken för att någon gång i livet vara med om en psykologiskt traumatisk händelse är hög vilket kan få djupgående negativ inverkan på ens psykiska hälsa. Majoriteten av drabbade individer kommer att gå igenom en process av naturlig läkning och endast uppleva kortvariga reaktioner. De vanligaste långvariga reaktionerna som beskrivs i traumaområdet är akut stressyndrom och posttraumatiskt stressyndrom (PTSD). Efter att ha varit med om traumatiska händelser där någon avsiktligen försökt skada en kommer en tredjedel av de drabbade utveckla PTSD under det första året. De finns därför ett stort behov av tidiga insatser för att minska och lindra initiala reaktioner och förhindra att reaktionerna blir kroniska. Eftersom utlösaren till PTSD är känd, en traumatisk händelse, möjliggör det tidig identifiering av och intervention för de drabbade. Tidiga psykologiska interventioner som baseras på traumafokuserad kognitiv beteendeterapi har visat lovande resultat, särskilt hos dem som uppfyller diagnosen akut stressyndrom.

Syfte: Det övergripande syftet med denna avhandling har varit att utveckla och utvärdera nya tidiga psykologiska interventioner efter exponering för en potentiellt traumatisk händelse (PTE) för att underlätta återhämtning och minska omedelbara reaktioner och lidande. De specifika målen för varje studie i denna avhandling var att undersöka:

• Genomförbarhet, godtagbarhet och effekt av en kort intervention baserad på prolonged exposure (PE) med start inom 72 h efter en potentiellt traumatisk händelse i akutsjukhusmiljö och vid en akutavdelning för våldtäktsoffer (Studier I och II).

• Genomförbarhet, godtagbarhet och effekt av en kort, digital intervention som bygger på PE (Condensed Internet-delivered Prolonged Exposure, CIPE) nära inpå en potentiellt traumatisk händelse (studier III och V).

• Deltagarnas upplevevelse av att genomgå CIPE som en tidig intervention efter en potentiellt traumatisk händelse (studie IV).

Metoder: Fem studier (I-V) som utvärderade PE som tidig intervention efter trauma med olika typer av metoder i rekrytering, bedömning och sätt att ge interventionen (fysiska sessioner och digital intervention) genomfördes inom detta doktorandprojekt. Studie I och II undersökte genomförbarhet och effekt av PE med fysiska besök med start inom 72 timmar efter exponering för trauma. Studie I var en randomiserad kontrollerad studie (RCT) med det ursprungliga syftet att slumpa 352 deltagare till tre sessioner av PE eller icke-direktivt stöd. Studie II utvärderade genomförbarheten av tidig PE med samma upplägg för våldtäktsoffer i en icke-randomiserad pilotstudie (N = 10). I studie III utvecklades en kort, digital intervention baserad på PE (CIPE) som utvärderades avseende genomförbarhet, godtagbarhet och preliminära effekter i en randomiserad pilotstudie (N = 33) när den gavs inom de första två månaderna efter exponering för trauma. Studie IV (N = 11) använde kvalitativ tematisk analys för att undersöka deltagarnas upplevelser och erfarenheter av CIPE. Studie V var en randomiserad studie (N = 102) i syfte

att undersöka effekten av CIPE mot en väntelista upp till 7 veckor från förmätningen och inklusion.

Resultat: I studie I hade vi problem med en hög grad av bortfall och med att inkludera deltagare och studien avslutades i förtid på grund av oväntade organisationsförändringar på sjukhuset där studien genomfördes. I studie II var följsamheten till interventionen när det gällde närvaro på sessioner och hemuppgifter hög. Samtidigt var det endast en liten del av patienterna som uppfyllde inklusionskriterierna för studien. Studie III visade att CIPE var en genomförbar och acceptabel intervention som preliminärt ledde till större minskning i symtom på posttraumatisk stress jämfört med väntelistgruppen. Data från studie IV visade att deltagarna tyckte att CIPE var en påfrestande och effektivt intervention. Deltagarna beskrev CIPE som en trovärdigt, acceptabel och lärorik intervention som motiverade dem att engagera sig i exponering. Imaginativ exponering upplevdes vara både den viktigaste för återhämtning efter trauma och också den mest påfrestande. Studie V visade att CIPE var mer effektiv i att minska symtom på posttraumatisk stress än väntelistegruppen upp till 7 veckor efter baslinjen. Mellangruppseffektstorleken var i det medelstora intervallet vid avslutad intervention efter 3 veckor (bootstrapped d = 0,71 [95% CI; 0,33 till 1,05]) och stor vid 1 månaders uppföljning (bootstrapped d = 0,83; [95% Cl 0,46 till 1,19]). Resultaten bibehölls efter sex månader. Inga allvarliga biverkningar i samband med interventionen rapporterades i någon av studierna.

Slutsats: Studierna i denna avhandling visar att rekrytering av deltagare från svenska akutsjukhus och att ge en intervention så tidigt som inom de första 72 timmarna efter exponering för trauma inte var så genomförbart som vi ursprungligen trodde. Det blev därför nödvändigt att göra en del metodologiska ändringar. Den möjliga tidsramen från exponering för trauma och inkludering förlängdes, vi riktade interventionen enbart till personer med ett visst mått av reaktioner och rekryterings-, bedömnings- och interventionsprocedurerna överfördes till ett digitalt format (CIPE). Resultaten indikerar att CIPE är en genomförbar, acceptabel och effektiv tidig intervention efter trauma när den gavs de första två månaderna efter exponering för PTE till symtomatiska individer. CIPE kan avsevärt öka tillgången till denna typ av tidiga insatser och kan visa sig vara en intervention som är lätt att sprida och med fördelen att den kan användas exakt när det behövs.

ABSTRACT

Background: The life-time incidence of exposure to traumatic events is high and can have a profound negative impact on mental health. The majority of individuals exposed to trauma will go through a process of natural recovery and experience short-lived reactions. The most widely reported long-term reactions in the traumatic stress literature are acute stress disorder (ASD) and post-traumatic stress disorder (PTSD). After intentional traumatic events, one-third of the exposed will develop PTSD in the first year. That stresses the necessity and importance of early scalable interventions to alleviate initial reactions and change the trajectory away from a chronic course. The key precursor for PTSD is exposure to a specific traumatic event which allows for early identification and intervention. Early psychological interventions based on trauma-focused cognitive behavioural therapy (CBT-T) has shown promising results, especially for those who meet the diagnostic threshold for ASD.

Aims: The general aim of this thesis was to develop and evaluate novel early psychological interventions after exposure to a potentially traumatic event(s) (PTE) in order to facilitate recovery and reduce immediate distress. The specific aims of each study in this thesis were to investigate:

- The feasibility, acceptability and efficacy of brief prolonged exposure (PE) provided face-to-face in the early aftermath of a potentially traumatic event in an emergency hospital setting and at an emergency department for rape victims (Studies I and II)
- The feasibility, acceptability and efficacy of condensed internet-delivered PE (CIPE) in the early aftermath of a potentially traumatic event (Studies III and V)
- The participants experience of CIPE in the early aftermath of a potentially traumatic event (Study IV).

Methods: Five studies (I-V) that evaluated PE as an early intervention after trauma using different types of methodology in recruitment, assessment and form of delivery were conducted within this doctoral project. Study I and II investigated feasibility, acceptability and efficacy of PE delivered face-to-face within 72 hours of exposure to trauma. Study I was a randomised controlled trial (RCT) with the original aim to allocate 352 participants to three sessions of PE or non-directive support. Study II evaluated feasibility of the same face-to-face protocol for rape victims in a non-randomised pilot study (N=10). In study III, a condensed internet-delivered prolonged exposure intervention was developed and tested for feasibility, acceptability and preliminary effects in a pilot randomised trial (N=33) when provided within the first two months after exposure to trauma. Study IV (N=11) used a qualitative thematic analysis to explore participants experiences of the intervention. Study V was a randomised trial (N=102) with the aim to investigate the effectiveness of CIPE against a waiting list up to 7 weeks from baseline.

Results: In study I, we experienced problems with high attrition and low recruitment rate and the trial was terminated beforehand due to unexpected organisational changes at the recruiting site. In study II, the compliance to the intervention in terms of session attendance and home-work assignments completion was high. Nevertheless, only a small proportion of patients at the recruiting clinic were eligible for the study. Study III showed that CIPE was feasible, acceptable and preliminary led to greater reductions in post-traumatic stress symptoms compared to the waiting list group. Data from study IV showed that participants found CIPE to be a demanding yet effective intervention. Participants described CIPE as a credible, tolerable and educative intervention that motivated them to engage in exposure. Imaginal exposure was perceived to be both the most important in recovery after trauma and also the most distressing one. Study V demonstrated that CIPE was more effective in reducing symptoms of post-traumatic stress than the waiting list group up to 7 weeks after baseline. The between-group effect size was in the moderate range at intervention completion after 3 weeks (bootstrapped *d*=0.71 [95% CI; 0.33 to 1.05]) and large at the 1-month follow up (bootstrapped *d*=0.83; [95% CI 0.46 to 1.19]). Results were maintained after six months. No serious adverse events associated with the intervention were found in either of the studies.

Conclusions: The results from the studies in this thesis put the light on that recruiting participants from Swedish emergency hospitals and delivering an early intervention face-to-face within the first 72 hours of exposure to trauma was not as feasible as originally expected. A change in methodology was therefore necessary. The time-frame from exposure to trauma and inclusion was extended, an indicated approach to inclusion was used and the recruitment, assessment and intervention procedures were transferred to an online format (CIPE). Results indicate that CIPE was a feasible, acceptable and effective early intervention after trauma when delivered within the first two months after exposure to PTE to symptomatic individuals. CIPE could greatly increase access to this type of intervention and may prove to be a highly scalable intervention with the benefit to be used in the exact moment when needed.

LIST OF SCIENTIFIC PAPERS

I. **Bragesjö M.,** Arnberg F. K, & Andersson E. (Manuscript) Prevention of Post-Traumatic Stress Disorder: Lessons Learned from a Terminated RCT of Prolonged Exposure.

II. **Bragesjö, M**., Larsson, K., Nordlund, L., Anderbro, T., Andersson, E., & Möller, A. (2020). Early Psychological Intervention After Rape: A Feasibility Study. *Frontiers in Psychology l, 11*(1595). doi:10.3389/fpsyg.2020.01595

III. **Bragesjö M.**, Arnberg F. K, Särnholm, J. Olofsdotter Lauri, K. & Andersson E. (2021) Condensed internet-delivered prolonged exposure provided soon after trauma: a randomised pilot trial. *Internet Interventions, 23*, 100358. doi:https://doi.org/10.1016/j.invent.2020.100358

IV. **Bragesjö M**., Arnberg F. K, Jelbring, A., Nolkrantz, J., Särnholm, J. Olofsdotter Lauri, K., von Below C. & Andersson, E. (2021) Demanding and effective: participants' experiences of internet-delivered prolonged exposure provided within two months after exposure to trauma. *European Journal of Psychotraumatology, 12*(1), 1885193. doi:10.1080/20008198.2021.1885193

V. **Bragesjö M**., Arnberg F. K., Olofsdotter Lauri,. K., Aspvall. K., Särnholm, J. & Andersson, E. (Manuscript). Condensed internet-delivered prolonged exposure provided soon after trauma: a randomised trial.

CONTENTS

1 INTRODUCTION 1
2 LITERATURE REVIEW 3
2.1 Definitions of the term trauma 3
2.2 Prevalence and course 3
2.3 The impact of trauma 4
2.3.1 Short term consequences after a PTE 4
2.3.2 Long term consequences after a PTE 5
2.4 Risk indicators for long term reactions 6
2.4.1 Pre-trauma indicators 6
2.4.2 Peri-trauma indicators 7
2.4.3 Post-trauma indicators 7
2.5 Emotional processing theory 7
2.5.1 Treatment of long-term reactions after PTE 8
2.6 The need for early interventions after exposure to PTE 9
2.6.1 Psychological early interventions 11
2.7 Room for improvement 13
3 RESEARCH AIMS 15
3.1 Study I 15
3.2 Study II 15
3.3 Study III 15
3.4 Study IV 15
3.5 Study V 15
4 EMPIRICAL STUDIES 16
4.1 The intervention 16
4.2 PE provided early after exposure to PTE 16
4.3 The participants 18
4.4 Study 1: Provision of PE to trauma patients in a hospital emergency department 19
4.4.1 Research approach 19
4.4.2 Main results 19
4.5 Study II: Provision of PE to rape victims at an emergency department 19
4.5.1 Research approach 19
4.5.2 Main results 19
4.6 Study III: A pilot feasibility trial of condensed internet-delivered PE 20
4.6.1 Research approach 20
4.6.2 Main results 21
4.7 Study IV: Qualitative investigation of study III 22
4.7.1 Research approach 22
4.7.2 Main results 22
4.8 Study V: An efficacy trial of condensed internet-delivered PE 22
4.8.1 Research approach 22

4.8.2 Results 23
4.9 Ethical considerations 23
5 DISCUSSION 26
5.1 The research process and main findings 26
5.2 Clinical importance of the findings 29
5.3 For whom is CIPE effective for? 30
5.4 What is the optimal way to do exposure? 31
5.5 The role of negative cognitions about oneself and the world 32
5.6 Limitations 32
6 SUMMARY AND FUTURE DIRECTIONS 33
7 ACKNOWLEDGEMENTS 33
8 REFERENCES 37

LIST OF ABBREVIATIONS

AE	Adverse event
ASD	Acute stress disorder
CBT-T	Trauma-focused cognitive behaviour therapy
CIPE	Condensed Internet-delivered Prolonged exposure
DSM	Diagnostic Statistical Manual for Mental Disorders
EQ-5D	Euroqol-5 Dimensions
ICD	International Classification of Diseases
I-CBT	Internet-based cognitive behaviour therapy.
MADRS-S	Montgomery Åsberg Depression Rating Scale-Self rated version
PCL-5	PTSD Symptom Checklist for DSM-5
PE	Prolonged exposure
PTE	Potentially traumatic event
PTSD	Post-traumatic stress disorder
RCT	Randomised controlled trial
WL	Waiting list

1 INTRODUCTION

Exposure to trauma has accompanied humans through history. The earliest written description of symptoms of post-traumatic stress disorder (PTSD) may be the one depicted in the epic Hindu love story, Ramayana, believed to be written around 5000 BCE. The story revolves around the god Rama and his wife Sita. The demon-king Ravana asks his brother Marrich to abduct Sita and bring her to him. When asked, Marrich's mouth is described to turn dry and his heart to be filled with terror. A previous traumatic event where Rama hit Marrich with an arrow that threw him in the sea, a hundred miles from the shore, seems to haunt him (Sheth et al., 2010). The extracts below taken from the dialogue can be seen as examples from the different clusters of symptoms that now constitute the PTSD diagnosis.

Now, in every tree, I see Rama with bow and arrow, wearing black deer skin. Lord Rama appears to me like the God of Death. Sometimes I see thousands of Rama and I am filled with terror (Verse: 15, Chapter 39 Aranyakand, Valmiki Ramayana).

*When I sit in solitude, I see nothing but Rama. Sometimes I see Rama in my dreams and I often lose consciousness. Sometimes I think that Rama is pervading the whole universe (*Verse: 16, 17, and 18, Chapter 39).

I see Rama and his brother Laxmana everywhere. Both are extremely valiant and cannot be defeated in war (Verse 24, Aranyakand, Ramcharit Manas).

I am unable to hear the name of things which start with the letter 'R'. When I hear that, I begin to tremble, because the letter 'R' reminds me of Rama. So, I avoid Rath (chariot), Ratna (gems) and other things that begin with 'R (Verse 18, Aranyakand, Valmiki Ramayana).

The earliest attempts to label the disorder were mainly focused on the traumatic event itself (e.g., shell shock, abused child syndrome, or concentration camp syndrome). The focus has subsequently shifted to the long-term psychological reactions that share similarities regardless of trauma type as the precursor. The diagnosis PTSD was first introduced in the Diagnostic Statistical Manual for Mental Disorders in the third 1981 revision. Today, several evidence-based treatments for PTSD exist, such as trauma-focused CBT (CBT-T) but the gap between the demand and supply of treatment is huge. One way to bridge the gap would be to deliver short and easily scalable interventions in the early aftermath of trauma. Still, there are uncertainties regarding the effectiveness of these types of early interventions.

I embarked on my PhD journey on a gloomy day in late December 2015. My mission, to paraphrase one of my favourite tv-shows Stark Trek, *to boldly go where no (wo)man has gone before* and investigate the use of prolonged exposure (PE) as an early intervention after trauma.

I never imagined that I would end up having so many more things in common with the Starship Enterprise's journeys than just the introductory text. Metaphorically speaking, my own Enterprise crashed (study I) and I had to salvage the wreck. Reaching the strange new worlds unknown to me in the beginning not only enriched the journey, but in the end, also turned out to be the best places to set up camp. My experience from working with this thesis is that there are many challenges in delivering face-to-face interventions targeting all trauma afflicted who seek medical attention at a hospital emergency department. In my experience, a more feasible approach involves providing digital psychological interventions to people who have been exposed to trauma, and who display symptoms of post-traumatic stress within the months after the traumatic event. But first, a time warp to the beginning.

I treated my first patient with PTSD (thank you for putting up with my, at times, blundering attempts to provide prolonged exposure) during my seventh semester as a psychology student in 1997. Treating long-term trauma reactions made me curious of how memories from events long ago can still haunt you decades later, and how remarkable it is that quite time limited psychological treatment can reverse this effect. After graduation, I started to work with patients with borderline personality disorder who often had been exposed to trauma and suffered from PTSD and other comorbidities. Over the years, my frustration over the long period between exposure to trauma and receiving treatment grew and became my incentive for trying to find a way to find and treat trauma exposed at an earlier stage.

The change in paths, from a clinician to a PhD-student has not always been easy. My clinical background has strengthened me in many ways, helped me devise relevant, clinical research questions and made me headstrong. Yet, at times my background has been a challenge. I have been forced to let go of some of my established preconceptions and scientifically test them out. If someone would have suggested during my clinical years that I would one day develop a digital intervention for recently exposed trauma I would have probably just laughed and thought they were joking. I had my own clinical bias at the time and was convinced that face to face interventions were needed for this particular group. And here I am, an advocate for not only its use but also its wider implementation.

Solna 2021-04-30

Maria Bragesjö

2 LITERATURE REVIEW

2.1 DEFINITIONS OF THE TERM TRAUMA

The term trauma comes from Greek meaning 'injury' or 'wound'. Historically, is has been used in the field of medicine to describe physical injury. The definition of trauma has later broadened to incorporate psychologically stressful, typically life-threatening events. Hence, psychologically traumatic events can be considered a wound of the soul.

The Diagnostic Statistical Manual for Mental Disorders (DSM-5) defines a psychologically traumatic event as exposure to actual or threatened death, serious injury or sexual violence (American Psychiatric Association, 2013). Exposure to the event may occur to oneself directly or indirectly, with the latter meaning witnessing the event, learning that someone close to you has been exposed to trauma or repeated exposure to aversive material.

No specific set of objectively differentiated characteristics of what constitutes a traumatic event has been found to lead to long term negative consequences such as PTSD (Boals & Schuettler, 2009; Bodkin et al., 2007; Rosen & Lilienfeld, 2008). The subjective experience of the threatening nature of the event appears to be one of the key factors in predicting long term consequences (Heir et al., 2016). For that reason, the term potentially traumatic event (PTE) has come to be used and is the term I will use through the thesis.

2.2 PREVALENCE AND COURSE

The epidemiology of trauma exposure has been extensively described with consistent results. The World Mental Health (WMH) Surveys are the most recent and largest epidemiologic study. Data from these surveys shows that exposure to potentially traumatic events are common around the globe. In the 24 participating countries the estimated lifetime exposure to a PTE was reported to be 70% (Benjet et al., 2016). In addition, as much as one-third of the afflicted report exposure to more than four PTEs. The most commonly reported types of PTE in the studies were witnessing death or serious injury, the unexpected death of a loved one, being mugged, being in a life-threatening car accident and experiencing a life-threatening illness or injury. Women generally reported a lower exposure rate to PTE than men and had a considerably higher risk of exposure to intimate partner or sexual violence. Prior exposure to a PTE was found to be a risk factor for future exposure PTEs, especially when the PTE involved physical and/or sexual violence (Benjet et al., 2016; Hannan et al., 2017).

2.3 THE IMPACT OF TRAUMA

Reactions after exposure to PTE vary considerably. Adverse reactions such as nightmares, avoidance of trauma related cues and hyperarousal are to be expected and seen as an adaptive process moving from survival mode to adjustment and adaption (Shalev, 2002). Long-term psychological consequences as the emergence of psychiatric disorders e.g., depression, anxiety and substance abuse are common. An estimated 23-31% of PTE exposed individuals meet the criteria for a mental health disorder within 12 months after exposure to a PTE (Bryant et al., 2010; Zatzick et al., 2008). The most common psychiatric disorder, and considered the cardinal psychopathology after exposure to PTE is arguably PTSD which has consequently become the focus of the majority of studies in the field of traumatic stress (Bryant, 2019). PTSD is a mental disorder with four symptom clusters: intrusions, avoidance, cognitive and mood changes, and arousal symptoms requiring presence of symptoms for more than a month, and distress or functional impairment in the afflicted (American Psychiatric Association, 2013). Around two thirds of individuals diagnosed with PTSD at 4–6 weeks post trauma exposure will not remit by 3 months (Santiago et al., 2013). The WMH Surveys estimate the lifetime prevalence rate of PTSD in exposed to PTE at 5.6% (Benjet et al., 2016). In addition, data suggests that exposure to PTE may have continuing consequences on upcoming generations through epigenetic mechanisms (Yehuda & Lehrner, 2018).

2.3.1 Short term consequences after a PTE

Although distressing during the time they present, reactions after exposure to PTE typically diminish over the first three months, a process called natural recovery (e.g. Bryant, 2003; Galea et al., 2002; Koenen et al., 2017). Based on that, early interventions with the aim to ameliorate distressing, short-term reactions are generally initiated within 3 months after exposure to PTE (Roberts et al., 2019).

The two large classification systems for mental disorders used in the world today (the DSM-5 and the International Classification of Diseases (ICD-11)) takes different approaches to early symptoms of post-traumatic stress. ICD-11 propose that acute stress reactions should not be considered pathological or a mental disorder unless prolonged or disruptive to everyday life. Accordingly, in the ICD-11 acute stress reactions as conceptualised as normal reactions classified in the chapter, ‘Factors influencing health status and contact with services’. The chapter is dedicated to conditions not considered to be diseases or disorders but may be reasons for health encounters. The DSM-5 takes a different approach in interpreting acute stress reactions and provides the possibility to use the diagnosis of acute stress disorder (ASD) if reactions cause disruption during the first month following the PTE (American Psychiatric

Association, 2013). In that sense, the ICD-11 offers a much less pathologizing mean to describe acute stress reactions than the DSM-5 and still identify those who may need assistance. The DSM-5 can be said to build on the argument that the provision of a mental disorder diagnosis in the early phase after a PTE is necessary as mental health services typically require a diagnosis before providing access to treatment. ASD was originally considered an antecedent to PTSD, but research has only indicated ASD to be a modest predictor of subsequent PTSD (Bryant, 2011).

The fact that the predictive value of ASD for subsequent development of PTSD is merely modest stresses the importance of recognising that the trajectory is not linear from exposure to PTE and short and long-term consequences. On the contrary, reactions and symptoms fluctuate during months and even years after exposure to PTE (Bryant, 2017). Neither of the diagnostical systems, set aside the controversies regarding pathology vs. non-pathology, can be said to capture the heterogeneity of reactions after exposure to PTE.

A common way to classify trajectories after exposure to a PTE is often based on the severity of reactions following time since exposure. Four classes are often described: a resilient class consistently showing few symptoms of post-traumatic stress, a recovery class with initial distress followed by gradual remission, a delayed reaction class who initially show few or no symptoms but whose symptoms then increase over time, and a chronic distress class with consistently high levels of symptoms (Galatzer-Levy et al., 2018).

2.3.2 Long term consequences after a PTE

PTSD is one of the most common psychiatric disorders in the world with a life-time prevalence rate of 3.9% (Benjet et al., 2016). Women are reported to have twice as high life-time prevalence rate of PTSD than men (McLean et al., 2011). The mean remission rate has been reported to be 44% during the 40 months following diagnosis (Morina et al., 2014; Steinert et al., 2015). The mean conditional risk of developing PTSD after exposure to PTE is estimated to be around 4 % (Shalev et al., 2017) whereas it is substantially elevated after exposure to interpersonal trauma (Forbes et al., 2013). For example, the conditioned prevalence after rape is reported to be between 19 and 50% (Breslau et al., 1998; Kessler et al., 2005; Liu et al., 2017; Tiihonen Moller et al., 2014).

PTSD has a strong link to comorbid psychiatric and somatic problems after its onset. The prevalence rates of co-occurring mood and anxiety disorders are reported to be as high as between 52 and 92% (Kessler et al., 2005; Perkonigg et al., 2000; Rytwinski et al., 2013; Yehuda & McFarlane, 1995). Furthermore, meeting the criteria for PTSD is shown to elevate

the risk of drug and alcohol dependence as well as suicide. The onset and course of PTSD have also shown to increase the risk of various medical conditions ranging from neurological, cardiovascular, respiratory, gastrointestinal and autoimmune diseases, accelerated aging, and diabetes (Boscarino, 2006; Kubzansky et al., 2007; McFarlane et al., 1994; Miller & Sadeh, 2014; Roberts et al., 2015; Song et al., 2018). Unsurprisingly, these psychiatric and somatic impairments have a negative impact on perceived quality of life (Holbrook et al., 2001).

The societal burden for PTSD is considerate with higher rates of work impairment, sick leave, hospitalisation, and healthcare visits than other anxiety disorders (Greenberg et al., 1999). Disability-adjusted life year (DALY) is often used to estimate the burden of disease. In a review of injury patients seeking help at hospital emergency departments for somatic reasons, the inclusion of PTSD increases the burden of injuries with 53% (Haagsma et al., 2011). Compared to other anxiety disorders, patients with PTSD have a higher degree of sickness absence, failure to return to work and reduced work performance (Wald & Taylor, 2009).

2.4 RISK INDICATORS FOR LONG TERM REACTIONS

The probability of developing PTSD after a PTE seems to depend on a set of biopsychological risk indicators (Bryant, 2003; Hoge et al., 2014; Ozer et al., 2003). Currently there is no reliable way to distinguish those individuals that after exposure to PTE with certainty will develop PTSD.

The established way to classify risk indicators are according to timing relative to the PTE: pre-trauma (before the PTE), peri-trauma (during the PTE) and post-trauma (after the PTE).

2.4.1 Pre-trauma indicators

Gender is considered to be the pre-trauma factor with the strongest link to the development of PTSD: the prevalence of PTSD is twice as high in women compared to men (McLean et al., 2011; Olff et al., 2007). No single explanation can fully account for the reported differences but the high conditioned prevalence after rape and sexual assault may be one part, as rape has been shown to be the most common onset for PTSD in women (Kessler et al., 1995). Gonadal hormones, found to effect memory consolidation processes and extinction learning, have also been suggested to play a role in the gender difference of PTSD (Glover et al., 2012; Pineles et al., 2016; Zoladz & Diamond, 2013). Some authors argue for a multi-variable model. Women are found to experience higher levels of associated risk indicators overall than men which may account for the difference (Christiansen & Hansen, 2015; Olff et al., 2007).

Previous exposure to a PTE has been shown to be a risk factor of more intensive immediate trauma reactions as well as development of PTSD (Gould et al., 2020). The same goes for experiencing mental disorders prior to exposure to the PTE (Brewin et al., 2000; Ozer et al., 2003). In addition, sociodemographic factors – such as young age, being unmarried, have fewer years of schooling, have lower household income, and unemployment – have been associated with increased risk of PTSD. Genetics may also be an important factor. Twin studies have estimated the heritability of PTSD to be between 24–72% (Ryan et al., 2016; Sartor et al., 2011; Stein et al., 2002; True et al., 1993). Data suggests heritability among women to be up to two to three times higher than among men (Duncan et al., 2018).

2.4.2 Peri-trauma indicators

Level of perceived threat during the PTE (Ozer et al., 2003; Resnick et al., 1992) is the most highly correlated peri-trauma indicator to later development of PTSD. High levels of emotions or dissociative reactions during the PTE (Marmar et al., 1996; Ozer et al., 2003; Sijbrandij et al., 2012) and certain characteristics of the PTE may influence the risk of subsequent PTSD. There is an increased risk for the onset of PTSD following exposure to interpersonal violence (Bromet et al., 1998; Kessler et al., 1995; Liu et al., 2017; Lowe et al., 2014; Smith et al., 2016; White et al., 2015) and after prolonged or severe, repeated exposure to PTE (Ozer et al., 2003).

2.4.3 Post-trauma indicators

Perceived low degree of social support is the post-trauma risk indicator with the strongest correlation of subsequent PTSD (Ozer et al., 2003). Other post PTE risk indicators are catastrophic appraisal of the PTE (Bryant & Guthrie, 2005) and financial stress (Sareen, 2014). Some studies have demonstrated a relationship between biomarkers such as heightened concentrations of cytokines and C-reactive protein and elevated heart rate early after a PTE and later development of PTSD (Michopoulos et al., 2017; Morris et al., 2016). The presence of involuntary images of the PTE in the form of flashback memories has also been implicated in the onset of later PTSD (Bryant et al., 2017).

2.5 EMOTIONAL PROCESSING THEORY

There are several psychological theories that try to explain the onset and maintenance of symptoms of post-traumatic stress. The theories relevant for the work in this thesis are the two most influential – learning theory and emotional processing theory.

Mowrer's two-factor model (Mowrer, 1960) conceptualises chronic reactions after a PTE occurring through respondent and operant conditioning. The PTE is considered an

unconditional stimulus that has been paired with a number of conditioned stimuli (PTE related cues) associated with a conditional response (e.g., anxiety). They are thought to form a discriminant stimulus signalling avoidance and escape. Avoidance and escape behaviours in turn become negatively reinforced, and result in maintaining avoidance behaviours and the symptoms of PTSD.

Foa and Kozak (1986) extended Mowrer's two-factor model by incorporating cognitive elements from Lang's bioinformational theory (Lang, 1979). In their theoretical framework – namely emotional processing theory – Foa and Kozak stipulate that exposure to PTE creates mental fear structures with the aim to avoid danger. This fear structure holds information about the stimuli, the fear response as well as interpretations of the stimuli and the fear response. For example, a rape victim's fear structure can include representations of the physical features of the assailant and representations of responses such as increased heart rate during the rape. In addition, the meaning assigned to the stimuli, such as 'blue-eyed men are dangerous' or the meaning of increased heart rate as 'I am in danger' are thought to be incorporated in the fear structure. The fear structure in the memory is considered to be a 'blueprint' for escaping danger and to function as a trigger for effective responses to danger. If danger is still present, a functional fear structure will contribute to keeping the individual safe. The fear structure can also be activated in objectively safe environments, creating excessive and non-adaptive escape and avoidance behaviours. These avoidance behaviours are thought to maintain the fear structure in its pathological state.

The presumed mechanism of recovery in this theory is emotional processing. To achieve emotional processing, the theory posits that 1) the pathological fear structure needs to be activated in order to modify the fear structure and 2) new, incompatible information needs to be incorporated. New experiences are thus hypothesised to form a new functional cognitive structure competing with the pathological (Brown et al., 2019; Cooper et al., 2017).

2.5.1 Treatment of long-term reactions after PTE

Most published clinical guidelines suggest that one of the first line treatment for long-term reactions after PTE (PTSD) is trauma-focused CBT (CBT-T) (Hamblen et al., 2019). PE is one form of CBT-T based on emotional processing theory presented above that has considerable empirical support for the treatment of PTSD in various trauma type groups (Cusack et al., 2016). The treatment usually consists of up to 15 individual weekly 90-minute sessions (Foa et al., 2019). Emotional processing theory stipulates that the pathological fear structure needs to be activated and access to corrective information made available for treatment success. In PE,

this is done through the use of two core treatment components – in vivo and imaginal exposure, i.e., confrontation of avoided trauma related situations, including revisiting the memory of the traumatic event and break avoidance that is considered to maintaining the symptoms of PTSD (Foa et al., 2019).

The repeated exposure to trauma-related cues is thought to facilitate emotional processing by decreased emotional responding within and across sessions (Brown et al., 2019). The negative cognitions about the world and oneself often seen in patients with PTSD are thought to disrupt natural recovery through the promotion of avoidance. Accordingly, PE focuses on the modification of negative cognitions during and after exposure. By repeated exposure and reappraisal of cognitions, emotional processing is believed to create a competing fear structure. Following a successful PE treatment, two competing fear structures (one pathological and one functional) are thought to have been formed. Either of them may be retrieved and activated depending on their associative strength to the contextual cues.

PE also comprises two minor components: psychoeducation about common trauma reactions and controlled breathing, the latter is taught as a tool to reduce everyday distress and anxiety (Foa et al., 2019).

2.6 THE NEED FOR EARLY INTERVENTIONS AFTER EXPOSURE TO PTE

There is a substantial discrepancy between demand and availability – referred to by Kazdin (2017) as the treatment gap – of evidence-based trauma-focused treatments for PTSD. Research has consistently demonstrated the factors that maintain the gap in patients, providers, organisational and intervention levels (Finch et al., 2020; Foa et al., 2013). The first problem involves the detection of patients in need of help. Around only half of patients with PTSD have been found to actually seek help for their problems (Kessler, 2000). Barriers preventing patients from seeking help are thought to include the stigma, shame and fear of rejection, low ability to understand and utilise medical information, lack of knowledge and treatment-related doubt, fear of negative social consequences, limited resources, time and expenses as well as fear of elevated re-experiencing symptoms (Kantor et al., 2017). At the provider level, several other barriers have been found. Many clinicians do not conduct effective assessment procedures to detect PTSD cases (Al-Saffar et al., 2002), and lack proper training in evidence-based treatments for PTSD (Jonas et al., 2013). Provision of training is not always a certain way to increase access to evidence-based interventions. Large dissemination projects, with the aim to train providers in evidence-based trauma-focused treatment, have not proven to address the problem in a satisfactory way. Training in evidence-based treatment has been found to

positively impact knowledge, attitudes, and self-efficacy, but not necessarily influence the provider's actual usage and intention to implement exposure-based interventions – despite the strong evidence base (Finch et al., 2020; Trivasse et al., 2020). For example, Ruzek et al. (2017) reported that providers trained in PE used the treatment for merely 14% of their weekly PTSD cases. Providers report negative beliefs about exposure and that patients will not be able to tolerate the treatment component (Deacon & Farrell, 2013; Jonas et al., 2013). Research suggests that common provider concerns revolve around risk of symptom exacerbation and the presence of rather subjective contraindications of treatment that are not supported in the literature (e.g. the presence of comorbid conditions such as borderline personality disorder or major depressive disorder; Cook et al., 2014; Foy et al., 1996; van Minnen et al., 2010). Another key barrier at the organisational level is the lack of support of the use of evidence-based treatment (Finch et al., 2020). For example, too few incentives or no mandates for implementation, no access to supervision, lack of support from colleagues and organisational leaders, insufficient resources, and providers may have a too high case-load that prevent them from scheduling patients for weekly 90-minute appointments as is recommended by the PE treatment manual.

The treatment gap is resulting in a major public health burden and draws attention to the need for new strategies. The long-term prognosis for untreated PTSD cases is poor, with reduced physical health, low quality of life, disability and associated psychiatric symptom, further highlighting the need to treat afflicted in risk for that trajectory early. One possible way forward could be to deliver early, brief and easily scalable interventions, before adverse reactions become psychiatric symptoms. The rationale for the provision of PE early on after exposure to PTE could be said to assist in the natural recovery process and break avoidance which is the stipulated maintenance factor of symptoms of post-traumatic stress. This type of intervention could provide a way to faster alleviate symptoms of post-traumatic stress and may possibly prevent the subsequent development of other comorbidities.

In preventive research, interventions are typically divided into universal (targeting the whole population), selective (targeting sub-groups or individuals at higher risk for the disorder than the average population), and indicated (targeting high risk groups with detectable signs or symptoms foreshadowing the mental disorder or biological markers indicating predisposition for the disorder) approaches (Saxena et al., 2006). In the field of early interventions after PTE, interventions targeted at everyone involved (universal approach) or interventions targeted only at symptomatic individuals (indicated approach) are the most common.

2.6.1 Psychological early interventions

Critical incident stress debriefing is a well-known intervention that has historically often been provided to people recently exposed to a PTE. Its use has declined after findings have indicated that not only is it an ineffective intervention, it may actually worsen long-term trauma-related symptoms for some individuals (Rose et al., 2002). With this in mind, new psychological interventions for individuals recently exposed to PTE need careful and rigorous clinical testing.

Several studies have shown that CBT-T interventions consisting of five to six sessions to individuals with ASD a couple of weeks after the PTE is more effective than control conditions to reduce long-term reactions of post-traumatic stress (Bryant et al., 1998; Bryant et al., 2008; Bryant et al., 2003; Bryant et al., 2000; Bryant et al., 2005; Shalev et al., 2012; Sijbrandij et al., 2007). A study on victims of sexual or non-sexual assault found a similar CBT-T intervention to be more effective in the prevention of chronic PTSD than assessment only (Foa et al., 1995). CBT-T has furthermore been tested in the days following exposure to PTE. Rothbaum et al. (2012) recruited trauma victims at an emergency department and evaluated a three-session PE protocol initiated 12-24 hours after exposure to a PTE. The randomised trial (N=137) showed that the brief PE intervention was more effective in reducing symptoms of posttraumatic stress and depression after 12 weeks than assessment only (Rothbaum et al., 2012). Additional analysis showed that the intervention reduced the genetic risk for PTSD (Rothbaum et al., 2014). However, these promising results were not replicated in a comparison of the three-session protocol (n=35) against a one-session protocol (n=36) and assessment only (n=24) (Maples-Keller et al., 2020). Reasons for the null findings may be low statistical power to detect differences between groups, the universal recruitment approach with a low symptom severity in participants and a lower proportion of rape victims than in the original study.

Adaptation of PE has been made to fit patients with PTSD detected early in primary care settings (primary care PE, PC-PE). The treatment period is shortened compared to the original PE protocol and only four 30-minute sessions focused on imaginal and in vivo exposure are provided. This treatment protocol has shown promising results in some recent research trials (Cigrang et al., 2017; Fedynich et al., 2019; Rauch et al., 2017).

Another CBT-T intervention with encouraging results is tailored specifically to rape victims for use immediately before they are forensically examined. Resnick et al. (2007) has developed and evaluated a 17-minute video presentation with content that includes information about the forensic examination, psychoeducation about common reactions after a rape and coping strategies to handle anxiety. One randomised trial that compared the intervention to standard

care showed a larger decrease in post-traumatic stress symptoms and marijuana abuse in the intervention group (Miller et al., 2015).

Furthermore, one attempt has been made to adapt parts from CBT-T to an internet-delivered format using a universal recruitment strategy. Mouthaan et al. (2013) investigated if an unguided internet-delivered intervention with components such as psychoeducation, stress management/relaxation and in vivo exposure, could reduce early symptoms of post-traumatic stress in patients seeking medical attention at an hospital emergency department. Results from a randomised controlled trial could not prove superiority of the intervention against a control group. One limitation in this trial was that less than 40% of the participants in the study logged in more than once to the intervention platform.

Basic psychoeducation about psychological trauma and how to cope with trauma symptoms, delivered via a self-help booklet has not demonstrated any effect in the prevention of symptoms of post-traumatic stress (Scholes et al., 2007; Turpin et al., 2005). However, psychoeducation may be used to enhance resilience and if needed help-seeking behaviour (Wessely et al., 2008). The addition of a brief structured writing task to information about common reactions as a form of self-help have neither been found to prevent the onset of PTSD symptoms (Bugg et al., 2009) nor shown superiority over CBT-T (van Emmerik et al., 2008)

Experimental research with roots in cognitive science has focused on how to reduce intrusive flashback memories directly following a PTE. The intervention, a visuospatial task (playing the computer game Tetris), has been evaluated in the first six hours after exposure before memory consolidation is thought to occur. Promising results have been found in reducing intrusive flashback memories in the first week after trauma exposure when delivered via a game console (Horsch et al., 2017; Iyadurai et al., 2018). In a more recent pilot RCT where the visuo-spatial task was delivered as a mobile app and the time-frame for inclusion was extended to 72 hours, larger reductions in the number of intrusive, flashback memories were found to arise in week 1 and week 5 post-trauma, compared to an active control condition (Kanstrup et al., 2021). Another study that used a different mobile app game thought to have the same characteristics as Tetris did not replicate these promising results (Asselbergs et al., 2018). Nor did an RCT that investigated a semi-immersive Virtual reality visuospatial intervention (Freedman et al., 2020).

To summarise, the evidence-base for early interventions is scarce. Specifically, there is little evidence that supports the use of early interventions aimed at everyone exposed to a PTE. For individuals recently exposed to PTE who are symptomatic before entering an intervention,

findings are promising – when using symptom severity of post-traumatic stress as outcome. Two recent reviews conclude that there is no support to recommend any early intervention for routine care for everyone exposed to PTE, however, early routine detection and assessment as well as provision of intervention for symptomatic individuals with CBT-T are advocated (International Society for Traumatic Stress Studies, 2020; National Institute for Health and Care Excellence, 2018).

2.7 ROOM FOR IMPROVEMENT

Exposure to PTE is common, with the majority of afflicted individuals experiencing acute stress reactions such as intrusive memories of the event, avoidance of PTE-related cues and hyperarousal and a significant minority developing long-term symptoms. There is no reliable decision algorithm after exposure to PTE for singling out individuals who will suffer long term consequences such as PTSD. Trauma-focused psychological treatments are effective in treating PTSD, but there are several barriers that create a shortage of supply of evidence-based ones.

One way to overcome many of the barriers could be to deliver brief and easily scalable early interventions after exposure to PTE. Emerging evidence suggests that early CBT-T may be effective. Little is known about how these results can be applied to a Swedish healthcare context, hence there is a need to investigate feasibility, acceptability and effectiveness. The studies in this thesis extend the research on psychological interventions provided in the early aftermath of PTE.

3 RESEARCH AIMS

The aim of this thesis was to develop and test out new early psychological interventions after exposure to potentially traumatic events in order to facilitate recovery and reduce immediate distress for those exposed.

3.1 STUDY I

The primary aim of study I was to investigate PE as an early intervention for people recently exposed to PTE who have sought medical help at a Swedish hospital emergency department. The hypothesis was that PE provided within the first 72 hours after PTE exposure would be superior for preventing the development of symptoms of post-traumatic stress compared to an active control condition. The study also aimed to investigate cost-effectiveness and mediators of intervention response.

3.2 STUDY II

Study II tested if PE is a feasible early intervention for rape victims. The hypothesis was that PE would be feasible for that specific trauma group and lead to significant reductions on symptoms of post-traumatic stress.

3.3 STUDY III

The aim of study III was to evaluate if condensed internet-delivered PE (CIPE) is a feasible and acceptable early intervention following PTE. The main hypothesis was that CIPE would prove to be feasible and acceptable. In addition, the study's secondary objective was to investigate if CIPE is a potentially effective intervention for estimating how to properly power a subsequent large-scale trial.

3.4 STUDY IV

Study IV aimed to explore the participants' experiences of engaging in the CIPE intervention early after exposure to PTE.

3.5 STUDY V

Study V evaluated the short and long-term effects of the CIPE intervention compared to a waiting list control condition in a RCT. The hypothesis was that participants in the CIPE group would experience larger short and long-term reductions in symptoms of post-traumatic stress.

4 EMPIRICAL STUDIES

4.1 THE INTERVENTION

This thesis covers the development and evaluation of early interventions after exposure to PTE based on the PE manual developed by Foa et al. (2019). The intervention was provided in different formats (face-to-face and digitally) and at different time points after exposure to PTE.

As previously discussed in the introduction, PE is based on emotional processing theory. Long-term reactions and PTSD are seen as signs that the traumatic memory has not been sufficiently processed and a pathological fear structure has formed. The way to recover and emotionally process the traumatic event is therefore to change the pathological fear structure. The way to change this pathological process is through exposure to fear-related cues (i.e., in vivo exposure to avoided trauma related situations and imaginal exposure by revisiting the memory of the traumatic event followed by processing). Negative cognitions about the world and oneself is hypothesised to disrupt natural recovery and mediate the development and maintenance of symptoms through promoting avoidance. Consequently, PE focuses on modifying these negative cognitions during and after exposure exercises.

4.2 PE PROVIDED EARLY AFTER EXPOSURE TO PTE

In studies I and II, the idea was to replicate and extend the promising findings from the Rothbaum et al. (2012) trial. The study authors provided us with the intervention protocol which was then translated into Swedish and adapted to fit the settings in a Swedish emergency hospital setting. The brief intervention comprises of three face-to-face sessions intended to prevent the development of symptoms of post-traumatic stress. The first session involves psychoeducation about common reactions after trauma, imaginal exposure to the memory of the PTE, a review of breathing retraining as a technique to alleviate daily stress and a plan for how to conduct in vivo exposure out in the 'real world'. After the first session, the participant receives three homework assignments; listen to a recording of the imaginal exposure daily at home, practice breathing retraining and in vivo exposure as much as possible. The remaining sessions follow the same structure mainly focusing on exposure exercises.

Study III, IV and V investigated a condensed internet-delivered prolonged exposure (CIPE) protocol that was developed based on the experiences from study I and II. CIPE is a three-week therapist-guided digital intervention with the aim to ameliorate early reactions of post-traumatic stress. The material such as the rationale for and instructions how to conduct exposure are text-based, although it can be accessed in a audio format. Case vignettes are used to illustrate intervention components. Participants gain successive access to the four modules

after completion of the previous and the associated homework exercises. Each module has a different theme: 1. psychoeducation, 2. imaginal exposure, 3. imaginal exposure to the worst parts of the traumatic memory, so called hot spots, and in vivo exposure and 4. maintenance of progress made. For a detailed description, see table 1.

Table 1. An overview of the content and exercises in each of the four modules in CIPE.

	Content	Homework
Module 1	Introduction to the internet platform Psychoeducation about common reactions to trauma Overall rationale for the intervention Case vignettes Instruction for controlled breathing	Quiz Practise controlled breathing
Module 2	Rationale and instructions for imaginal exposure and processing Common pitfalls with imaginal exposure Case vignettes	Quiz Practise controlled breathing Daily practise of imaginal exposure followed by processing
Module 3	Rationale and instructions for imaginal exposure focusing in on hot spots Rationale and instructions for exposure in vivo and how to construct a in vivo hierarchy Common pitfalls with exposure in vivo Case vignettes	Quiz Practise controlled breathing Daily practise of imaginal exposure of the hot spot followed by processing Practise exposure in vivo according to a predetermined hierarchy
Module 4	Summary of gains Case vignettes Maintenance and relapse prevention plan	Create a maintenance and relapse prevention plan Practise controlled breathing Practise imaginal exposure of the hot spot daily Practise exposure in vivo according to a predetermined hierarchy

The intervention is provided via a digital platform where the participant securely can communicate with the psychologist using an integrated email system. The psychologist normally responds within 24 hours on weekdays after reviewing the digital worksheets used and provides tailored feedback and support. Participants conduct exposure exercises

independently; no psychologist is physically present and there is no face-to-face contact throughout the intervention period.

4.3 THE PARTICIPANTS

In all studies, the recruited participants were Swedish residents exposed to a PTE according to the definition used in the DSM-5 (American Psychiatric Association, 2013). In studies I and II, participants were recruited within 72 hours after the index event. In studies III and V, the corresponding timeframe was 2 months.

In studies III and V, an indicative recruitment approach was used where only participants with at least some level of symptoms of post-traumatic stress were included. Inclusion criteria in study III stipulated the occurrence of a minimum of one daily intrusive, flashback memory from the index event on the week before inclusion. In study V, we changed the inclusion criteria to consist of a self-rated symptom severity of ≥ 10 points on the PTSD Symptom Checklist for DSM-5 (PCL-5).

Exclusion criteria in all studies were mainly based upon the occurrence of other serious psychiatric comorbidity of primary concern (ongoing psychotic symptoms or ongoing manic episode, suicidal ideation). Participants who were intoxicated with alcohol or other drugs at the time of assessment and initiation of intervention, or who were assessed as having low cognitive capacity were excluded in study I and II.

In studies III and V, applicants with ongoing trauma-related threats (e.g., living with a violent spouse) or in current CBT-T treatment were excluded. In study III, participants taking antidepressant medication were included if they had been on a stable dose for 1 month prior to inclusion in the study. This threshold was lowered to 2 weeks in study V.

The most common trauma types were exposure to death, rape, interpersonal violence, and accidents. Typically, participants were women in their mid-forties with a college education. In addition, the typical participant fulfilled the criteria for at least one psychiatric diagnosis. The mean baseline symptom burden of post-traumatic stress using the PCL-5 sum score was between 43-53 points. In a Swedish sample, a cut-off of 29 has been found to be indicative of probable PTSD (Bondjers, 2020).

4.4 STUDY 1: PROVISION OF PE TO TRAUMA PATIENTS IN A HOSPITAL EMERGENCY DEPARTMENT

4.4.1 Research approach

Study I was a randomised controlled trial with a target size of 352 participants and was launched after a successful pilot feasibility study. The study was conducted at a large emergency hospital department and used a universal recruitment approach. Participants were allocated to three 60-minute sessions of either PE or non-directive social support that started within 72 hours of exposure to PTE. Blinded assessors administered the primary outcome measure, the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5: Weathers et al., 2013), at 2-month and 6-month follow-ups. Secondary outcome measures included the PCL-5 (Blevins et al., 2015) and the Montgomery Åsberg Depression Rating Scale – Self rated version (MADRS-S: Svanborg & Asberg, 1994).

4.4.2 Main results

A major organisational change at the hospital that affected recruitment meant that the trial was terminated after 32 participants. Given the small sample size, we did not conduct any statistical analyses to investigate effectiveness. The trial also acknowledged a high degree of attrition; at the 2-month follow-up only three out of four participants returned for assessment and at the 6-month follow-up only one-third did. It was generally experienced as difficult to motivate the participants to come back to the hospital for the assessments. Moreover, the 72-hour time limit for inclusion was hard to keep with patients that had left the emergency hospital department. The study could therefore neither support nor reject the hypothesis that PE provided as an early intervention would be superior in reducing symptoms of post-traumatic stress compared to non-directive support.

4.5 STUDY II: PROVISION OF PE TO RAPE VICTIMS AT AN EMERGENCY DEPARTMENT

4.5.1 Research approach

Study II was a non-randomised feasibility study in which 10 rape victims recruited at an emergency department for rape (Emergency department for rape, Södersjukhuset in Stockholm Sweden) were provided with three sessions of brief, early PE. The same methodology as in study I was used.

4.5.2 Main results

Homework compliance and session attendance were high during the PE intervention and participants experienced clinically meaningful reductions in symptoms of post-traumatic stress

and depression. Yet, as little as 5.2% of the patients screened were eligible to be included in the study. The time criteria of 72 hours to initiate the intervention posed the greatest hurdle, both for patients as well as for clinicians. The hypothesis that PE would be a feasible intervention was only partly supported.

4.6 STUDY III: A PILOT FEASIBILITY TRIAL OF CONDENSED INTERNET-DELIVERED PE

4.6.1 Research approach

The strategies used in studies I and II for recruitment and provision of the intervention was not feasible yet provided valuable information. Therefore, several methodological changes were made in study III.

The time criteria used for inclusion in study I and II posed a barrier to recruitment and an extension of the timeframe were hypothesised to substantially increase the number of afflicted we could reach and help. Accordingly, the time criterion in study III was extended to two months. The high attrition rate found in study I was partly hypothesised to be a consequence of the universal approach to recruitment i.e., many participants were probably not very motivated to participate in the trial. The assumption that adherence would improve by only offering the intervention to individuals with a certain level of symptoms of post-traumatic stress was made. Consequently, study III used an indicative approach to recruitment with an inclusion criterion of experiencing daily, intrusive memories or flashback memories from the index event one week before inclusion. The reason for choosing intrusive, flashback memories as indicator to intervention is because they constitute one of the hallmark symptoms of PTSD. In addition, the presence of symptoms from the intrusion cluster in the acute post-trauma phase have been shown to be a risk indicator for long-term psychiatric problems such as PTSD (Bryant et al., 2017). For the purpose of collecting data on number of intrusive recollections or flashback memories and its associated distress and vividness, a smartphone app was developed in the form of an intrusive memory diary. Before inclusion in the study, the applicants used the intrusive memory diary for one week. In order to solve many of the other problems experienced in study I, the recruitment, assessment and intervention procedures in study III were done remotely instead of face-to-face.

Study III was a randomised feasibility trial (N=33) in which participants were allocated three weeks of condensed internet-delivered PE (CIPE) or a waiting list control condition for the same amount of time. Participants were recruited using adverts in social media, newspapers and flyers at primary care and psychiatric units. Feasibility was assessed by looking into

number of exposure exercises during the intervention, module completion, frequency of log-ins and messages sent to the psychologists, participant satisfaction, and the frequency of possible negative side effects and adverse events related to the intervention. Acceptability was assessed according to the definition by Sekhon et al. (2017) that states that acceptability is the extent to which a healthcare intervention is considered appropriate based on anticipated or experienced cognitive and emotional outcomes. Secondary outcome measures included distressing and vivid daily intrusions in the week following intervention completion, symptoms of post-traumatic stress, depressive symptoms, and quality of life. Data from the intrusive memory app was analysed using a generalised estimating equations model with a negative binomial distribution. For the self-rated measures, preliminary effects of CIPE were calculated using group, time, and group*time interaction effects in a mixed models effects regression framework from baseline to intervention completion.

4.6.2 Main results

The findings supported our hypothesis that CIPE is a feasible and acceptable early intervention after exposure to PTE. The remote recruitment, assessment and intervention procedures were overall successful. Nevertheless, there were some technical difficulties associated with the usage of the app. The majority of participants (82%) completed all modules in CIPE and the mean number of logins to the intervention platform were almost daily (M = 19.6, SD = 11.8). The completion rate of CIPE was lower in the waiting list control group when receiving the intervention after the controlled time period of 3 weeks. Participants reported to be satisfied with the intervention, the exposure exercises were tolerable and we did not find any serious adverse events associated with the intervention. As for our secondary aim – investigating the preliminary effects of CIPE in reducing symptoms of post-traumatic stress – results did not indicate any interaction effects on number of intrusions. However, we found a statistically significant reduction of vividness and distress associated with the intrusions at post-intervention in the CIPE group compared to the waiting list control group. The results were more pronounced when looking at the data collected from the self-rated measure PCL-5 where a more favourable reduction in symptoms of post-traumatic stress were found in the CIPE group than in the waiting list control group. The between-group effect sizes were in the large range at post-intervention (bootstrapped d = 0.85, 95% CI [0.25–1.45]). Intervention effects were sustained at a 6-month follow-up.

4.7 STUDY IV: QUALITATIVE INVESTIGATION OF STUDY III

4.7.1 Research approach

Study IV was a qualitative study that investigated participants' experiences of CIPE. We tried to contact all 16 participants randomised to CIPE six months after intervention completion and were able to reach 11 that consented to be interviewed about their experience with CIPE. The interviews lasted between 30 and 60 minutes. A semi-structured interview schedule was used containing six themes: general experiences or adverse events of the intervention, the intervention process, the level of care and contact with the designated psychologist, the experience of being given an intervention early after exposure to PTE, experiences of conducting intervention exercises in everyday life, unmet expectations and suggestions for improvement. All interviews were audio recorded and transcribed verbatim by the same interviewer that conducted the interview. The interviewers were two clinical psychologists not involved in study III and they also coded the transcripts. The framework of thematic analysis (Braun & Clarke, 2006) was used to code the data and categorise the codes into main themes and subthemes.

4.7.2 Main results

The participants perceived CIPE as a demanding, yet effective intervention for reducing symptoms of post-traumatic stress. Participants considered the two types of exposure exercises tolerable in the digital format. Imaginal exposure was perceived as both the most distressing part of the intervention and as the most important one. The possibility of daily contact with the therapist helped them engage in exposure. CIPE was perceived as credible and participants found the autonomy of the online format to be a helpful way of engaging with the intervention. In addition, the participants found the internet platform to be a secure forum for self-disclosure. The digital format helped some participants share details of the traumatic event that they perceived would not have been possible if the contact would have been face to face.

4.8 STUDY V: AN EFFICACY TRIAL OF CONDENSED INTERNET-DELIVERED PE

4.8.1 Research approach

Study V expanded on the results from study III in a larger RCT (N=102) while controlling for a longer period of natural recovery in order to investigate the long-term effects of CIPE. In this trial, a cut off of ≥10 points on the PCL-5 was used as indicative of a need for the intervention. Symptoms of post-traumatic stress were assessed weekly. Participants randomised to the waiting list crossed over to CIPE after the controlled study period (week 7). Secondary outcome

measures included the MADRS-S and the EQ-5D. The efficacy of the intervention was evaluated using a mixed effects regression with maximum likelihood estimation. Included in the model were fixed effects of group (CIPE vs. waiting list), time (baseline, week 1, week 2, week 3, week 4 week 5, week 6, week 7), and group*time interaction. The model also included a random intercept.

4.8.2 Results

The findings supported our hypothesis that participants in the CIPE group would experience larger short and long-term reductions in symptoms of post-traumatic stress compared to a waiting list control condition. The between-group effect size was moderate at intervention completion (bootstrapped *d*=0.71 [95% CI; 0.33 to 1.05]) and large at the 1-month follow up (bootstrapped *d*=0.83; [95% CI 0.46 to 1.19]).

A greater decrease in depressive symptoms were found at the 1-month follow up (β=4.04, Z =2.39, p= 0.02; bootstrapped *d*=0.40; [95% CI 0.08 to 0.72, *p*=0.02), compared with the waiting list group. In addition, quality of life was increased compared to the waiting list group at the same time-point (β=0.07, Z =2.04, *p*= 0.04; bootstrapped *d* =0.40; [95% CI 0.07 to 0.75).

Results were sustained at the 6-months follow up and longer-term follow-up will be conducted at 12 months post-intervention.

4.9 ETHICAL CONSIDERATIONS

Ethical considerations are of utter importance for research in general, and particularly during the investigation of new interventions for recently PTE exposed individuals that may be emotionally, cognitively and physically vulnerable. The ambition has been to strive for high ethical standards through the entire process in planning the studies and potential risks for the participants have been thoroughly assessed. All the studies included in this thesis were approved by the Regional Ethical Review Board in Stockholm, Sweden or the Swedish Ethical Review Authority Sweden. Some specific ethical considerations concerning recently PTE exposed individuals are stressed below.

Enquiring about exposure to PTE and psychological reactions after the event may be associated with a risk of discomfort for participants. Nevertheless, previous studies have shown that participants who experience discomfort in the presence of PTE related cues have a positive attitude towards participating in research. The perceived importance of being able to contribute to increased knowledge seems to make the – generally speaking – transient discomfort worthwhile (Ferrier-Auerbach et al., 2009; Galea et al., 2005; Griffin et al., 2003).

Another important issue is to not pathologize natural, early reactions after exposure to PTE. During recruitment and intervention, we tried to normalise reactions and conveyed the notion of possibility of natural recovery. The British Psychological Society (2017) states that research participants in internet-delivered interventions should generally not be exposed to greater risk of harm than in normal life. The participants in every study in this thesis were provided with oral and written information about the studies, what to expect, possible adverse events and possible gains by participating. In addition, participants were informed of their right to discontinue their participation in the intervention/study at any time, stressing that it would not affect their regular care. The eligibility criteria for participating in the interventions were carefully chosen to maximise patient safety. Several steps were taken to ensure quality and safety in assessment. The participants in each study underwent an in-depth telephone or face-to-face assessment from a psychologist or a trained student in the final semester of their 5-year clinical psychology degree program to ensure that there were no other serious psychiatric comorbidities of primary concern in need of treatment. The self-rated measures in studies III and V were conducted via an internet platform with double authentication procedures that securely stored sensitive data in accordance with applicable laws and regulations.

The assessors in all the studies used written routines developed by the research team to provide the excluded participants with advice on how to seek help from regular mental health care services.

Prior to the studies conducted in the thesis, there had only been few or no studies on PE as an early intervention in the different settings used (face-to-face, internet-delivered, different timeframes for inclusion). As with all novel interventions, a smaller pilot study was important for investigating whether the intervention was suitable and acceptable and ensure that the intervention was not associated with any unwanted effects before determining whether a more comprehensive evaluation was justified. Consequently, the larger trials were not initiated until a pilot, feasibility study gave the green light to move forward.

An important ethical procedure throughout all the studies in the thesis was to closely monitor adverse events, as previous studies on critical incident debriefing have shown some adverse effects. In studies I and II, we collected data on adverse events at each session during the intervention period and at the different follow up time points. For study III and study V, the participants had the possibility to have daily online contact with the psychologist during weekdays via the platform and could communicate sudden deterioration in symptoms or other possible adverse events. Studies III and V used a specific self-rated questionnaire regarding

adverse events during and after the intervention period. The use of weekly measures in study V provided us with continuous data on changes in levels of symptoms of post-traumatic stress and possible adverse events associated with the intervention. The participants were given contact information for the study personnel and their psychologist so they were able to get in touch to discuss worsening on symptoms or possible adverse events.

In every study included in the thesis, the burden of filling out measurements was balanced with maximizing quality of data. Assessment measures were primarily chosen to capture symptoms of post-traumatic stress and the most common associated problems such as depression. In study III, the intrusion app we used for registration of intrusive or flashback memories was designed to be an easy tool to collect data. Unfortunately, the app came with some software malfunctions and some participants found its usage tiresome. The decision to discard the app and reduce assessment burden in study V was in part based on ethical considerations.

For the qualitative research included in the thesis, study IV, some specific ethical issues were considered regarding participant confidentiality. The quotes and demographic information presented in the manuscript to illustrate the themes were carefully chosen with the specific aim not to convey more information than deemed necessary.

In closing, given the measures taken to reduce or obviate the risks, the potential gains of finding effective early intervention for recently exposed to PTE can be said to outweigh the concerns of potentially harming the participants.

5 DISCUSSION

The general aim of this thesis was to develop and test out novel early psychological interventions after exposure to a potentially traumatic event(s) in order to facilitate recovery and reduce immediate distress in the exposed.

5.1 THE RESEARCH PROCESS AND MAIN FINDINGS

The original study plan for the thesis only included studies I and study II. The experiences gained from these two initial studies changed the direction of the research, hence changes were made in the delivery format of the intervention, assessment procedures and target population and the study plan was revised to include study III, IV and V. Below follows a discussion of the experiences and results from each of the included studies.

The RCT trial in study I was launched after a successful pilot study but had to be terminated beforehand due to organisational changes. The study procedures were developed to specifically fit the specific recruiting site (Karolinska University Hospital in Solna, Sweden) and could not be transferred elsewhere. In addition, one fourth of the potential participants were excluded due to the time criterion of 72 hours and the level of attrition was high. Our experience was that patients who had left the emergency hospital department were generally not very motivated to come back right away for assessment and potential intervention sessions at the hospital. It was also difficult to motivate participants to return to the hospital for additional follow-up assessments, especially after 6 months. The experiences gained from study I led us to believe that digital recruitment, assessment, and intervention procedures could be a way to circumvent some of the problems we encountered in study I. We stipulated that a digital format could provide better flexibility when and where applicants enrol and fill in assessments and ensure independence from a specific recruitment site. The experiences also led us to believe that an extension of the time-frame from exposure to PTE could increase the recruitment base.

The same study procedure as study I was used in the simultaneously conducted study II. Again, we found a low degree of eligible participants where as much as 40% of the screened sample was excluded due to the 72-hour time criterion. The generally low recruitment rate in both study I (varied from 30% and fell to 2.8% of all screened participants) and study II (5.2% of all screened participants) is reported in other studies conducted in similar contexts (Iyadurai et al., 2018; Rothbaum et al., 2012). One way to solve this would have been to station study personnel at the recruitment site around the clock, but that approach was not feasible at the clinic. The results from study II further supported us in our decision to change the research approach.

In study III, the research team made extensive changes to the research methodology. In terms of recruitment, we became independent of a specific clinic and interested applicants could, regardless of where in Sweden they lived, self-refer themselves through a secure website operated by Karolinska Institutet. The assessment and intervention procedures were administered online and the time frame used for inclusion was expanded to 2 months after the PTE. Furthermore, the decision to use an indicated recruitment approach and target individuals with a certain level of post-traumatic stress reactions in order to be eligible for study participation was made.

A major challenge in study III was to develop an intervention that could provide the participants sufficient information and motivation to confront PTE related stimuli without a face-to-face therapist. The rationales and instructions needed to be extensive enough to ensure a clear understanding of the intervention components. At the same time, many PTE exposed individuals experience concentration difficulties and we saw a need to simplify and condense the content in each module, while balancing the need for details. In order to improve user experience and increase accessibility and flexibility in the intervention, the material was audio recorded and could be accessed on a digital device. Additional case vignettes were incorporated and designed to further personalise the CIPE intervention and increase perceived relevance for the participants. The vignettes were also used to illustrate symptoms of post-traumatic stress, how to conduct exposure exercises, obstacles that may arise during exposure and how to overcome these and maintaining intervention gains. The addition of the possible daily contact with the therapists on weekdays and the provision with phone numbers to the study personnel ensured participants' safety and that participants did not get stuck in interventions components.

The results from study III were informative for several reasons. The recruitment strategy proved to be effective and we managed to reach our target size (N=33) in about 6 months. The mean time since exposure to PTE was around 1 month. Compliance to CIPE was high and data attrition was low, which stands in contrast to a previous trial on internet-delivered early interventions after PTE (Mouthaan et al., 2013). Furthermore, the results contrast with a review on internet-based CBT for PTSD that showed elevated drop-out rates compared to waiting list group conditions (Simon et al., 2019). The addition of high-level of therapist-support may have constituted one characteristic of success. In previous studies, internet-based therapist-supported treatments have shown to provide better effects than unguided interventions (Baumeister et al., 2014). The use of automated reminders has also been shown to increase engagement (Price et al., 2018; Smith et al., 2018) and might have been another factor explaining the high compliance rate in study III. Finally, study III only included individuals who had some degree

of trauma symptoms and who were motivated enough to complete an extensive online screening procedure.

Study III provided preliminary evidence that CIPE can reduce symptoms of post-traumatic stress with sustained effects at the 6-month follow up. However, the completion rate of CIPE was markedly lower in the waiting list control group and the simple explanation may be study fatigue. The relatively comprehensive intrusion diary had to be filled in twice by the waiting list control group before they gained access to the intervention. There were also some technical difficulties with the app, which might have influenced adherence to the intervention. After extensive discussions in the research team, we decided to discard the intrusion diary app as outcome assessment in the subsequent efficacy RCT (study V).

Study IV explored the participants' experience of receiving CIPE and provided a far richer and more individualised and detailed information feedback than would have been able to capture with only quantitative data. The data from the interviews suggested that exposure exercises in the digital format with remote therapist support was tolerable and feasible. In addition, results indicated that the imaginal exposure was the most distressing part of the intervention, however it was also described as the most vital for recovery. CIPE was perceived as a credible intervention that allowed flexibility in when and where to engage in the intervention. The flexibility together with the possibility of daily support was regarded as helpful for participants to engage in exposure. The digital format was described as a secure way to disclose details about the index trauma and reactions afterwards and even helped some participants overcome shame that otherwise would have led to avoidance if they would have met the therapist face to face. The results share similarities with a previous trial that investigated military veterans' views on prolonged exposure and showed that perceived initial distress during exposure is well tolerated and that the symptom reduction associated with repeated exposure actually helps participants engage in treatment (Hundt et al., 2017). Participants reported that they conducted the *in vivo* exposure component in a less structured way than described in the intervention. These findings are suggested to be investigated further.

The work in study V corroborated the promising results from CIPE and our experiences from study III regarding the new research approach. The recruitment rate kept stable throughout the study period, compliance to assessment and intervention was high and dropout rates were low. Study V provided evidence that CIPE was effective in reducing short and long-term symptoms of post-traumatic stress. The between-group effect size was moderate at completion of the intervention and large at the 1-month follow up. The effects on depressive symptoms and quality of life were less pronounced, and still statistically significant at the 1-month follow-up.

No serious adverse events were reported. Our clinical experience from study V was that weekly PCL-5 measures were very helpful for keeping regular track of participants' symptom levels, and if needed, provided useful clinical information to adjust the intervention accordingly. Based on our combined experience, we found the most feasible and effective way to deliver early interventions is to target symptomatic individuals within 2 months after exposure to PTE and use digital recruitment, assessment, and delivery of intervention

5.2 CLINICAL IMPORTANCE OF THE FINDINGS

The reversed effects on symptoms of post-traumatic stress seen in studies on critical incident stress debriefing has sometimes led clinicians to believe that it is in general contraindicated to talk about traumatic events in the early post-trauma phase (Rose et al., 2002). The results from studies III, IV and V do not suggest any harmful effects of CIPE. On the contrary, CIPE may come with the benefit of solving some of the known problems associated with reaching and providing interventions in the acute phase post-trauma. The evidence for feasibility and tolerability of remotely delivered imaginal exposure as part of an early intervention after trauma is an important clinical finding.

Trauma has a huge negative impact on the public mental health and there is a clear need for early interventions for this large population. Given that a substantial proportion of those exposed to PTE will not seek help from mental health services (Kessler, 2000; Shalev et al., 2011) interventions such as CIPE with the potential to lower the threshold to seek help are important. The early detection of symptoms and provision of early interventions can be argued to lower the incidence of chronic disorders and associated secondary problems. Clinically important, internet-based interventions can be used in the exact moment they are needed (Yeager & Benight, 2018). Study IV holds important clinical implications regarding the provision of CIPE. Given the novelty of the intervention and possible concerns clinicians may have about digitally provided exposure in a self-guided manner with no face-to-face therapist contact, examining how individuals actually experience CIPE became important. The results help to inform therapist that the digital support was indeed an important factor and emphasize that imaginal exposure can be perceived as a demanding treatment component. Still, no indication that the participants would have preferred to meet with a face-to-face therapist were found. The feedback given by some participants did however suggest the add-on of telephone calls with the designated therapist. The results from several studies investigating that kind of accompaniment to internet-delivered interventions found it to have an additive effect (Greaney et al., 2012; Pihlaja et al., 2020; Titov et al., 2011) while others have not (Andersson et al., 2003; Farrer et al., 2011; Lindner et al., 2014). Future research could therefore investigate if

the addition of phone calls could have beneficial effects on the results of CIPE. Further, another important clinical implication is that the anonymity in CIPE may come with particular advantages for trauma victims struggling with shame, stigma, fear of rejection and negative social consequences – all common barriers to seeking treatment. The findings in study IV emphasise that the digital format helped participants overcome avoidance behaviours caused by shame and as a result dared to self-disclose about their experiences.

Exposure-based therapies have not been found to precipitate adverse events more than non-exposure based ones (Taylor, 2003). Despite this, many clinicians still have concerns of providing exposure interventions for trauma victims (van Minnen et al., 2010). The too-cautious delivery of exposure that may be the consequence of these beliefs risk reinforcing and maintaining trauma-related symptoms (Foa et al., 2019; Zoellner et al., 2011). Therefore, the standardised elements of CIPE that ensure consistent delivery of the intervention hold important clinical implications as it might prove helpful for overcoming avoidance in therapists and reduce risk of therapy drift. The inexperienced therapists in study V could deliver CIPE under supervision and the intervention structure may have helped there as well. At the same time, previous research suggests that providers that perceive interventions to be too rigid are less prone to use them (Finch et al., 2020). Our clinical experience was that the emotional strain on the therapist was lower in CIPE compared to when conducting PE in a traditional face-to-face treatment context. The participant did not send in recordings or their written trauma narrative to the therapist and the support and feedback in CIPE were provided through an email system after review of digital worksheets. Future research should investigate the therapist's experience as a CIPE provider and compare results with therapists delivering face-to-face treatments. One idea would be to further study CIPE as a training tool for inexperienced trauma therapists. Lastly, the low level of therapist time needed per participant could potentially provide a solution to the lack of suitably trained clinicians in CBT-T and may prove to be a cost-efficient way to provide early intervention to recently PTE exposed.

All in all, the results highlight CIPE as effective and feasible for recently PTE exposed with the benefit of potentially increasing outreach of early interventions. The use of digital interventions might be especially relevant during the current Covid-19 pandemic with travel restrictions and physical distancing in place.

5.3 FOR WHOM IS CIPE EFFECTIVE FOR?

In study IV, some participants speculated in whether CIPE may or may not be suitable for victims of particularly severe trauma such as rape. These concerns are similar to previous

research on healthcare providers and their concerns about exposure-based therapies for PTSD (Deacon & Farrell, 2013). The reluctance among clinicians to utilise exposure therapy is particularly prominent in the presence of comorbid conditions (Cook et al., 2014). Participants in study III or study V were not excluded if they had comorbid conditions, per se. The data collected in studies III and V could therefore be analysed to investigate whether type of trauma and/or comorbidity affects outcome. The dose of therapist support needed for different levels of symptoms of post-traumatic stress could also be investigated further.

5.4 WHAT IS THE OPTIMAL WAY TO DO EXPOSURE?

Emotional processing theory highlights fear activation, decreased emotional responding between sessions, and decreased emotional responding within sessions as important processes during treatment. Evidence supports that fear activation, between-session habituation, and cognitive change, but not in-session habituation, are important factors for treatment effects (Brown et al., 2019). The fact that the necessity of in-session habituation has not been empirically supported has led to a shift towards investigating shorter length sessions than the originally stipulated 40-45 minutes per each imaginal exposure session. Studies investigating the amount of time needed to be spent each session on imaginal exposure have not shown any difference in treatment effects when using 30-minute (van Minnen & Foa, 2006), 20-minute (Nacasch et al., 2015) or 10-minute sessions (Bryant et al., 2019). Therefore, we decided to encourage participants to revisit the memory of the PTE for 20 to 30 minutes. Nevertheless, it is still unclear to what degree the participants in studies III and V adhered to the 20 to 30 minutes imaginal exposures. Data from the participants worksheets in studies III and V should therefore be further analysed and investigated to see if individual differences in length of imaginal exposure in CIPE predicts long-term outcome. Future studies could further investigate the optimal length of imaginal exposure when conducted as an early intervention.

In study IV, participants reported doing the in vivo exposure in a more flexible and independent way than written in the CIPE rationales. The participants described that they confronted PTE related situations whenever opportunities came up in everyday life rather than carefully planning them according to a predetermined hierarchy. Still, participants described the in vivo exposure component as effective. There may be several questions regarding the mechanism of change in in vivo exposure as included in CIPE to investigate further. Can in vivo exposure be effective without the use of a predetermined hierarchy, as some research suggests (Culver et al., 2015; Kircanski et al., 2012; Rowe & Craske, 1998)? Could unplanned flexible in vivo exposure in various contexts be a more effective way to treat PTE related avoidance? The latter would be in line with studies on context-renewal

memory processing (Balooch et al., 2012; Bandarian-Balooch et al., 2015; Shiban et al., 2013). One way to investigate this issue further could be to use ecological momentary analysis during each in vivo exposure exercise in the CIPE intervention where participants would quantitively assess the degree of planning for each in vivo exposure exercise. Another way forward to shed further light on this important issue would be to use an experimental design and compare unstructured exposure with traditional exposure according to a pre-determined hierarchy.

5.5 THE ROLE OF NEGATIVE COGNITIONS ABOUT ONESELF AND THE WORLD

CIPE comes with the specific aims of reducing avoidance and facilitating emotional processing of the traumatic memory. Unsurprisingly, the largest effect sizes, when comparing the four subscales on PCL-5, were found on the avoidance and intrusions subscales. Previous data has suggested that changes in negative cognitions about oneself and the world associated with PTSD is an important mechanism of change in PE and has been implicated to correlate with reductions in symptoms of PTSD (Kumpula et al., 2017; McLean et al., 2015). One idea for future research would therefore be to use data from study V and investigate if changes on the cognitions and mood subscale on the PCL-5 predict subsequent change in other symptoms of post-traumatic stress. This would provide science with tentative data on potential mechanisms of change in CIPE.

5.6 LIMITATIONS

The studies in this thesis acknowledge some limitations. First, selection bias might have affected the results. Participants in studies I and II may represent a certain group from the recruitment sites and the data collected may therefore not be generalisable to the whole patient population at the two different emergency departments. Furthermore, participants in studies III, IV and V were self-referred which also poses a risk of the results not being generalisable to the wider population of PTE exposed individuals. The recruited sample still share typical characteristics seen in patients with PTSD patients, such as an overrepresentation of women. The trauma types in the sample are similar to those found in The WMH Surveys to be the most common precursors of PTSD (Benjet et al., 2016). The high rates of psychiatric comorbidity in the sample was also comparable to what is typically found in patients with PTSD. A second major limitation is that studies III and V relied on self-reported data and future trials may therefore benefit from corroborating the results using clinician-assessed instruments and blinded assessors. A third limitation was the use of a waiting list control group in studies III and V. This may pose a threat to the external validity as waiting list control groups

have been shown to produce higher between-group effect sizes than placebo controls (Gold et al., 2017). A next step could therefore be to include an active comparator. A fourth limitation was that we had no systematic control for treatment fidelity of the intervention in neither of the studies; instead, we relied solely on a 'supervision on demand' approach. Future research may want to investigate this issue in more detail and investigate possible therapist drift when providing PE interventions early after PTE. Finally, qualitative studies like study IV are sensitive to interviewer bias and in addition, recall bias may have affected the results. The participants may have shared only specific aspects of their experience.

6 SUMMARY AND FUTURE DIRECTIONS

Notwithstanding the limitations of the studies, the findings provide initial evidence for CIPE as a feasible, acceptable, and efficacious intervention in reducing short- and long-term reactions of post-traumatic stress relative to a waiting list condition, when provided the first two months after exposure to PTE to individuals with symptoms of post-traumatic stress. The intervention is highly scalable and easy to disseminate, requires less therapist time than regular care and inexperienced therapist can provide the intervention after a short training. These promising results need to be replicated under randomised controlled conditions. Future studies are suggested to use an active control condition and clinician administered measures.

7 ACKNOWLEDGEMENTS

Erik Andersson, my principal supervisor. It's been one hell of a ride. Together we have walked through fire. You have always been generous with your time and knowledge, for which I will be forever in your debt. Promise me that you will never lose your big heart. I could not have gone on this PhD journey without you.

Filip Arnberg, my co-supervisor. Thank you for guiding me in in the field of traumatic stress studies accompanied by your dry humour. You have taught me to pay close attention to and be careful with details. For that I'm grateful.

Tatja Hirvikoski, my mentor. Thank you for listening when I needed it, and for generously sharing your wisdom and career advice in academia as a woman researcher.

To my former clinical supervisors and role-models

Kicki Kyhle, my PTP-supervisor. Time flies! You gave me the best possible foundation that a newly graduated psychologist could wish for. I will be forever grateful for introducing me to DBT.

Edna Foa, the mother of PE. You are the closest to a rock star as I have come in psychology. I admire your tireless work in further developing and continuous implementation of PE. Thank you for training me and inviting me to the PE trainer community. I aim for the same energy, strength and knowledge in the field of post-traumatic stress as you.

Tracey Lichner, who supervised me during my PE-certification. Thank you for sharpening my clinical skills!

Melanie Harned, thank you for giving me the courage, and evidence-base, to treat highly symptomatic PTSD patients with comorbid emotional instability and self-harm. I dream of having you and Annie McCall coming to Stockholm again to do a workshop. You two are the best!

Charlie Swenson, I still fondly remember that day out on Djurgården when we decided that Anna and I would come to Northampton to assist you in the first DBT intensive training together. You are a role model both, professionally and personally. The dialectical stance you take to life is something I aspire.

To my friends. Love you all.

Katrine, Karin and Emma, our book club has forced me to read something else than just scientific articles and books. I thank you for that! Katrine, my BFF, thank you for keeping my feet on the ground and for always being there when I need you. Karin, all the crazy things we have done together have really helped me create a solid platform for taking on challenges. Please move home to Sweden again ;-).

Johanna, we stick together like glue. A true friend, always in my heart no matter where you are, even if you were living on Mars (which it has sometimes felt like!). It has been so helpful to share similar journeys in academia.

Jessica, I'm so happy to have someone to *not* talk psychology with. Thank you for your pep-talks and after works. It has helped me keep my thesis work going.

Anna, it feels like I have known you since the dark ages. We have shared so much. Knowing that you have been by my side has helped me choose the unknown paths. Thank you for encouraging me to listen to and follow my own wise mind. I'm grateful for our friendship.

Malin, how lucky I was to have met you in Säter, of all places. My first informal mentor when you had just got your license as a psychologist a year before me. Through the years we have formed a close friendship. With your sharp intellect you help keep my brain alert.

My clinical and academic colleagues

The future stars in research on psychological treatments: Klara, Josefin and Kristina. Thank you for support and good advice along the way. I hope to continue our collaborations further.

Ida and Kristina. Thank you for adopting me into the KCKP Uppsala research group. You kick ass!

A warm thank you to my former colleagues at the Karolinska University Hospital. Jessica, Björn, Martin, Rebecca, and Marie, thanks for all the help in study I. Thank you Emma for asking the right, difficult, questions during supervision. Thank you Maria for support and the best lunch company one can have. Anna Miley Åkerstedt and Anna Strandqvist, thank you for sharing your experience on how to combine clinical work with academia.

Thank you Agneta, Rikard, Mike and Linda for approving my research leave.

My research group: Brjánn Ljótsson, thank you for providing a safe haven in your research group. The constellation has changed over the years as new members join in and others leave. Thank you for journal clubs and support; Klara, Josefin, Maria H-L, Martin, Erland, Jenny, Charlotte, Amira, Dorian, Björn, Johan, Hanna, Marianne and Maria L.

My family

Mum and dad. You always told me that I can do whatever I set my mind to. Just work hard. For that I'm forever grateful. And for your unconditional love and support.

My daughters, Klara and Julia. You make me want to be a better person.

8 REFERENCES

Al-Saffar, S., Borga, P., & Hallstrom, T. (2002). Long-term consequences of unrecognised PTSD in general outpatient psychiatry. *Soc Psychiatry Psychiatr Epidemiol*, *37*(12), 580-585. https://doi.org/10.1007/s00127-002-0586-z

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®)*. American Psychiatric Publishing.

Andersson, G., Lundström, P., & Ström, L. (2003). Internet-based treatment of headache: does telephone contact add anything? *Headache*, *43*(4), 353-361. https://doi.org/10.1046/j.1526-4610.2003.03070.x

Asselbergs, J., Sijbrandij, M., Hoogendoorn, E., Cuijpers, P., Olie, L., Oved, K., Merkies, J., Plooijer, T., Eltink, S., & Riper, H. (2018). Development and testing of TraumaGameplay: an iterative experimental approach using the trauma film paradigm. *Eur J Psychotraumatol*, *9*(1), 1424447. https://doi.org/10.1080/20008198.2018.1424447

Balooch, S. B., Neumann, D. L., & Boschen, M. J. (2012). Extinction treatment in multiple contexts attenuates ABC renewal in humans. *Behav Res Ther*, *50*(10), 604-609. https://doi.org/10.1016/j.brat.2012.06.003

Bandarian-Balooch, S., Neumann, D. L., & Boschen, M. J. (2015). Exposure treatment in multiple contexts attenuates return of fear via renewal in high spider fearful individuals. *J Behav Ther Exp Psychiatry*, *47*, 138-144. https://doi.org/10.1016/j.jbtep.2014.12.006

Baumeister, H., Reichler, L., Munzinger, M., & Lin, J. (2014). The impact of guidance on Internet-based mental health interventions—A systematic review. *Internet Interventions*, *1*(4), 205-215. https://doi.org/https://doi.org/10.1016/j.invent.2014.08.003

Benjet, C., Bromet, E., Karam, E. G., Kessler, R. C., McLaughlin, K. A., Ruscio, A. M., Shahly, V., Stein, D. J., Petukhova, M., Hill, E., Alonso, J., Atwoli, L., Bunting, B., Bruffaerts, R., Caldas-de-Almeida, J. M., de Girolamo, G., Florescu, S., Gureje, O., Huang, Y., Lepine, J. P., Kawakami, N., Kovess-Masfety, V., Medina-Mora, M. E., Navarro-Mateu, F., Piazza, M., Posada-Villa, J., Scott, K. M., Shalev, A., Slade, T., ten Have, M., Torres, Y., Viana, M. C., Zarkov, Z., & Koenen, K. C. (2016). The epidemiology of traumatic event exposure worldwide: results from the World Mental Health Survey Consortium. *Psychol Med*, *46*(2), 327-343. https://doi.org/10.1017/s0033291715001981

Blevins, C. A., Weathers, F. W., Davis, M. T., Witte, T. K., & Domino, J. L. (2015). The Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5): Development and Initial Psychometric Evaluation. *Journal of Traumatic Stress 28*(6), 489-498. https://doi.org/10.1002/jts.22059

Boals, A., & Schuettler, D. (2009). PTSD symptoms in response to traumatic and non-traumatic events: the role of respondent perception and A2 criterion. *J Anxiety Disord*, *23*(4), 458-462. https://doi.org/10.1016/j.janxdis.2008.09.003

Bodkin, J. A., Pope, H. G., Detke, M. J., & Hudson, J. I. (2007). Is PTSD caused by traumatic stress? *Journal of Anxiety Disorders*, *21*(2), 176-182. https://doi.org/https://doi.org/10.1016/j.janxdis.2006.09.004

Bondjers, K. (2020). *Post-traumatic Stress Disorder–Assessment of current diagnostic definitions* (PhD dissertation, Acta Universitatis Upsaliensis). *Retrieved from http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-403118]*.

Boscarino, J. A. (2006). Posttraumatic stress disorder and mortality among US Army veterans 30 years after military service. *Annals of epidemiology*, *16*(4), 248-256.

Breslau, N., Kessler, R. C., Chilcoat, H. D., Schultz, L. R., Davis, G. C., & Andreski, P. (1998). Trauma and posttraumatic stress disorder in the community: The 1996

detroit area survey of trauma. *Archives of General Psychiatry*, *55*(7), 626-632. https://doi.org/10.1001/archpsyc.55.7.626
Brewin, C. R., Andrews, B., & Valentine, J. D. (2000). Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. *J Consult Clin Psychol*, *68*(5), 748-766.
Bromet, E., Sonnega, A., & Kessler, R. C. (1998). Risk factors for DSM-III-R posttraumatic stress disorder: findings from the National Comorbidity Survey. *Am J Epidemiol*, *147*(4), 353-361.
Brown, L. A., Zandberg, L. J., & Foa, E. B. (2019). Mechanisms of change in prolonged exposure therapy for PTSD: Implications for clinical practice. *Journal of Psychotherapy Integration*, *29*(1), 6.
Bryant, R. A. (2003). Early predictors of posttraumatic stress disorder. *Biological psychiatry*, *53*(9), 789-795. https://www.ncbi.nlm.nih.gov/pubmed/12725971
Bryant, R. A. (2011). Acute stress disorder as a predictor of posttraumatic stress disorder: a systematic review. *J Clin Psychiatry*, *72*(2), 233-239. https://doi.org/10.4088/JCP.09r05072blu
Bryant, R. A. (2017). Acute stress disorder. *Curr Opin Psychol*, *14*, 127-131. https://doi.org/https://doi.org/10.1016/j.copsyc.2017.01.005
Bryant, R. A. (2019). Post-traumatic stress disorder: a state-of-the-art review of evidence and challenges. *World Psychiatry*, *18*(3), 259-269. https://doi.org/10.1002/wps.20656
Bryant, R. A., Creamer, M., O'Donnell, M., Forbes, D., McFarlane, A. C., Silove, D., & Hadzi-Pavlovic, D. (2017). Acute and Chronic Posttraumatic Stress Symptoms in the Emergence of Posttraumatic Stress Disorder: A Network Analysis. *JAMA Psychiatry*, *74*(2), 135-142. https://doi.org/10.1001/jamapsychiatry.2016.3470
Bryant, R. A., & Guthrie, R. M. (2005). Maladaptive Appraisals as a Risk Factor for Posttraumatic Stress: A Study of Trainee Firefighters. *Psychological science*, *16*(10), 749-752. http://www.jstor.org/stable/40064308
Bryant, R. A., Harvey, A. G., Dang, S. T., Sackville, T., & Basten, C. (1998). Treatment of acute stress disorder: a comparison of cognitive-behavioral therapy and supportive counseling. *Journal of consulting and clinical psychology*, *66*(5), 862-866.
Bryant, R. A., Kenny, L., Rawson, N., Cahill, C., Joscelyne, A., Garber, B., Tockar, J., Dawson, K., & Nickerson, A. (2019). Efficacy of exposure-based cognitive behaviour therapy for post-traumatic stress disorder in emergency service personnel: a randomised clinical trial. *Psychological Medicine*, *49*(9), 1565-1573. https://doi.org/10.1017/S0033291718002234
Bryant, R. A., Mastrodomenico, J., Felmingham, K. L., Hopwood, S., Kenny, L., Kandris, E., Cahill, C., & Creamer, M. (2008). Treatment of acute stress disorder: a randomized controlled trial. *Arch Gen Psychiatry*, *65*(6), 659-667. https://doi.org/10.1001/archpsyc.65.6.659
Bryant, R. A., Moulds, M., Guthrie, R., & Nixon, R. D. (2003). Treating acute stress disorder following mild traumatic brain injury. *Am J Psychiatry*, *160*(3), 585-587. https://doi.org/10.1176/appi.ajp.160.3.585
Bryant, R. A., Moulds, M. L., & Guthrie, R. M. (2000). Acute Stress Disorder Scale: a self-report measure of acute stress disorder. *Psychologial Assessment*, *12*(1), 61-68. https://www.ncbi.nlm.nih.gov/pubmed/10752364
Bryant, R. A., Moulds, M. L., Guthrie, R. M., & Nixon, R. D. V. (2005). The additive benefit of hypnosis and cognitive-behavioral therapy in treating acute stress disorder. *J Consult Clin Psychol*, *73*(2), 334-340. https://doi.org/10.1037/0022-006x.73.2.334

Bryant, R. A., O'donnell, M. L., Creamer, M., McFarlane, A. C., Clark, C. R., & Silove, D. (2010). The psychiatric sequelae of traumatic injury. *American Journal of Psychiatry*, *167*(3), 312-320.

Bugg, A., Turpin, G., Mason, S., & Scholes, C. (2009). A randomised controlled trial of the effectiveness of writing as a self-help intervention for traumatic injury patients at risk of developing post-traumatic stress disorder. *Behav Res Ther*, *47*(1), 6-12. https://doi.org/10.1016/j.brat.2008.10.006

Christiansen, D. M., & Hansen, M. (2015). Accounting for sex differences in PTSD: A multi-variable mediation model. *Eur J Psychotraumatol*, *6*, 26068-26068. https://doi.org/10.3402/ejpt.v6.26068

Cigrang, J. A., Rauch, S. A., Mintz, J., Brundige, A. R., Mitchell, J. A., Najera, E., Litz, B. T., Young-McCaughan, S., Roache, J. D., Hembree, E. A., Goodie, J. L., Sonnek, S. M., & Peterson, A. L. (2017). Moving effective treatment for posttraumatic stress disorder to primary care: A randomized controlled trial with active duty military. *Fam Syst Health*, *35*(4), 450-462. https://doi.org/10.1037/fsh0000315

Cook, J. M., Dinnen, S., Simiola, V., Thompson, R., & Schnurr, P. P. (2014). VA residential provider perceptions of dissuading factors to the use of two evidence-based PTSD treatments. *Professional Psychology: Research and Practice*, *45*(2), 136.

Cooper, A. A., Clifton, E. G., & Feeny, N. C. (2017). An empirical review of potential mediators and mechanisms of prolonged exposure therapy. *Clin Psychol Rev*, *56*, 106-121. https://doi.org/10.1016/j.cpr.2017.07.003

Culver, N. C., Vervliet, B., & Craske, M. G. (2015). Compound Extinction:Using the Rescorla–Wagner Model to Maximize Exposure Therapy Effects for Anxiety Disorders. *Clinical Psychological Science*, *3*(3), 335-348. https://doi.org/10.1177/2167702614542103

Cusack, K., Jonas, D. E., Forneris, C. A., Wines, C., Sonis, J., Middleton, J. C., Feltner, C., Brownley, K. A., Olmsted, K. R., Greenblatt, A., Weil, A., & Gaynes, B. N. (2016). Psychological treatments for adults with posttraumatic stress disorder: A systematic review and meta-analysis. *Clin Psychol Rev*, *43*, 128-141. https://doi.org/10.1016/j.cpr.2015.10.003

Deacon, B. J., & Farrell, N. R. (2013). Therapist barriers to the dissemination of exposure therapy. In *Handbook of treating variants and complications in anxiety disorders* (pp. 363-373). Springer.

Duncan, L. E., Ratanatharathorn, A., Aiello, A. E., Almli, L. M., Amstadter, A. B., Ashley-Koch, A. E., Baker, D. G., Beckham, J. C., Bierut, L. J., Bisson, J., Bradley, B., Chen, C. Y., Dalvie, S., Farrer, L. A., Galea, S., Garrett, M. E., Gelernter, J. E., Guffanti, G., Hauser, M. A., Johnson, E. O., Kessler, R. C., Kimbrel, N. A., King, A., Koen, N., Kranzler, H. R., Logue, M. W., Maihofer, A. X., Martin, A. R., Miller, M. W., Morey, R. A., Nugent, N. R., Rice, J. P., Ripke, S., Roberts, A. L., Saccone, N. L., Smoller, J. W., Stein, D. J., Stein, M. B., Sumner, J. A., Uddin, M., Ursano, R. J., Wildman, D. E., Yehuda, R., Zhao, H., Daly, M. J., Liberzon, I., Ressler, K. J., Nievergelt, C. M., & Koenen, K. C. (2018). Largest GWAS of PTSD (N=20 070) yields genetic overlap with schizophrenia and sex differences in heritability. *Mol Psychiatry*, *23*(3), 666-673. https://doi.org/10.1038/mp.2017.77

Farrer, L., Christensen, H., Griffiths, K. M., & Mackinnon, A. (2011). Internet-based CBT for depression with and without telephone tracking in a national helpline: randomised controlled trial. *PLoS One*, *6*(11), e28099.

Fedynich, A. L., Cigrang, J. A., & Rauch, S. A. M. (2019). Brief Novel Therapies for PTSD—Treatment of PTSD in Primary Care. *Current Treatment Options in Psychiatry*, *6*(3), 179-187. https://doi.org/10.1007/s40501-019-00175-x

Ferrier-Auerbach, A. G., Erbes, C. R., & Polusny, M. A. (2009). Does trauma survey research cause more distress than other types of survey research? *J Trauma Stress*, *22*(4), 320-323. https://doi.org/10.1002/jts.20416

Finch, J., Ford, C., Grainger, L., & Meiser-Stedman, R. (2020). A systematic review of the clinician related barriers and facilitators to the use of evidence-informed interventions for post traumatic stress. *J Affect Disord*, *263*, 175-186. https://doi.org/https://doi.org/10.1016/j.jad.2019.11.143

Foa, E., Hembree, E. A., Rauch, S., & Rothbaum, B. O. (2019). *Prolonged Exposure Therapy for PTSD: Emotional Processing of Traumatic Experiences - Therapist Guide*. New York, NY: Oxford University Press. https://doi.org/10.1093/med-psych/9780190926939.001.0001

Foa, E. B., Gillihan, S. J., & Bryant, R. A. (2013). Challenges and Successes in Dissemination of Evidence-Based Treatments for Posttraumatic Stress: Lessons Learned From Prolonged Exposure Therapy for PTSD. *Psychological Science in the Public Interest*, *14*(2), 65-111. https://doi.org/10.1177/1529100612468841

Foa, E. B., Hearst-Ikeda, D., & Perry, K. J. (1995). Evaluation of a brief cognitive-behavioral program for the prevention of chronic PTSD in recent assault victims. *J Consult Clin Psychol*, *63*(6), 948-955.

Foa, E. B., & Kozak, M. J. (1986). Emotional processing of fear: exposure to corrective information. *Psychol Bull*, *99*(1), 20-35.

Forbes, D., Lockwood, E., Phelps, A., Wade, D., Creamer, M., Bryant, R. A., McFarlane, A., Silove, D., Rees, S., & Chapman, C. (2013). Trauma at the hands of another: distinguishing PTSD patterns following intimate and nonintimate interpersonal and noninterpersonal trauma in a nationally representative sample. *J Clin Psychiatry*, *75*(2), 147-153.

Foy, D. W., Kagan, B., McDermott, C., Leskin, G., Sipprelle, R. C., & Paz, G. (1996). Practical parameters in the use of flooding for treating chronic PTSD. *Clinical Psychology & Psychotherapy: An International Journal of Theory and Practice*, *3*(3), 169-175.

Freedman, S. A., Eitan, R., & Weiniger, C. F. (2020). Interrupting traumatic memories in the emergency department: a randomized controlled pilot study. *Eur J Psychotraumatol*, *11*(1), 1750170. https://doi.org/10.1080/20008198.2020.1750170

Galatzer-Levy, I. R., Huang, S. H., & Bonanno, G. A. (2018). Trajectories of resilience and dysfunction following potential trauma: A review and statistical evaluation. *Clin Psychol Rev*, *63*, 41-55.

Galea, S., Ahern, J., Resnick, H., Kilpatrick, D., Bucuvalas, M., Gold, J., & Vlahov, D. (2002). Psychological sequelae of the September 11 terrorist attacks in New York City. *N Engl J Med*, *346*(13), 982-987. https://doi.org/10.1056/NEJMsa013404

Galea, S., Nandi, A., Stuber, J., Gold, J., Acierno, R., Best, C. L., Bucuvalas, M., Rudenstine, S., Boscarino, J. A., & Resnick, H. (2005). Participant reactions to survey research in the general population after terrorist attacks. *J Trauma Stress*, *18*(5), 461-465. https://doi.org/10.1002/jts.20053

Glover, E. M., Jovanovic, T., Mercer, K. B., Kerley, K., Bradley, B., Ressler, K. J., & Norrholm, S. D. (2012). Estrogen levels are associated with extinction deficits in women with posttraumatic stress disorder. *Biological psychiatry*, *72*(1), 19-24.

Gold, S. M., Enck, P., Hasselmann, H., Friede, T., Hegerl, U., Mohr, D. C., & Otte, C. (2017). Control conditions for randomised trials of behavioural interventions in psychiatry: a decision framework. *Lancet Psychiatry*, *4*(9), 725-732. https://doi.org/10.1016/s2215-0366(17)30153-0

Gould, F., Harvey, P. D., Hodgins, G., Jones, M. T., Michopoulos, V., Maples-Keller, J., Rothbaum, B. O., Rothbaum, A. O., Ressler, K. J., & Nemeroff, C. B. (2020). Prior

trauma-related experiences predict the development of posttraumatic stress disorder after a new traumatic event. *Depress Anxiety*. https://doi.org/10.1002/da.23084

Greaney, M. L., Sprunck-Harrild, K., Bennett, G. G., Puleo, E., Haines, J., Viswanath, K. V., & Emmons, K. M. (2012). Use of email and telephone prompts to increase self-monitoring in a Web-based intervention: randomized controlled trial. *Journal of Medical Internet Research*, *14*(4), e96.

Greenberg, P. E., Sisitsky, T., Kessler, R. C., Finkelstein, S. N., Berndt, E. R., Davidson, J. R., Ballenger, J. C., & Fyer, A. J. (1999). The economic burden of anxiety disorders in the 1990s. *J Clin Psychiatry*, *60*(7), 427-435.

Griffin, M. G., Resick, P. A., Waldrop, A. E., & Mechanic, M. B. (2003). Participation in trauma research: is there evidence of harm? *J Trauma Stress*, *16*(3), 221-227. https://doi.org/10.1023/a:1023735821900

Haagsma, J. A., Polinder, S., Toet, H., Panneman, M., Havelaar, A. H., Bonsel, G. J., & van Beeck, E. F. (2011). Beyond the neglect of psychological consequences: post-traumatic stress disorder increases the non-fatal burden of injury by more than 50%. *Inj Prev*, *17*(1), 21-26. https://doi.org/10.1136/ip.2010.026419

Hamblen, J. L., Norman, S. B., Sonis, J. H., Phelps, A. J., Bisson, J. I., Nunes, V. D., Megnin-Viggars, O., Forbes, D., Riggs, D. S., & Schnurr, P. P. (2019). A guide to guidelines for the treatment of posttraumatic stress disorder in adults: An update. *Psychotherapy*, *56*(3), 359.

Hannan, S. M., Orcutt, H. K., Miron, L. R., & Thompson, K. L. (2017). Childhood Sexual Abuse and Later Alcohol-Related Problems: Investigating the Roles of Revictimization, PTSD, and Drinking Motivations Among College Women. *J Interpers Violence*, *32*(14), 2118-2138. https://doi.org/10.1177/0886260515591276

Heir, T., Blix, I., & Knatten, C. K. (2016). Thinking that one's life was in danger: perceived life threat in individuals directly or indirectly exposed to terror. *Br J Psychiatry*, *209*(4), 306-310. https://doi.org/10.1192/bjp.bp.115.170167

Hoge, C. W., Riviere, L. A., Wilk, J. E., Herrell, R. K., & Weathers, F. W. (2014). The prevalence of post-traumatic stress disorder (PTSD) in US combat soldiers: a head-to-head comparison of DSM-5 versus DSM-IV-TR symptom criteria with the PTSD checklist. *Lancet Psychiatry*, *1*(4), 269-277. https://doi.org/10.1016/s2215-0366(14)70235-4

Holbrook, T. L., Hoyt, D. B., Stein, M. B., & Sieber, W. J. (2001). Perceived threat to life predicts posttraumatic stress disorder after major trauma: risk factors and functional outcome. *J Trauma*, *51*(2), 287-292; discussion 292-283.

Horsch, A., Vial, Y., Favrod, C., Harari, M. M., Blackwell, S. E., Watson, P., Iyadurai, L., Bonsall, M. B., & Holmes, E. A. (2017). Reducing intrusive traumatic memories after emergency caesarean section: A proof-of-principle randomized controlled study. *Behav Res Ther*, *94*, 36-47. https://doi.org/10.1016/j.brat.2017.03.018

Hundt, N. E., Barrera, T. L., Arney, J., & Stanley, M. A. (2017). "It's Worth It in the End": Veterans' Experiences in Prolonged Exposure and Cognitive Processing Therapy. *Cognitive and Behavioral Practice*, *24*(1), 50-57. https://doi.org/10.1016/j.cbpra.2016.02.003

International Society for Traumatic Stress Studies. (2020). Posttraumatic stress disorder prevention and treatment guidelines. *Retrieved from http://www.istss.org/treating-trauma/new-istss-guidelines.aspx*

Iyadurai, L., Blackwell, S. E., Meiser-Stedman, R., Watson, P. C., Bonsall, M. B., Geddes, J. R., Nobre, A. C., & Holmes, E. A. (2018). Preventing intrusive memories after trauma via a brief intervention involving Tetris computer game play in the emergency department: a proof-of-concept randomized controlled trial. *Mol Psychiatry*, *23*(3), 674-682. https://doi.org/10.1038/mp.2017.23

Jonas, D. E., Cusack, K., Forneris, C. A., Wilkins, T. M., Sonis, J., Middleton, J. C., Feltner, C., Meredith, D., Cavanaugh, J., Brownley, K. A., Olmsted, K. R., Greenblatt, A., Weil, A., & Gaynes, B. N. (2013). AHRQ Comparative Effectiveness Reviews. In *Psychological and Pharmacological Treatments for Adults With Posttraumatic Stress Disorder (PTSD)*. Agency for Healthcare Research and Quality (US).

Kanstrup, M., Singh, L., Göransson, K. E., Widoff, J., Taylor, R. S., Gamble, B., Iyadurai, L., Moulds, M. L., & Holmes, E. A. (2021). Reducing intrusive memories after trauma via a brief cognitive task intervention in the hospital emergency department: an exploratory pilot randomised controlled trial. *Transl Psychiatry*, *11*(1), 30. https://doi.org/10.1038/s41398-020-01124-6

Kantor, V., Knefel, M., & Lueger-Schuster, B. (2017). Perceived barriers and facilitators of mental health service utilization in adult trauma survivors: A systematic review. *Clin Psychol Rev*, *52*, 52-68. https://doi.org/10.1016/j.cpr.2016.12.001

Kazdin, A. E. (2017). Addressing the treatment gap: A key challenge for extending evidence-based psychosocial interventions. *Behaviour Research and Therapy*, *88*, 7-18. https://doi.org/https://doi.org/10.1016/j.brat.2016.06.004

Kessler, R. C. (2000). Posttraumatic stress disorder: the burden to the individual and to society. *J Clin Psychiatry*, *61 Suppl 5*, 4-12; discussion 13-14.

Kessler, R. C., Chiu, W., Demler, O., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month dsm-iv disorders in the national comorbidity survey replication. *Archives of General Psychiatry*, *62*(6), 617-627. https://doi.org/10.1001/archpsyc.62.6.617

Kessler, R. C., Sonnega, A., Bromet, E., Hughes, M., & Nelson, C. B. (1995). Posttraumatic stress disorder in the national comorbidity survey. *Archives of General Psychiatry*, *52*(12), 1048-1060. https://doi.org/10.1001/archpsyc.1995.03950240066012

Kircanski, K., Mortazavi, A., Castriotta, N., Baker, A. S., Mystkowski, J. L., Yi, R., & Craske, M. G. (2012). Challenges to the traditional exposure paradigm: variability in exposure therapy for contamination fears. *J Behav Ther Exp Psychiatry*, *43*(2), 745-751. https://doi.org/10.1016/j.jbtep.2011.10.010

Koenen, K. C., Ratanatharathorn, A., Ng, L., McLaughlin, K. A., Bromet, E. J., Stein, D. J., Karam, E. G., Meron Ruscio, A., Benjet, C., Scott, K., Atwoli, L., Petukhova, M., Lim, C. C., Aguilar-Gaxiola, S., Al-Hamzawi, A., Alonso, J., Bunting, B., Ciutan, M., de Girolamo, G., Degenhardt, L., Gureje, O., Haro, J. M., Huang, Y., Kawakami, N., Lee, S., Navarro-Mateu, F., Pennell, B. E., Piazza, M., Sampson, N., Ten Have, M., Torres, Y., M, C. V., Williams, D., Xavier, M., & Kessler, R. C. (2017). Posttraumatic stress disorder in the World Mental Health Surveys. *Psychological Medicine*, 1-15. https://doi.org/10.1017/S0033291717000708

Kubzansky, L. D., Koenen, K. C., Spiro, A., Vokonas, P. S., & Sparrow, D. (2007). Prospective study of posttraumatic stress disorder symptoms and coronary heart disease in the Normative Aging Study. *Archives of General Psychiatry*, *64*(1), 109-116.

Kumpula, M. J., Pentel, K. Z., Foa, E. B., LeBlanc, N. J., Bui, E., McSweeney, L. B., Knowles, K., Bosley, H., Simon, N. M., & Rauch, S. A. (2017). Temporal Sequencing of Change in Posttraumatic Cognitions and PTSD Symptom Reduction During Prolonged Exposure Therapy. *Behav Ther*, *48*(2), 156-165. https://doi.org/10.1016/j.beth.2016.02.008

Lang, P. J. (1979). A Bio-Informational Theory of Emotional Imagery. *Psychophysiology*, *16*(6), 495-512. https://doi.org/10.1111/j.1469-8986.1979.tb01511.x

Lindner, P., Olsson, E. L., Johnsson, A., Dahlin, M., Andersson, G., & Carlbring, P. (2014). The impact of telephone versus e-mail therapist guidance on treatment outcomes,

therapeutic alliance and treatment engagement in Internet-delivered CBT for depression: A randomised pilot trial. *Internet Interventions*, *1*(4), 182-187.
Liu, H., Petukhova, M. V., Sampson, N. A., Aguilar-Gaxiola, S., Alonso, J., Andrade, L. H., Bromet, E. J., de Girolamo, G., Haro, J. M., Hinkov, H., Kawakami, N., Koenen, K. C., Kovess-Masfety, V., Lee, S., Medina-Mora, M. E., Navarro-Mateu, F., O'Neill, S., Piazza, M., Posada-Villa, J., Scott, K. M., Shahly, V., Stein, D. J., Ten Have, M., Torres, Y., Gureje, O., Zaslavsky, A. M., Kessler, R. C., & World Health Organization World Mental Health Survey, C. (2017). Association of DSM-IV Posttraumatic Stress Disorder With Traumatic Experience Type and History in the World Health Organization World Mental Health Surveys. *JAMA Psychiatry*, *74*(3), 270-281. https://doi.org/10.1001/jamapsychiatry.2016.3783
Lowe, S. R., Walsh, K., Uddin, M., Galea, S., & Koenen, K. C. (2014). Bidirectional relationships between trauma exposure and posttraumatic stress: a longitudinal study of Detroit residents. *J Abnorm Psychol*, *123*(3), 533-544. https://doi.org/10.1037/a0037046
Maples-Keller, J. L., Post, L. M., Price, M., Goodnight, J. M., Burton, M. S., Yasinski, C. W., Michopoulos, V., Stevens, J. S., Hinrichs, R., Rothbaum, A. O., Hudak, L., Houry, D., Jovanovic, T., Ressler, K., & Rothbaum, B. O. (2020). Investigation of optimal dose of early intervention to prevent posttraumatic stress disorder: A multiarm randomized trial of one and three sessions of modified prolonged exposure. *Depress Anxiety*. https://doi.org/10.1002/da.23015
Marmar, C. R., Weiss, D. S., Metzler, T. J., & Delucchi, K. (1996). Characteristics of emergency services personnel related to peritraumatic dissociation during critical incident exposure. *Am J Psychiatry*, *153*(7 Suppl), 94-102. https://doi.org/10.1176/ajp.153.7.94
McFarlane, A. C., Atchison, M., Rafalowicz, E., & Papay, P. (1994). Physical symptoms in post-traumatic stress disorder. *J Psychosom Res*, *38*(7), 715-726. http://www.ncbi.nlm.nih.gov/pubmed/7877126
McLean, C. P., Asnaani, A., Litz, B. T., & Hofmann, S. G. (2011). Gender differences in anxiety disorders: prevalence, course of illness, comorbidity and burden of illness. *J Psychiatr Res*, *45*(8), 1027-1035. https://doi.org/10.1016/j.jpsychires.2011.03.006
McLean, C. P., Yeh, R., Rosenfield, D., & Foa, E. B. (2015). Changes in negative cognitions mediate PTSD symptom reductions during client-centered therapy and prolonged exposure for adolescents. *Behaviour Research and Therapy*, *68*, 64-69. https://doi.org/10.1016/j.brat.2015.03.008
Michopoulos, V., Powers, A., Gillespie, C. F., Ressler, K. J., & Jovanovic, T. (2017). Inflammation in Fear- and Anxiety-Based Disorders: PTSD, GAD, and Beyond. *Neuropsychopharmacology*, *42*(1), 254-270. https://doi.org/10.1038/npp.2016.146
Miller, K. E., Cranston, C. C., Davis, J. L., Newman, E., & Resnick, H. (2015). Psychological Outcomes After a Sexual Assault Video Intervention: A Randomized Trial. *J Forensic Nurs*, *11*(3), 129-136. https://doi.org/10.1097/jfn.0000000000000080
Miller, M. W., & Sadeh, N. (2014). Traumatic stress, oxidative stress and post-traumatic stress disorder: neurodegeneration and the accelerated-aging hypothesis. *Mol Psychiatry*, *19*(11), 1156.
Morina, N., Wicherts, J. M., Lobbrecht, J., & Priebe, S. (2014). Remission from post-traumatic stress disorder in adults: a systematic review and meta-analysis of long term outcome studies. *Clin Psychol Rev*, *34*(3), 249-255. https://doi.org/10.1016/j.cpr.2014.03.002
Morris, M. C., Hellman, N., Abelson, J. L., & Rao, U. (2016). Cortisol, heart rate, and blood pressure as early markers of PTSD risk: A systematic review and meta-analysis. *Clin Psychol Rev*, *49*, 79-91. https://doi.org/10.1016/j.cpr.2016.09.001

Mouthaan, J., Sijbrandij, M., de Vries, G.-J., Reitsma, J. B., van de Schoot, R., Goslings, J. C., Luitse, J. S. K., Bakker, F. C., Gersons, B. P. R., & Olff, M. (2013). Internet-Based Early Intervention to Prevent Posttraumatic Stress Disorder in Injury Patients: Randomized Controlled Trial. *Journal of Medical Internet Research*, *15*(8), e165. https://doi.org/10.2196/jmir.2460

Mowrer, O. H. (1960). *Learning theory and behavior* [doi:10.1037/10802-000]. John Wiley & Sons Inc. https://doi.org/10.1037/10802-000

Nacasch, N., Huppert, J. D., Su, Y. J., Kivity, Y., Dinshtein, Y., Yeh, R., & Foa, E. B. (2015). Are 60-minute prolonged exposure sessions with 20-minute imaginal exposure to traumatic memories sufficient to successfully treat PTSD? A randomized noninferiority clinical trial. *Behav Ther*, *46*(3), 328-341. https://doi.org/10.1016/j.beth.2014.12.002

National Institute for Health and Care Excellence. (2018). Evidence reviews for psychological, psychosocial and other non-pharmacological interventions for the prevention of PTSD in adults: NICE guideline NG116. *Retrieved from https://www.nice.org.uk/guidance/ng116*.

Olff, M., Langeland, W., Draijer, N., & Gersons, B. P. (2007). Gender differences in posttraumatic stress disorder. *Psychological bulletin*, *133*(2), 183. https://doi.org/https://doi.org/10.1037/0033-2909.133.2.183

Ozer, E. J., Best, S. R., Lipsey, T. L., & Weiss, D. S. (2003). Predictors of posttraumatic stress disorder and symptoms in adults: a meta-analysis. *Psychol Bull*, *129*(1), 52-73.

Perkonigg, A., Kessler, R. C., Storz, S., & Wittchen, H. U. (2000). Traumatic events and post-traumatic stress disorder in the community: prevalence, risk factors and comorbidity. *Acta Psychiatr Scand*, *101*(1), 46-59.

Pihlaja, S., Lahti, J., Lipsanen, J. O., Ritola, V., Gummerus, E.-M., Stenberg, J.-H., & Joffe, G. (2020). Scheduled Telephone Support for Internet Cognitive Behavioral Therapy for Depression in Patients at Risk for Dropout: Pragmatic Randomized Controlled Trial. *Journal of Medical Internet Research*, *22*(7), e15732-e15732. https://doi.org/10.2196/15732

Pineles, S. L., Nillni, Y. I., King, M. W., Patton, S. C., Bauer, M. R., Mostoufi, S. M., Gerber, M. R., Hauger, R., Resick, P. A., & Rasmusson, A. M. (2016). Extinction retention and the menstrual cycle: Different associations for women with posttraumatic stress disorder. *J Abnorm Psychol*, *125*(3), 349.

Price, M., Van Stolk-Cooke, K., Legrand, A. C., Brier, Z. M. F., Ward, H. L., Connor, J. P., Gratton, J., Freeman, K., & Skalka, C. (2018). Implementing assessments via mobile during the acute posttrauma period: feasibility, acceptability and strategies to improve response rates. *Eur J Psychotraumatol*, *9*(Suppl 1), 1500822. https://doi.org/10.1080/20008198.2018.1500822

Rauch, S. A. M., Cigrang, J., Austern, D., & Evans, A. (2017). Expanding the Reach of Effective PTSD Treatment Into Primary Care: Prolonged Exposure for Primary Care. *Focus (Am Psychiatr Publ)*, *15*(4), 406-410. https://doi.org/10.1176/appi.focus.20170021

Resnick, H., Acierno, R., Waldrop, A. E., King, L., King, D., Danielson, C., Ruggiero, K. J., & Kilpatrick, D. (2007). Randomized controlled evaluation of an early intervention to prevent post-rape psychopathology. *Behav Res Ther*, *45*(10), 2432-2447. https://doi.org/10.1016/j.brat.2007.05.002

Resnick, H. S., Kilpatrick, D. G., Best, C. L., & Kramer, T. L. (1992). Vulnerability-stress factors in development of posttraumatic stress disorder. *J Nerv Ment Dis*, *180*(7), 424-430. https://www.ncbi.nlm.nih.gov/pubmed/1624923

Roberts, A. L., Agnew-Blais, J. C., Spiegelman, D., Kubzansky, L. D., Mason, S. M., Galea, S., Hu, F. B., Rich-Edwards, J. W., & Koenen, K. C. (2015). Posttraumatic

stress disorder and incidence of type 2 diabetes mellitus in a sample of women: a 22-year longitudinal study. *JAMA Psychiatry*, *72*(3), 203-210. https://doi.org/10.1001/jamapsychiatry.2014.2632

Roberts, N. P., Kitchiner, N. J., Kenardy, J., Lewis, C. E., & Bisson, J. I. (2019). Early psychological intervention following recent trauma: A systematic review and meta-analysis. *Eur J Psychotraumatol*, *10*(1), 1695486.

Rose, S., Bisson, J., Churchill, R., & Wessely, S. (2002). Psychological debriefing for preventing post traumatic stress disorder (PTSD). *Cochrane Database Syst Rev*(2), Cd000560. https://doi.org/10.1002/14651858.Cd000560

Rosen, G. M., & Lilienfeld, S. O. (2008). Posttraumatic stress disorder: an empirical evaluation of core assumptions. *Clin Psychol Rev*, *28*(5), 837-868. https://doi.org/10.1016/j.cpr.2007.12.002

Rothbaum, B. O., Kearns, M. C., Price, M., Malcoun, E., Davis, M., Ressler, K. J., Lang, D., & Houry, D. (2012). Early intervention may prevent the development of posttraumatic stress disorder: a randomized pilot civilian study with modified prolonged exposure. *Biol Psychiatry*, *72*(11), 957-963. https://doi.org/10.1016/j.biopsych.2012.06.002

Rothbaum, B. O., Kearns, M. C., Reiser, E., Davis, J. S., Kerley, K. A., Rothbaum, A. O., Mercer, K. B., Price, M., Houry, D., & Ressler, K. J. (2014). Early intervention following trauma may mitigate genetic risk for PTSD in civilians: a pilot prospective emergency department study. *J Clin Psychiatry*, *75*(12), 1380-1387. https://doi.org/10.4088/JCP.13m08715

Rowe, M. K., & Craske, M. G. (1998). Effects of varied-stimulus exposure training on fear reduction and return of fear. *Behav Res Ther*, *36*(7-8), 719-734. https://doi.org/10.1016/s0005-7967(97)10017-1

Ruzek, J. I., Eftekhari, A., Crowley, J., Kuhn, E., Karlin, B. E., & Rosen, C. S. (2017). Post-training Beliefs, Intentions, and Use of Prolonged Exposure Therapy by Clinicians in the Veterans Health Administration. *Adm Policy Ment Health*, *44*(1), 123-132. https://doi.org/10.1007/s10488-015-0689-y

Ryan, J., Chaudieu, I., Ancelin, M. L., & Saffery, R. (2016). Biological underpinnings of trauma and post-traumatic stress disorder: focusing on genetics and epigenetics. *Epigenomics*, *8*(11), 1553-1569. https://doi.org/10.2217/epi-2016-0083

Rytwinski, N. K., Scur, M. D., Feeny, N. C., & Youngstrom, E. A. (2013). The co-occurrence of major depressive disorder among individuals with posttraumatic stress disorder: A meta-analysis. *Journal of Traumatic Stress*, *26*(3), 299-309.

Santiago, P. N., Ursano, R. J., Gray, C. L., Pynoos, R. S., Spiegel, D., Lewis-Fernandez, R., Friedman, M. J., & Fullerton, C. S. (2013). A systematic review of PTSD prevalence and trajectories in DSM-5 defined trauma exposed populations: intentional and non-intentional traumatic events. *PLoS One*, *8*(4), e59236. https://doi.org/10.1371/journal.pone.0059236

Sareen, J. (2014). Posttraumatic stress disorder in adults: impact, comorbidity, risk factors, and treatment. *Can J Psychiatry*, *59*(9), 460-467. https://doi.org/10.1177/070674371405900902

Sartor, C. E., McCutcheon, V. V., Pommer, N. E., Nelson, E. C., Grant, J. D., Duncan, A. E., Waldron, M., Bucholz, K. K., Madden, P. A., & Heath, A. C. (2011). Common genetic and environmental contributions to post-traumatic stress disorder and alcohol dependence in young women. *Psychol Med*, *41*(7), 1497-1505. https://doi.org/10.1017/s0033291710002072

Saxena, S., Jane-Llopis, E., & Hosman, C. (2006). Prevention of mental and behavioural disorders: implications for policy and practice. *World Psychiatry*, *5*(1), 5-14. https://www.ncbi.nlm.nih.gov/pubmed/16757984

Scholes, C., Turpin, G., & Mason, S. (2007). A randomised controlled trial to assess the effectiveness of providing self-help information to people with symptoms of acute stress disorder following a traumatic injury. *Behav Res Ther*, *45*(11), 2527-2536. https://doi.org/10.1016/j.brat.2007.06.009

Sekhon, M., Cartwright, M., & Francis, J. J. (2017). Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. *BMC Health Services Research*, *17*(1), 88. https://doi.org/10.1186/s12913-017-2031-8

Shalev, A., Liberzon, I., & Marmar, C. (2017). Post-Traumatic Stress Disorder. *N Engl J Med*, *376*(25), 2459-2469. https://doi.org/10.1056/NEJMra1612499

Shalev, A. Y. (2002). Acute stress reactions in adults. *Biological psychiatry*, *51*(7), 532-543. https://doi.org/10.1016/S0006-3223(02)01335-5

Shalev, A. Y., Ankri, Y., Israeli-Shalev, Y., Peleg, T., Adessky, R., & Freedman, S. (2012). Prevention of posttraumatic stress disorder by early treatment: results from the Jerusalem Trauma Outreach And Prevention study. *Arch Gen Psychiatry*, *69*(2), 166-176. https://doi.org/10.1001/archgenpsychiatry.2011.127

Shalev, A. Y., Ankri, Y. L. E., Peleg, T., Israeli-Shalev, Y., & Freedman, S. (2011). Barriers to receiving early care for PTSD: Results from the Jerusalem trauma Outreach and prevention study. *Psychiatric Services*, *62*(7), 765-773. https://doi.org/10.1176/appi.ps.62.7.765

Sheth, H. C., Gandhi, Z., & Vankar, G. K. (2010). Anxiety disorders in ancient Indian literature. *Indian journal of psychiatry*, *52*(3), 289-291. https://doi.org/10.4103/0019-5545.71009

Shiban, Y., Pauli, P., & Mühlberger, A. (2013). Effect of multiple context exposure on renewal in spider phobia. *Behav Res Ther*, *51*(2), 68-74. https://doi.org/10.1016/j.brat.2012.10.007

Sijbrandij, M., Engelhard, I. M., Opmeer, B. C., van de Schoot, R., Carlier, I. V., Gersons, B. P., & Olff, M. (2012). The structure of peritraumatic dissociation: a cross validation in clinical and nonclinical samples. *J Trauma Stress*, *25*(4), 475-479. https://doi.org/10.1002/jts.21716

Sijbrandij, M., Olff, M., Reitsma, J. B., Carlier, I. V., de Vries, M. H., & Gersons, B. P. (2007). Treatment of acute posttraumatic stress disorder with brief cognitive behavioral therapy: a randomized controlled trial. *Am J Psychiatry*, *164*(1), 82-90. https://doi.org/10.1176/ajp.2007.164.1.82

Simon, N., McGillivray, L., Roberts, N. P., Barawi, K., Lewis, C. E., & Bisson, J. I. (2019). Acceptability of internet-based cognitive behavioural therapy (i-CBT) for post-traumatic stress disorder (PTSD): a systematic review. *Eur J Psychotraumatol*, *10*(1), 1646092-1646092. https://doi.org/10.1080/20008198.2019.1646092

Smith, H. L., Summers, B. J., Dillon, K. H., & Cougle, J. R. (2016). Is worst-event trauma type related to PTSD symptom presentation and associated features? *J Anxiety Disord*, *38*, 55-61. https://doi.org/10.1016/j.janxdis.2016.01.007

Smith, K. V., Thew, G. R., & Graham, B. (2018). Conducting ethical internet-based research with vulnerable populations: a qualitative study of bereaved participants' experiences of online questionnaires. *Eur J Psychotraumatol*, *9*(Suppl 1), 1506231. https://doi.org/10.1080/20008198.2018.1506231

Song, H., Fang, F., Tomasson, G., Arnberg, F. K., Mataix-Cols, D., Fernandez de la Cruz, L., Almqvist, C., Fall, K., & Valdimarsdottir, U. A. (2018). Association of Stress-Related Disorders With Subsequent Autoimmune Disease. *JAMA*, *319*(23), 2388-2400. https://doi.org/10.1001/jama.2018.7028

Stein, M. B., Jang, K. L., Taylor, S., Vernon, P. A., & Livesley, W. J. (2002). Genetic and environmental influences on trauma exposure and posttraumatic stress disorder

symptoms: a twin study. *Am J Psychiatry*, *159*(10), 1675-1681. https://doi.org/10.1176/appi.ajp.159.10.1675
Steinert, C., Hofmann, M., Leichsenring, F., & Kruse, J. (2015). The course of PTSD in naturalistic long-term studies: high variability of outcomes. A systematic review. *Nord J Psychiatry*, *69*(7), 483-496. https://doi.org/10.3109/08039488.2015.1005023
Svanborg, P., & Asberg, M. (1994). A new self-rating scale for depression and anxiety states based on the Comprehensive Psychopathological Rating Scale. *Acta Psychiatr Scand*, *89*(1), 21-28.
Taylor, S. (2003). Outcome predictors for three PTSD treatments: exposure therapy, EMDR, and relaxation training. *Journal of Cognitive Psychotherapy*, *17*(2), 149-162.
The British Psychological Society. (2017). Ethics Guidelines for Internet-mediated Research. *Retrieved from https://www.bps.org.uk*
Tiihonen Moller, A., Backstrom, T., Sondergaard, H. P., & Helstrom, L. (2014). Identifying risk factors for PTSD in women seeking medical help after rape. *PLoS One*, *9*(10), e111136. https://doi.org/10.1371/journal.pone.0111136
Titov, N., Dear, B. F., Schwencke, G., Andrews, G., Johnston, L., Craske, M. G., & McEvoy, P. (2011). Transdiagnostic internet treatment for anxiety and depression: a randomised controlled trial. *Behaviour Research and Therapy*, *49*(8), 441-452.
Trivasse, H., Webb, T. L., & Waller, G. (2020). A meta-analysis of the effects of training clinicians in exposure therapy on knowledge, attitudes, intentions, and behavior. *Clin Psychol Rev*, *80*, 101887. https://doi.org/https://doi.org/10.1016/j.cpr.2020.101887
True, W. R., Rice, J., Eisen, S. A., Heath, A. C., Goldberg, J., Lyons, M. J., & Nowak, J. (1993). A twin study of genetic and environmental contributions to liability for posttraumatic stress symptoms. *Arch Gen Psychiatry*, *50*(4), 257-264.
Turpin, G., Downs, M., & Mason, S. (2005). Effectiveness of providing self-help information following acute traumatic injury: randomised controlled trial. *Br J Psychiatry*, *187*, 76-82. https://doi.org/10.1192/bjp.187.1.76
van Emmerik, A. A., Kamphuis, J. H., & Emmelkamp, P. M. (2008). Treating acute stress disorder and posttraumatic stress disorder with cognitive behavioral therapy or structured writing therapy: a randomized controlled trial. *Psychother Psychosom*, *77*(2), 93-100. https://doi.org/10.1159/000112886
van Minnen, A., & Foa, E. B. (2006). The effect of imaginal exposure length on outcome of treatment for PTSD. *J Trauma Stress*, *19*(4), 427-438. https://doi.org/10.1002/jts.20146
van Minnen, A., Hendriks, L., & Olff, M. (2010). When do trauma experts choose exposure therapy for PTSD patients? A controlled study of therapist and patient factors. *Behaviour Research and Therapy*, *48*(4), 312-320. https://doi.org/https://doi.org/10.1016/j.brat.2009.12.003
Wald, J., & Taylor, S. (2009). Work impairment and disability in posttraumatic stress disorder: A review and recommendations for psychological injury research and practice. *Psychological injury and law*, *2*(3-4), 254-262.
Weathers, F. W., Blake, D. D., Schnurr, P. P., Kaloupek, D. G., Marx, B. P., & Keane, T. M. (2013). *The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). Retrieved from www.ptsd.va.gov.*
Wessely, S., Bryant, R. A., Greenberg, N., Earnshaw, M., Sharpley, J., & Hughes, J. H. (2008). Does psychoeducation help prevent post traumatic psychological distress? *Psychiatry*, *71*(4), 287-302. https://doi.org/10.1521/psyc.2008.71.4.287
White, J., Pearce, J., Morrison, S., Dunstan, F., Bisson, J. I., & Fone, D. L. (2015). Risk of post-traumatic stress disorder following traumatic events in a community sample.

Epidemiol Psychiatr Sci, *24*(3), 249-257. https://doi.org/10.1017/s2045796014000110

Yeager, C. M., & Benight, C. C. (2018). If we build it, will they come? Issues of engagement with digital health interventions for trauma recovery. *Mhealth*, *4*, 37. https://doi.org/10.21037/mhealth.2018.08.04

Yehuda, R., & Lehrner, A. (2018). Intergenerational transmission of trauma effects: putative role of epigenetic mechanisms. *World Psychiatry*, *17*(3), 243-257.

Yehuda, R., & McFarlane, A. C. (1995). Conflict between current knowledge about posttraumatic stress disorder and its original conceptual basis. *Am J Psychiatry*, *152*(12), 1705-1713. https://doi.org/10.1176/ajp.152.12.1705

Zatzick, D., Jurkovich, G. J., Rivara, F. P., Wang, J., Fan, M. Y., Joesch, J., & Mackenzie, E. (2008). A national US study of posttraumatic stress disorder, depression, and work and functional outcomes after hospitalization for traumatic injury. *Ann Surg*, *248*(3), 429-437. https://doi.org/10.1097/SLA.0b013e318185a6b8

Zoellner, L. A., Feeny, N. C., Bittinger, J. N., Bedard-Gilligan, M. A., Slagle, D. M., Post, L. M., & Chen, J. A. (2011). Teaching Trauma-Focused Exposure Therapy for PTSD: Critical Clinical Lessons for Novice Exposure Therapists. *Psychological trauma*, *3*(3), 300-308. https://doi.org/10.1037/a0024642

Zoladz, P. R., & Diamond, D. M. (2013). Current status on behavioral and biological markers of PTSD: a search for clarity in a conflicting literature. *Neurosci Biobehav Rev*, *37*(5), 860-895. https://doi.org/10.1016/j.neubiorev.2013.03.024