Table of Contents

The best of prophet of the future is the past

Lord George Byron

Preface

Despite decades of knowledge, theory, research, we have yet to master the skills required to remedy the disruptive impact of traumatic experiences. Our current methods are effective for some, but others remain desolately unaffected. Humans are diverse, simple, complex and enigmatic. Comprehending the nature of therapeutic recovery after traumatic experiences on occasion compares to a tumble down Alice's rabbit hole from the famous novel by Lewis Carroll. We are surrounded by theories and facts, riddles and stories, yet we are unable to predict who will recover. The present dissertation provides a few stepping stones through the rabbit hole and may answer some of the Mad Hatter's riddles or the Dodo Birds proclamations.

Every story has central-characters, a plot, and a theme or setting. Our story begins with our protagonist; the veteran with posttraumatic stress disorder. A soldier tormented by dreadful deployment related memories and at times overwhelming feelings of fear, anxiety and sometimes depression. In the struggle to overcome psychotrauma related pathology, our veteran finds himself or herself seeking help from specialist centres that aid soldiers in psychosocial distress. Therapeutic treatment can last for weeks, months or years. Dedicated professionals employ the latest evidence-based practice methods to target deployment related pathology. Forces unseen shape the treatment trajectory, oscillating between the application of superior guideline interventions and personalized care, using *different strokes [methods] for different folks [patients]*.

The strongest warrior does not always win the battle. Ultimately, the hero of our story will either recover or have to change his outlook on health and recovery. The present dissertation attempts to pull apart the threads to answer whether the actors [patients], play [intervention], or décor [setting] set the stage for therapeutic recovery. The first stage of our journey involves exploratory analyses to identify some of the mechanisms of therapeutic recovery. The second stage questions our current assumptions about purported mechanisms of therapeutic recovery. The results may provide insight on how to extend the effectiveness of therapeutic recovery for veterans with disturbances after traumatic experiences – and may eventually benefit all people with PTSD.

Chapter 1

Introduction

Introduction

Veterans

Over half a million Dutch veterans participated in almost a hundred peace keeping missions since 1940. They served under war conditions or similar circumstances on a global scale. The most notable deployments included military actions in the former Dutch colonies Dutch East Indies (1945-1949) and New Guinea (1950-1962), as well as the Korean War (1950-1955), the United Nations Interim Force in Lebanon (UNIFIL) (1979-1985), the United Nations Transitional Authority for Cambodia (UNTAC) (1992-1993), the Kosovo Force (KFOR) (1998-2000), the United Nations Protection Force (UNPROFOR) in former Yugoslavia (1991-1995), the International Security Assistance Force (ISAF) in Afghanistan (2001-2003), the Stabilisation Force Iraq (SFIR) (2003-2005), as well as extensive missions in Africa. There are currently 117.450 veterans living[1] in the Netherlands.

Mission experiences

Es ist der Krieg ein roh gewaltsam Handwerk und Mann kommt nicht aus mit sanften Mitteln.

Friedrich Schiller

Working in war conditions invariable signifies a vanguard position on human violence, tragedy and suffering. Dutch veterans recounted numerous threatening or shocking situations during our studies reported in this dissertation. These situations included - but were not limited to - the necessity to kill in order to survive, being shot at, sustaining injuries, losing colleagues and buddies, witnessing extreme human suffering, being held hostage, being threatened at gun-point, exposure to impending attacks, and feeling responsible for the death and suffering of innocent civilians. These experiences were often accompanied by intense emotions of fear, anger, disgust, helplessness, guilt, and at times evoked existential and moral crises.

[1] http://www.veteraneninstituut.nl/veteranen-hun-missies

The horrors I saw were very extreme; they were inhumane. I saw ordinary people die in a hail of machine gun bullets, including children. I felt terrible that I was not allowed and unable to intervene. At that moment, I felt incredibly small and powerless.

A veteran

Wounded Warriors: The psychological aftermath of war

Despite exposure to stressful and shocking events, the majority (>70%) of veterans evaluated their deployment(s) as positive events. They felt engaged in important work that contributed to the protection and welfare of their deployment communities, or experienced a personal growth and understanding (Schok, Kleber, Elands, & Weerts, 2008). In spite of such positive deployment associations for most, a considerable minority returns with psychological distress or adaptation issues (Ambaum & Van den Berg, 2012). Some develop chronic pathology and become psychologically Wounded Warriors (a term that has been used in veteran medicine, psychology and practice since at least 1988 (Johnson, 1988).

Posttraumatic stress disorder (PTSD) is the most prevalent combat-related psychological disorder (VA-DOD, 2004). It is a stress-related disorder that can occur after exposure to potentially traumatic events. It has four core symptom dimensions that include: involuntary re-experience of traumatic memories, avoidance of trauma reminders, negative alterations in cognitions and mood, and hyperarousal symptoms (American Psychiatric Association [APA], 2013). A PTSD diagnosis can be established by a mental health professional if these symptoms persist for at least one month and cause significant clinical and functional distress and impairment.

You can't take a 19-year-old brain and subject it to the constant threat of death or injury by rocket fire and expect it not to be affected.

A veteran

PTSD prevalence chronicity and comorbidity

A full-blown PTSD affected 3-4% of the returning Dutch soldiers five months after deployment in Iraq (Engelhard et al., 2007). These rates are slightly rosier than the PTSD rates (5-9%) reported by US counterparts from national veteran samples at various decades after deployment (Dohrenwend et al., 2006; Marmar et al., 2015; Wisco et al., 2015). Findings highlight that prevalence rates show a gradual decrease over time, but also demonstrate the enduring and unabated nature, even after 40 years, of combat-related PTSD (Marmar et al., 2015).

PTSD is one of multiple responses after exposure to extreme stress and rarely occurs alone. Most veterans with PTSD (60%) reported *at least one other* comorbid psychological disorder (Skodol et al., 1996), and are roughly three times as likely to experience *triple* comorbidities instead of solitary PTSD (Ginzburg, Ein-Dor, & Solomon, 2010). The most common comorbid disorders are major depression (37-51%) and substance use (21%) (Marmar et al., 2015; Petrakis, Rosenheck, & Desai, 2011; Wisco et al., 2014). Veterans with PTSD are reportedly three times as likely to develop a major depressive disorder and personality disorder, and twice as likely to report a substance use disorder compared to veterans without PTSD (Skodol et al., 1996).

PTSD and any associated comorbid disorders exercise a widespread and profound negative effect on all aspects of a person's life. For example, veterans with a probable PTSD reported significantly more work-related difficulties (43% vs. 13%), job loss (35% vs. 16 %), relational conflicts (63% vs. 27%) and divorce or separation (46% vs. 27%) than their non-traumatized counterparts (Sayer et al., 2010).

> *I may have cheated death, but just like Joe prophetically said in smoke fuelled haze all those years ago, life has cheated me.*
>
> A veteran

PTSD treatment

There are multiple therapeutic methods to promote recovery if natural and social processes fail to mitigate PTSD. Most methods are derived from the major psychotherapeutic approaches that include humanism, psychoanalysis, behaviourism, and cognitivism. A cognitive-behaviourism perspective currently dominates the field of PTSD psychotherapy. Most guidelines also endorse

this perspective on PTSD intervention (American Psychological Association [APA], 2017; Australian Centre for Posttraumatic Mental Health [ACPMH], 2013; Institute of Medicine [IOM], 2008; National Institute for Health and Clinical Excellence [NICE], 2005; Veterans Affairs Department of Defence [VA-DoD], 2010). Recommended interventions include trauma focused cognitive behaviour therapies [prolonged exposure therapy, cognitive processing therapy, cognitive therapy, and narrative exposure therapy], as well as some alternative approaches, such as eye movement desensitization and reprocessing and brief eclectic psychotherapy. Most interventions directly engage the traumatic memory to promote symptom amelioration via various mechanism that may include activating the fear network and subsequent fear-extinction, cognitive restructuring, meaning-making processes, and retrieval and recoding (reconsolidation) of traumatic memories. Non-trauma focused psychological interventions are also considered, though not often recommended as first choice. They are mostly considered if patients are unwilling to commence trauma focused therapy or experience comorbid disorders that frustrate his or her engagement to trauma focused therapies. Non-trauma focused interventions include supportive therapies, systemic therapy and patient centered therapy.

Treatment can be provided in outpatient, day treatment and inpatient settings. Within these settings, therapy is further differentiated in individual and group sessions. Outpatient treatment is commonly delivered as a one or two hours of individual psychotherapy that takes place once every week, fortnight or month. Day treatment programs often consist of a combination of individual and group psychotherapy sessions and may include either socio- or creative therapy and mostly also psycho motor therapy. It takes place weekly (on average 6-12 hours) with a focus on PTSD, comorbid disorders, and/or related problem domains and behaviours. Inpatient treatment programs offer 24-hours living facilities with a daily psycho-, socio-, and creative therapy treatment regime for a limited number of months. Besides psychotherapeutic interventions, roughly two thirds to three quarters of the patients receive medication besides psychological treatment (Haagen, Smid, Knipscheer, & Kleber, 2015).

Treatment effectiveness: Is it about the forest or the trees

How does psychotherapy bring about therapeutic recovery? According to the *medical model for psychotherapy* mental ailments or disorders are best treated using interventions with specific therapeutic ingredients (procedures or techniques), to maximize the psychotherapeutic effect (Barlow, 2013; Wampold, Ahn, & Coleman, 2001). These specific-effects are responsible for therapeutic recovery and logically derived from psychological theories regarding treatment change. The model is based on the compartmentalization of psychopathology in selective disorders in accordance with diagnostic manuals, such as the ICD and DSM. The introduction of stringent RCT methodologies to isolate the specific-effects gave credibility to the field of psychotherapy (Castelnuovo, 2010). In accordance with the medical model, therapeutic exposure to traumatic memories can be considered a unique therapeutic-ingredient that provides superior specific-effects compared to alternative interventions (Bisson, Roberts, Andrew, Cooper, & Lewis, 2013).

The c*ommon factors model,* in contrast, states that psychotherapy success is the result of 'common factors' present in all psychotherapies, instead of specific interventions or techniques. These common factors are sometimes also referred to as placebo's or non-specific factors that produce general-effects or placebo-effects, and primarily focus on the therapeutic alliance, (treatment) expectations, instillation of hope, and a engaging in therapeutic activities that are believed credible and helpful (Wampold, Frost, & Yulish, 2016). Both models have existed since the birth of modern psychotherapy and have been almost as long at odds with each other (since the famous Dodo Bird statement by Saul Rosenzweig in 1936).

It remains a question whether the beneficial workings of psychotherapy is a story of the *trees* (i.e., the uniqueness of each intervention in bringing about of recovery), or a story about the *forest* (emphasizing the commonalities between most psychotherapies as instrumental for recovery) (Miller & Moyers, 2015). The medical model of psychotherapy, emphasising specific-effects, emerged as the dominant model, though the debate continues unrelenting (Wampold & Imel, 2015). The debate also extended to the field of PTSD with an ongoing discussion whether trauma focused interventions are superior to non-trauma focused interventions (Benish, Imel, & Wampold, 2008; Ehlers et al., 2010; Wampold et al., 2010).

Treatment effectiveness: An unfinished story

Recommended psychotherapies deliver only limited PTSD symptom reduction for veterans with PTSD and veterans benefit less from treatment than other PTSD populations (Bradley, Greene, Russ, Dutra, & Westen, 2005; Goodson's et al., 2011; Watts et al., 2013). Previous veteran treatment studies reported an average PTSD symptom reduction of 14-32% over the course of therapy (Creamer, Elliott, Forbes, Biddle & Hawthorn, 2006; Owens, Chard & Cox, 2008; Richardson, Elhai & Sarreen, 2011; Rooney et al., 2007). These findings are however based on group-averages that mask the large individual variability in treatment outcome. Creamer et al. (2006) highlighted this individual variability by separating their sample into treatment responders (33%), minimal responders (33%), and non-responders (33%). According to meta-analyses, the percentage of treatment non-responders may even reach 50% (Bradley et al., 2005; Goodson et al., 2011; Steenkamp et al., 2015). Four out of five US veterans with PTSD were still in PTSD treatment after four years of therapy (Congress of the United States, 2012). Some veterans may be locked in a cycle that offers insufficient treatment improvement and ongoing treatment for lack of alternatives. How many of these veterans will be able to function without mental health support remains the question. It places an ongoing burden on the individual, and by proxy, on intimate others, the healthcare system and society at large. The US annual healthcare costs alone were estimated at 3 billon dollar for half a million veterans that sought PTSD treatment (IOM, 2014).

Effectiveness versus efficacy outcome designs

To determine whether treatment works, interventions can be studied in optimal experimental conditions that allow for the determination of the exact contribution of a given intervention, whilst controlling for external factors (confounders) to minimize any threats to the validity of the results (Walach, 2016). Or, treatments can be studied in conditions that reflect the actual clinical practice in which these interventions are delivered to minimize any threats in the generalizability of the results. The first method investigates treatment *efficacy*, and the second method treatment *effectiveness* (Jacobson & Christensen, 1996).

Efficacy studies aim to establish causal agency. More specifically, they aim to establish the existence of a (superior) effect (Jacobson & Christensen, 1996), for a given intervention against another intervention or a waiting list (Hollon, 1996). The preferred or 'golden-standard' methodology for studying efficacy is the randomized controlled trial (RCT) design (Starcevic, 2003). The purpose of effectiveness studies is to establish its generalizability and feasibility of

treatment (Jacobson & Christensen, 1996). Effectiveness studies take place in the natural habitat of psychotherapy, they are observational and focus on unrestricted interventions to assess the nature of treatment, the natural variation in treatment outcome, and relationship with external variables, to determine their influence on treatment outcome (Hollon, 1996). Randomized efficacy studies are best used to establish *if* therapy works. Observational effectiveness studies can help follow-up on efficacy studies to explain *why* or for *whom* therapy works, though neither designs are mutually exclusive in answering these questions.

How to improve effectiveness: Using predictive research

Predictive research may hold the key for understanding why some patients benefit while others worsen with psychotherapy. Understanding who benefits enables us to identify factors that may impact treatment effectiveness and adapt our interventions or choice of treatment accordingly to improve their effectiveness (Riley et al., 2013). More effective interventions will alleviate the burden of PTSD for more patients and maximize resource allocation to decrease healthcare costs. Predictive research can be defined as 'the probability or risk of an individual developing a particular state of health (an outcome) over a specific time, based on his or her clinical and non-clinical profile' (Moons et al., 2009). If we transpose Moons' definition on PTSD psychotherapy, we can state that candidate patient, treatment, and organizational predictors [clinical and non-clinical profile] may predict PTSD symptom change [a particular state of health] after psychotherapy [a specific period of time].

How should we establish candidate predictors of PTSD treatment effectiveness. We could ask clinicians and patients at the end of treatment to identify pivotal factors that were instrumental in therapeutic recovery. However, it is next to impossible to assess a temporal relationship between the predictors and treatment outcome with such an approach, and likely vulnerable for a retrospective biases. We focus on clinical prediction. Alternatively, clinicians could predict for each patient who will respond to treatment and we could use this information to predict treatment outcome. Unfortunately, humans are notoriously prone to bias and their expert predictions are rarely accurate in complex (clinical) situations (Meehl, 1954; Kahneman, 2011). Paul Meehl proposed a cheaper alternative to clinical prediction that guides the field today; using prospective statistical models to predict future outcomes. In accordance with the vision of Paul Meehl, the present dissertation aims to predict treatment effectiveness using statistical models.

Prognostic PTSD psychotherapy research is an understudied field with a sparseness of available predictor studies. Most predictor variables have only been studied once or twice. We have chosen to exploratory identify potential predictors and use a best-practice approach applying a diagnostic set of questionnaires that were assembled by foremost Dutch diagnosticians, clinicians and researchers in the field of PTSD treatment for veterans. The questionnaire set represented key clinical features required to assess the scope of veteran PTSD deployment related pathology and factors that were expected to impact treatment outcome. The set measured several pathology dimensions (PTSD, hostility, dissociation and a number of general pathology dimensions), inventoried the use of different coping styles, and a patient's attachment style.

Exploratory versus confirmatory approaches

> *… to implement the confirmatory paradigm properly we need to do a lot of exploratory work. Neither exploratory nor confirmatory is sufficient alone.*
>
> (Tukey, 1980).

Predicting treatment outcome in an understudied field with a sparseness of available predictor studies prompted the use of exploratory (inductive) and confirmatory (deductive) approaches. Exploratory analyses generate questions and hypotheses about treatment working mechanisms, though it is unusual for exploratory research to deliver conclusive answers. Its flexible approach helps gain a deeper understanding of therapeutic processes that need to be confirmed by repetition (Tukey 1969). Confirmatory analyses, on the other hand, can be used to test hypotheses based on the exploratory work and established theories. Figure 1 illustrates how exploratory data analysis generates theoretical insights that translate in testable hypotheses and how confirmatory analysis are based on theoretical assumptions that translate into testable hypotheses to be statistically confirmed or refuted after analysis of the data.

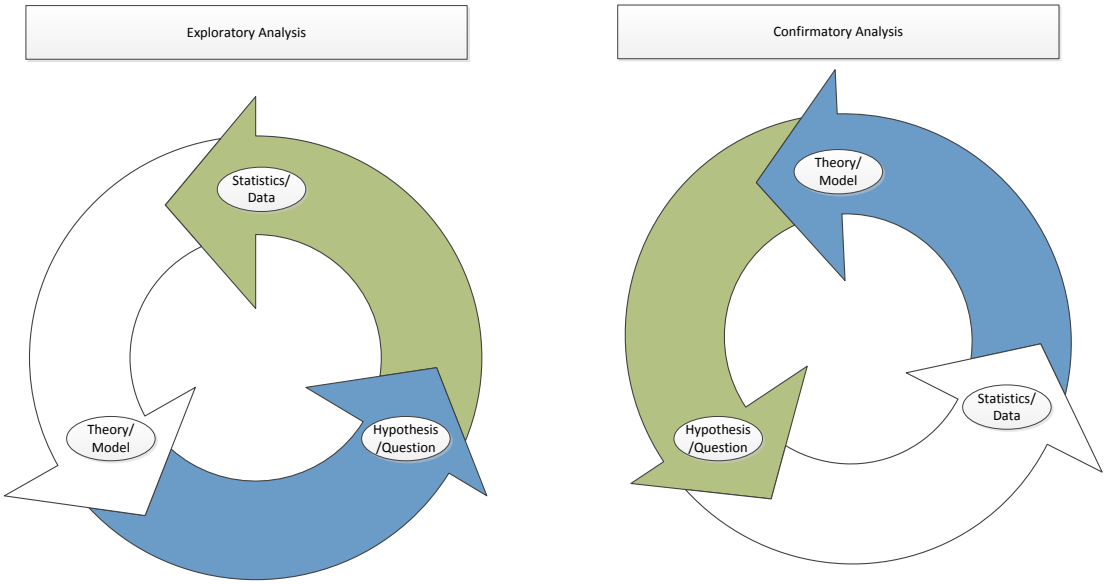

Figure 1. *Confirmatory and exploratory analysis pathways*

Objectives

The aim of this dissertation is to identify treatment outcome predictors for veterans with PTSD in order to better tailor PTSD treatment for patients and increase the effectiveness of current PTSD interventions. The central question is: can we predict PTSD treatment effectiveness based on specific characteristics of PTSD patients and PTSD interventions?

Part I will focus on exploratory identifying predictors of PTSD treatment outcome. Such an approach was chosen due to the sparseness of veteran treatment outcome predictor research. We identify treatment effectivity predictors and generate hypotheses how these predictors influence outcome.

Part II presents confirmatory research in which the hypotheses concerning the influence of the predictors on treatment outcome will be tested. In particular, empirical data will be presented to analyse the role of sleeping disturbances and dissociation as predictors of nonresponse (or low response) to therapy, as well as the assumption that trauma focused (exposure) therapy will be superior (more effective) in relation to non-trauma focused interventions.

Part III summarizes and integrates the results of the various studies and discusses their implications.

Outline

Part I: Exploratory Research

Chapter 2 *(The efficacy of recommended treatments for veterans with PTSD: A metaregression analysis)* reviews veteran PTSD treatment outcome predictor literature and describes the results of a meta-analysis of guideline recommended PTSD treatment interventions. We investigated the influence of several candidate patient and organizational predictors on treatment outcome using meta-ANOVA and metaregression analyses.

Refugees may experience to some extent comparable traumatic events as veterans. Both populations are exposed to the worst war has to offer, are considered difficult-to-treat, were exposed for a long(er) duration to multiple potentially traumatic events. Though there are also differences between both populations, for example, soldiers are better prepared for the circumstances of war compared to refugees. **Chapter 3** *(Predicting PTSD treatment response in refugees: Multilevel analysis)* is devoted to the identification of treatment outcome predictors for traumatized refugees based on data from a randomized controlled treatment trial (RCT). Candidate patient and organizational outcome predictors are examined in an exploratory multilevel fashion to maximize the detection of possible predictors and represent the nested nature of longitudinal data.

Part II: Confirmatory Research

PTSD treatment guidelines favour trauma focused interventions as a superior treatment approach. The preferential use of trauma focused interventions as opposed to non-trauma focused interventions has become a debate topic. **Chapter 4** *(The legitimacy of trauma focused psychotherapy in clinical settings: Conveying evidence into practice and practice into evidence for veterans with PTSD)* tests the assumption of superiority of trauma focused therapies for veterans with PTSD in a longitudinal multisite cohort study.

In **Chapter 5** *(The dissociative PTSD subtype: A treatment outcome cohort study in veterans with PTSD),* we examine the predictive value of the dissociative PTSD subtype. This subtype was only recently formally incorporated in the Diagnostic and Statistical Manual of

Mental Disorders of the American Psychiatric Association (2013). The present study uses latent profile analysis to establish a possible dissociative PTSD subtype, and examined whether veterans with dissociative and non-dissociative symptoms differed on demographic and clinical variables, and PTSD treatment outcome in a longitudinal multisite cohort study.

Chapter 6 *(Adverse consequences of disturbed sleep in veteran PTSD treatment)* focusses on the potential adverse consequences of disturbed sleep on treatment outcome for veterans with PTSD in a longitudinal multisite cohort study. The topic was inspired by a recent Dutch dissertation regarding the influence of sleep disturbances in mental healthcare (Schagen, 2016).

Part III: Discussion

Chapter 7 *(Using alternative frameworks to advance veteran PTSD psychotherapy effectiveness)* reflects on the workings of psychotherapy for veterans with PTSD, and discusses the controversy between the medical model of psychotherapy and common factors models. Several research, practice and policy implications are forwarded to enhance PTSD treatment effectiveness for veterans.

Chapter 8 offers a summary of the present findings and a discussion of their scientific implications. We propose several avenues for future research in our concluding remarks.

References

American Psychiatric Association. (2000) *Diagnostic and statistical manual of mental disorders DSM-IV-TR* (4th ed.). Washington, DC: American Psychiatric Association.

American Psychiatric Association. (2013) *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: American Psychiatric Association.

American Psychological Association, 2017. *Clinical Practice Guideline for the Treatment of Posttraumatic Stress Disorder (PTSD) in Adults*. [Adopted as APA Policy February 24 2017]. Published ahead of publication.

Ambaum J., & Van den Berg, C. (2012). De militaire context van blootstelling aan oorlog en uitzending. In: E. Vermetten, R.J. Kleber, & O. van der Hart (red.), *Handboek posttraumatische stressstoornissen.* Utrecht: De Tijdstroom.

Australian Centre for Posttraumatic Mental Health (ACPMH) (2013). *Australian Guidelines for the Treatment of Acute Stress Disorder and Posttraumatic Stress Disorder.* Melbourne, Victoria: ACPMH.

Benish, S., Imel, Z., &Wampold, B. (2008). The relative efficacy of bona fide psychotherapies for treating post-traumatic stress disorder: A meta-analysis of direct comparisons. *Clinical Psychology Review, 28,* 746–758. http://dx.doi.org/10.1016/j.cpr.2007.10.005.

Congress of the United States (CBO) (2012). The Veterans Health Administration's treatment of PTSD and traumatic brain injury among recent combat veterans. Washington, DC: Congressional Budget Office.

Creamer, M., Elliott, P., Forbes, D., Biddle, D., & Hawthorne, G. (2006). Treatment for combat-related posttraumatic stress disorder: Two-year follow-up. *Journal of traumatic stress, 19,* 675-685. doi:10.1002/jts.20155

Dohrenwend, B.P., Turner, J.B., Turse, N.A., Adams, B.G., Koenen, K.C., & Marshall, R. (2006). The psychological risks of Vietnam for US veterans: A revisit with new data and methods. *Science, 313*(5789), 979-982.

Ehlers, A., Bisson, J., Clark, D., Creamer, M., Pilling, S., Richards, D., et al. (2010). Do all psychological treatments really work the same in posttraumatic stress disorder? *Clinical Psychology Review, 30,* 269–276. http://dx.doi.org/10.1016/j.cpr.2009.12.001.

Engelhard, I. M., Van den Hout, M. A.,Weerts, J., Arntz, A., Hox, J. J. C. M., & McNally, R. (2007). Deployment-related stress and trauma in Dutch soldiers returning from Iraq. *British Journal of Psychiatry, 191*(2), 140–145.

Ginzburg, K., Ein-Dor, T., & Solomon, Z. (2010). Comorbidity of posttraumatic stress disorder, anxiety and depression: A 20-year longitudinal study of war veterans. *Journal of Affective Disorders, 123,* 249-257. doi:10.1016/j.jad.2009.08.006

Goodson, J., Helstrom, A., Halpern, J.M., Ferenschak, M.P., Gillihan, S.J., & Powers, M.B. (2011). Treatment of posttraumatic stress disorder in U.S. combat veterans: A meta-analytic review. *Psychological Reports, 2,* 573–599. http://dx.doi.org/10.2466/02.09.15.16.PR0.109.5.573-599.

Haagen, J.F.G., Smid, G.E., Knipscheer, J.W., & Kleber, R.J. (2015). The efficacy of recommended treatments for veterans with PTSD: A metaregression analysis. *Clinical Psychology Review 40,* 184–194. http://dx.doi.org/10.1016/j.cpr.2015.06.008

Institute of Medicine (IOM) (2008). *Treatment of posttraumatic stress disorder: An assessment of the evidence.* Washington, DC: The National Academies Press.

Institute of Medicine (IOM) (2014). Treatment for posttraumatic stress disorder in military and veteran populations: Final assessment. Washington, DC: National Academy of Sciences. Retrieved from http://iom.nationalacademies.org/~/media/Files/Report%20Files/2014/PTSD-II/PTSD-II-RB.pdf.

Johnson, S. (1988). Wounded Warrior. *Navy Medicine, 79*(5), 4-7.

Kahneman, D. (2013). *Thinking, fast and slow*. New York: Farrar, Straus and Giroux.

Marmar, C.R., Schlenger, W., Henn-Haase, C., Qian, M., Purchia, E., Li, M., ... Karstoft, K.I. (2015). Course of posttraumatic stress disorder 40 years after the Vietnam War: Findings from the National Vietnam Veterans Longitudinal Study. *JAMA psychiatry, 72,* 875-881. doi:10.1001/jamapsychiatry.2015.0803

Meehl, P. E. (1954). *Clinical versus statistical prediction: A theoretical analysis and a review of the evidence.* Minneapolis: University of Minnesota Press.

Miller, W. R., & Moyers, T. B. (2015). The forest and the trees: Relational and specific factors in addiction treatment. *Addiction, 110,* 401-413. doi:10.1111/add.12693

Moons, K.G.M., Altman, D.G., Vergouwe, Y., & Royston, P. (2009a). Prognosis and prognostic research: Application and impact of prognostic models in clinical practice. *Research Methods & Reporting, 338,* 1487–1490. http://dx.doi.org/10.1136/bmj.b606

Moons, K.G.M., Royston, P., Vergouwe, Y., Grobbee, D.E., & Altman, D.G. (2009b). Prognosis and prognostic research: What, why, and how? *Research Methods & Reporting, 338,* 1317–1320. http://dx.doi.org/10.1136/bmj.b375

National Institute for Clinical Excellence (NICE) (2005). *Post-traumatic stress disorder (PTSD). The management of PTSD in adults and children in primary and secondary care.* London: National Institute for Clinical Excellence.

Owens, G.P., Chard, K.M., & Cox, T.E. (2008). The relationship between maladaptive cognitions, anger expression, and posttraumatic stress disorder among Veterans in residential treatment. *Journal of Aggression, Maltreatment & Trauma, 17*(4), 439-452.

Petrakis, I.L., Rosenheck, R., & Desai, R. (2011). Substance use comorbidity among veterans with posttraumatic stress disorder and other psychiatric illness. *The American journal on addictions, 20,*185-9. doi:10.1111/j.1521-0391.2011.00126.x

Riley, R.D., Hayden, J.A., Steyerberg, E.W., Moons, K.G.M., Abrams, K., Kyzas, P.A., …Hemingway, H. (2013). Prognosis Research Strategy (PROGRESS) 2: Prognostic Factor Research. *PLoS Med, 10,* e1001380. doi:10.1371/journal.pmed.1001380

Rooney, K., Hunt, C., Humphreys, L., Harding, D., Mullen, M., & Kearney, J. (2007). Prediction of outcome for veterans with post-traumatic stress disorder using constructs from the transtheoretical model of behaviour change. *Australian and New Zealand Journal of Psychiatry, 41*, 590–597. http://dx.doi.org/10.1080/00048670701392825

Rosenzweig, S. (1936). Some implicit common factors in diverse methods of psychotherapy. *American Journal of Orthopsychiatry, 6*(3), 412–15.

Sayer, N.A., Noorbaloochi, S., Frazier, P., Carlson, K., Gravely, A., & Murdoch, M. (2010). Reintegration Problems and Treatment Interests Among Iraq and Afghanistan Combat Veterans Receiving VA Medical Care. *Psychiatric Services, 61*(6), 589-597.

Schagen, A. *Prevalence, correlates and treatment of nightmares in secondary mental healthcare.* Enschede/Amsterdam: Ipskamp Printing.

Schok, M.L., Kleber, R.J., Elands, M. & Weerts, J.M.P. (2008). Meaning as a mission: A review of empirical studies on appraisals of war and peacekeeping experiences. *Clinical Psychology Review, 28,* 357-365. https://doi.org/10.1016/j.cpr.2007.04.005

Skodol, A.E., Schwartz, S.H.A.R.O.N., Dohrenwend, B.P., Levav, I., Shrout, P.E., & Reiff, M. (1996). PTSD symptoms and comorbid mental disorders in Israeli war veterans. *The British Journal of Psychiatry*, *169*(6), 717-725.

The management of post-traumatic stress Working Group (2004). *VA/DoD clinical guidelines for the management of post-traumatic stress.* Department of Veterans Affairs, Department of Defence.

The management of post-traumatic stress Working Group (2010). *VA/DoD clinical practice guideline for management of post-traumatic stress. Update of 2004 guideline.* Department of Veterans Affairs, Department of Defence.

Tukey, J.W. (1969). Analyzing data: Sanctification or detective work? *American Psychologist, 24,* 83-91. doi:10.1037/h0027108

Tukey, J.W. (1980). We need both exploratory and confirmatory. *The American Statistician, 34*(1), 23-25.

Walach, H. (2016). The efficacy paradox and its consequences for research in psychotherapy (and elsewhere). *Psychology of Consciousness: Theory, Research, and Practice, 3*, 154. http://dx.doi.org/10.1037/cns0000083

Wampold, B. E., Imel, Z. E., Laska, K. M., Benish, S., Miller, S. D., Flückiger, C., … Budge, S. (2010). Determining what works in the treatment of PTSD. *Clinical Psychology Review, 30,* 923-933. doi:10.1002/jclp.20683

Watts, B.V., Schnurr, P.P., Mayo, L., Young-Xu, Y., Weeks, W.B., & Friedman, M.J. (2013). Meta-analysis of the efficacy of treatments for posttraumatic stress disorder. *Journal of Clinical Psychiatry, 74*, 541–550. http://dx.doi.org/10.4088/JCP.12r08225

Wisco, B.E., Marx, B.P., Wolf, E.J., Miller, M.W., Southwick, S.M., & Pietrzak, R.H. (2014). Posttraumatic stress disorder in the US veteran population: Results from the National Health and Resilience in Veterans Study. *The Journal of clinical psychiatry, 75*, 1338-1346. doi:10.4088/JCP.14m09328

Chapter 2

The efficacy of recommended treatments for veterans with PTSD: A metaregression analysis

Published as:

Haagen, J. F. G., Smid, G. E., Knipscheer, J. W., & Kleber, R. J. (2015). The efficacy of recommended treatments for veterans with PTSD: A metaregression analysis. *Clinical Psychology Review, 40,* 184-194. doi:10.1016/j.cpr.2015.06.008

Abstract

Soldiers and veterans diagnosed with PTSD benefit less from psychotherapy than non-military populations. The current meta-analysis identified treatment predictors for traumatised soldiers and veterans, using data from studies examining guideline recommended interventions, namely: EMDR, exposure, cognitive, cognitive restructuring, cognitive processing, trauma focused cognitive behavioural, and stress management therapies. A systematic search identified 57 eligible studies reporting on 69 treated samples. Exposure therapy and cognitive processing therapy were more effective than EMDR and stress management therapy. Group-only therapy formats performed worse compared with individual-only formats, or a combination of both formats. After controlling for study design variables, EMDR no longer negatively predicted treatment outcome. The number of trauma focused sessions, unlike the total number of psychotherapy sessions, positively predicted treatment outcome. We found a relationship between PTSD pre-treatment severity levels and treatment outcome, indicating lower treatment gains at low and high PTSD severity levels compared with moderate severity levels. Demographic variables did not influence treatment outcome. Consequently, soldiers and veterans are best served using exposure interventions to target PTSD. Our results did not support a group-only therapy format. Recommended interventions appear less effective at relatively low and high patient PTSD severity levels. Future high-quality studies are needed to determine the efficacy of EMDR.

Acknowledgment contribution authors

Designed research: Haagen, Smid, Kleber, Knipscheer

Performed research: Haagen

Analysed data: Haagen, Smid

Wrote the paper: Haagen, Smid, Kleber, Knipscheer

Introduction

Deployed soldiers and veterans have risked exposure to life-threatening stressors, such as combat, injury, and witnessing suffering and death. Whilst most veterans were healthy, resilient individuals able to cope with such stressors, between 3 and 17% developed posttraumatic stress disorder (PTSD) in the first years after deployment (Engelhard et al., 2007; Richardson, Frueh, & Acierno, 2010). PTSD is a mental disorder that evokes severe distress, chronic suffering and impairment. Its core symptoms comprise re-experiencing traumatic content, persistent avoidance of traumatic content, negative alterations in cognitions, and arousal and reactivity (American Psychiatric Association, 1994, 2013). More than half a million American veterans sought PTSD care at a cost of three billion dollars (Institute of Medicine [IOM], 2014).

Clinical-practice guidelines recommend psychological treatment interventions to target PTSD (Australian Centre for Posttraumatic Mental Health (ACPMH), 2007; IOM, 2008; International Society for Traumatic Stress Studies (ISTSS), 2009; National Institute for Clinical Excellence (NICE), 2005; The management of post-traumatic stress Working Group, 2004, 2010). The following first-choice interventions are recommended by most or all clinical practice guidelines: eye movement desensitization and reprocessing (EMDR), exposure therapy (ET), cognitive therapy (CT), cognitive restructuring therapy (CR), cognitive processing therapy (CPT), and trauma focused cognitive behavioural therapy (TF-CBT). Stress management therapy (SMT) has also been mentioned because the VA-DoD guidelines (The management of posttraumatic stress Working Group, 2010) recommend stress inoculation therapy (SIT), which is a SMT intervention. Recent empirical evidence confirmed that veterans respond reasonably well to these recommended interventions (Kitchiner, Roberts, Wilcox, & Bisson, 2012). However, veterans benefitted less from psychotherapy than non-military PTSD populations (Watts et al., 2013) and meta-analyses reported smaller treatment effect sizes for traumatised veterans (d = .68–.81) versus non-veterans (d = 1.04–1.83) (Bradley, Greene, Russ, Dutra, & Westen, 2005; Goodson et al., 2011). The majority of veterans with PTSD (78%) still receive PTSD treatment after four years of treatment (Congress of the United States (CBO), 2012). Psychotherapies apparently deliver only limited PTSD symptom-reduction in the veteran population. Psychotherapy studies face further critique that their findings are mostly based on the average responses of large treatment groups that ignore within-person variability (i.e., individual factors that influence outcome). As a response, researchers have begun to emphasize the importance of individual treatment responses and mechanisms of therapeutic change as ‘the surest way to enhance efficacy’ (Barlow, Bullis, Comer, & Ametaj, 2013).

There are various explanations why veterans benefit less from treatment than other PTSD populations. Several authors highlighted the intensive, repetitive and interpersonal nature of combat-related traumatic events as a complicating factor (Pietrzak, Whealin, Stotzer, Goldstein, & Southwick, 2011). Traumatic combat experiences are often less straightforward than single traumatic events (e.g., a car accident) and are known to decrease PTSD treatment effectiveness (Price, Gros, Strachan, Ruggiero, & Acierno, 2013). On a patient level, treatment complications are reported among more symptomatic veterans. These veterans experienced more severe symptoms and more comorbid disorders, and include severe PTSD levels (Belsher, Tiet, Garvert, & Rosen, 2012; Boden, Bernstein, et al., 2012; Boden, Kimerling, et al., 2012; Johnson & Lubin, 1997; Owens, Chard, & Cox, 2008), severe anger issues (Forbes, Creamer, Hawthorne, Allen, & McHugh, 2003; Forbes et al., 2008; Lloyd et al., 2014; Owens et al., 2008), comorbid alcohol abuse (Forbes et al., 2003, 2008), and comorbid depression (Forbes et al., 2003). The results however are not unequivocal, a minority of studies reported no negative and even positive treatment effects for more symptomatic veterans (Fontana, Rosenheck, & Desai, 2012; Forbes et al., 2002; Richardson et al., 2014; Steindl, Young, Creamer, & Crompton, 2003). From a developmental perspective, veterans diagnosed with a borderline personality disorder (Forbes et al., 2002), a 'disorders of extreme stress not otherwise specified' (DESNOS) diagnosis (Ford & Kidd, 1998), and dysfunctional attachment style (Forbes, Parslow, Fletcher, McHugh, & Creamer, 2010), fared worse in treatment. The results are again not unequivocal, Walter, Kiefer, and Chard (2012) did not find any effects for personality disorders on PTSD treatment, and early childhood experiences did not predict treatment outcome (Johnson & Lubin, 1997). From a social perspective, veterans performed worse in treatment if they were socially isolated (Forbes et al., 2002), had poor functioning families, and experienced marital distress (Evans, Cowlishaw, Forbes, Parslow, & Lewis, 2010; Evans, Cowlishaw, & Hopwood, 2009). Last, organisational and treatment factors also influence outcome. For example, PTSD treatment success was predicted by positive treatment expectations and longer treatment duration (Belsher et al., 2012), as well as a willingness for patients to therapeutically change (Rooney et al., 2007).

The evidence for treatment predictors may seem abundant from these articles, but is in reality scant. Most of these factors were studied only once or twice which does not offer a firm base for predictive statements. The vast majority of studies examined univariate relationships between a single predictor and treatment outcome, thus not taking the interrelatedness between predictor variables into account. Only a few studies investigated the effects of multiple predictors simultaneously (e.g., Forbes et al., 2008). Many questions related to mechanisms of change also remain unanswered. It is unclear whether important veteran patient characteristics such as age

and gender, should be treated in the same manner as civilians (IOM, 2008). There is also debate about the most optimal content and format for delivering treatment; is group-therapy formats are as effective as individual-therapy formats (The management of post-traumatic stress Working Group, 2010), and is a trauma-focus is imperative for PTSD treatment (Benish, Imel, & Wampold, 2008; Ehlers et al., 2010; Wampold et al., 2010). Consequently, there is a need to assess the influence of veteran patient and treatment characteristics on treatment outcome. Using meta-analysis, the information from numerous studies can be combined to strengthen predictive evidence, test treatment guideline recommendations and help resolve conflicting predictor study outcomes. Up till now, meta-analyses about predictive factors are however lacking.

Prognostic research offers novel opportunities to assess the impact of specific factors on treatment outcome. The term prognosis refers to the probability of an individual developing a particular state of health (e.g., treatment outcome) over a specific time, based on his or her clinical and non-clinical profile (Moons, Royston, Vergouwe, Grobbee, & Altman, 2009). Prognostic research thus allows us to make inferences or predictions about expected treatment outcomes for individual patients. It advances understanding of therapeutic change mechanisms, enables psychotherapy improvements, and the creation of clinical decision making tools (Altman, 2001; Moons, Altman, Vergouwe, & Royston, 2009). Such tools enable clinicians to select suitable interventions tailored to the specific needs of each individual. The present prognostic study aims to identify PTSD psychotherapy treatment efficacy predictors for traumatised veterans. It is the first meta-analysis to use data from guideline recommended PTSD psychotherapy intervention studies in search of predictors.

Method

Search strategy

We undertook a systematic literature search to retrieve all first-choice psychotherapy studies that target PTSD among veterans and active military personnel. The search was performed in the following databases and their accompanied search registries: PubMed (NCBI), Pilots (ProQuest), PsycINFO (Ovid), Embase (Elsevier),Medline (OvidSP), CINAHL (Ebsco Host), and Web of Science (ISI Web of Knowledge). The search domains and their respective synonyms were combined into search syntaxes using Boolean operators. For example, the PubMed search syntax was: (PTSD OR “Posttraumatic stress disorder” OR “Post traumatic stress disorder” OR “Post-traumatic stress disorder” OR “Combat disorder” OR Psychotrauma OR Traumatised OR

Traumatized) AND (Treatment OR Treatments OR Therap* OR Psychotherap* OR Intervention OR Interventions) AND (Veteran OR Veterans OR Troops OR War OR Ex-military OR Army OR Soldier OR Soldiers OR Peacemaker OR Peacemakers) AND (Effectiveness OR Effect OR Effectively OR Efficacy OR Efficiency OR Efficacious OR Efficient OR Success OR "Symptom reduction" OR "Symptom decrease" OR "Treatment outcome" OR "Treatment response"). The first author screened the reference list of each included study for additional suitable studies.

Study selection

Two researchers independently reviewed the retrieved studies consecutively on title, abstract and full text, using identical selection criteria. The retrieved studies were considered eligible for inclusion if they: (a) were peer-reviewed, (b) consisted of help-seeking veterans or active duty soldiers, (c) had a PTSD diagnosis, (d) examined a first-choice PTSD psychotherapy trial, and (e) reported pre- and post-treatment PTSD symptom severity data. No time, linguistic and geographical restrictions were employed. Twenty studies reported the proportion of veterans on psychotropic drugs. Over three quarters (76%) of the patients received medication at the start of psychotherapy. These results show that medication is a common practice among veterans and soldiers with PTSD. It was not considered an exclusion criterion because it reflects standard clinical practice.

The interventions were allowed to be imbedded in more extensive treatment programmes that included other interventions. This enables inferences concerning the influence of inpatient and day treatment settings that almost exclusively involve programmes in which trauma focused interventions consist of a single aspect of the total treatment programme. However, we excluded treatment programmes that did not define the content and number of first-choice treatment sessions, as well as case studies, secondary data-analyses, reviews and meta-analyses. Studies designed to investigate the effects of a specific medication to augment psychotherapy were also excluded. The search identified 57 eligible studies that tested 69 interventions among 6878 patients (see Appendix A). Authors were contacted for: (a) missing data, (b) pre- and post-treatment PTSD symptom severity outcome correlations, and (c) clarification regarding suspected secondary data analysis. A follow-up e-mail was sent if no response was forthcoming.

Data extraction

The first author extracted and coded all the reports. A second coder checked the accuracy of the first coder. Both coders were in agreement 95.8% of the time. The disagreement observations (4.2%) were further scrutinised and, after reaching consensus, led to (1%) coding changes.

Various predictors were included in the meta-analyses. Patient characteristics: age (mean age in years), gender (% male), ethnicity (% Caucasian, Afro-American, and Hispanic), marital (% divorced), employment (% unemployed), and military status (veteran versus active duty), and pre-treatment PTSD symptom severity level (% of severity calculated by dividing the mean sample score by the maximum score on the instrument). Treatment characteristics: treatment setting (outpatient or inpatient), modality (individual, group, or combination format), delivery (face-to-face, internet-based, or using virtual reality simulations), number of sessions, and number of trauma focused sessions. The number of trauma focused sessions was only examined in outpatient settings because most inpatient studies were unclear about the number of trauma focused sessions compared to the total number of sessions. Study characteristics: PTSD measurement instrument, treatment allocation strategy (randomised versus not-randomised), and whether intent-to-treat or completer analyses were used.

We gathered pre- and post-treatment correlations to calculate the effect size for each intervention. The majority of the correlations (57%) between the pre- and post-treatment PTSD measures were attained directly from the article, or calculated from dependent t-test analyses provided in the article, or via author communications. The remaining correlations (43%) were imputed using predictive mean matching (10 imputations). Predictive mean matching is a recommended multiple imputation technique to increase the reliability of the results (Vink, Frank, Pannekoek, & Van Buuren, 2014). To inform the prediction of the missing data in the imputation models, we included variables that were considered missing at random (MAR). These consisted of a range of demographic, treatment, and design variables, as well as the dependent variable (treatment effect size). Multiple instruments ascertained the PTSD severity; the Clinician-Administered PTSD Scale (CAPS) was considered the 'gold standard'.

Methodological quality

The first author assessed the methodological quality of each study using the 'Methodology checklist for prognostic studies'—an assessment tool developed by NICE (2009). Several topics were inspected regarding their potential for bias, namely: (a) study sample representability, (b) loss of follow-up data, (c) adequate measurement of prognostic factors, (d) adequate measurement of outcome of interest, and (e) potential confounders. The appropriateness of the topic of statistical analysis was not inspected, since the current meta-analysis did not include pre-analysed data. Instead of reporting a 'yes', 'no', or 'unclear' risk of bias, the current study reported 'low', 'moderate', or 'high' risk of bias. The risk of bias was assessed based on an appraisal of the quality of each topic as formulated in the employed methodology checklist. For

example, to address the quality of the study sample representability, points to consider were: is the population of interest adequately described with respect to key characteristics, sampling frame and recruitment, inclusion and exclusion criteria, etc. (see NICE, 2009 Appendix J for the complete checklist). After evaluating the quality of each topic the overall quality of each article was assessed. Articles with a low risk of bias on each topic and a moderate risk of bias on no more than one topic were considered to be at low risk of bias. Articles with a moderate risk of bias on two or more topics and with no more than one high risk of bias topic were considered to be at moderate risk of bias. Articles with two or more high risk of bias topics were considered to be at high risk of bias. Twenty percent of the studies were independently assessed for risk of bias by a second rater. The interrater reliability was good (.85 kappa).

The treatment effect sizes were calculated using Hedges' g for each intervention. We calculated the pooled effect size using macro's developed by Wilson (2005) for SPSS statistical software. The same macro was used to perform subgroup analysis (analogue to the one-way ANOVA) and meta-regression analyses for categorical and continuous predictors. Categorical variables that were significantly associated with effect sizes in univariate analyses were dummy coded to enable inclusion in multivariate regression analyses. Pre-treatment PTSD severity was also investigated using quadratic regression because of conflicting predictive findings from previous studies (Forbes et al., 2003; Perconte & Griger, 1991). Quadratic regression variables were standardised (mean-centred) to avoid multicollinearity. A random-effects model was chosen because of the expected heterogeneity between the studies. We estimated the model using the iterative maximum likelihood estimation.

The authors assessed the heterogeneity using the Q statistic and a significance test of the Q-statistic (p-value), the ratio of true heterogeneity to total observed variation (I^2), and investigated the possibility of publication bias using an Egger test to detect funnel plot asymmetry (Borenstein, Hedges, Higgins, & Rothstein, 2009). Two sensitivity analyses tested whether the exclusion of low quality (with risk of bias) studies, or the removal of any one study, influenced the results.

Results

Figure 1 shows an overview of the study search and selection process. Forest plots for random-effects meta-analysis are presented in Figure 2. The search was performed in June 2014 and yielded 2149 unique articles from five databases. The majority of articles (n = 2092) were excluded after screening. Major reasons for exclusion were: absence of PTSD diagnosis in study sample (n = 374), no veteran or active soldier sample (n = 511), not a psychotherapy study, or

psychotherapy did not target PTSD, or PTSD measurements were not included (n = 844), secondary analysis (including reviews and meta-analyses), books (chapters), or protocols (*n* = 166), and studies investigating a psychotherapy that was not considered first-choice, or with unspecified treatment content (*n* = 142). The database search identified 55 eligible studies. Two additional studies were added after screening the reference lists of all eligible studies, resulting in 57 reporting on 69 eligible samples.

Table 1 describes the data collected from each study. The studies were almost exclusively from North-American origin (93%). The remaining four studies originated from Australia (*n* = 2), Israel (*n* = 1), and Portugal (*n* = 1). Most studies consisted of either ET or CPT therapy (90%). The CAPS and PTSD Checklist (PCL) were the primary PTSD outcome measures in 86% of the studies. Most studies had an observational design (67%), whilst a third (33%) had a randomized controlled trial (RCT) design. The majority of interventions delivered psychotherapy in an individual format (58%) and in an outpatient setting (65%). 17% were treated in an inpatient setting and another 17% had an unknown treatment setting. Some studies reported very large effect sizes (max. 3.1), whereas other studies reported a worsening of symptoms after treatment (min. −.46). Most studies involved veterans (88%) instead of active duty soldiers (12%). The average amount of patients per study was 104 patients (*SD* = 246), with *n* = 5 as the lowest number of patients, and *n* = 1888 as the highest number of patients in a study. For additional details the reader is referred to a supplementary table (Appendix B). The quality of each included study is summarised in Appendix C, almost half (48%) of the studies were considered of high quality with a low overall risk of bias, 22% were of moderate quality, and 23% of low quality. The pooled effect size for all interventions was *g* = 1.12 (95% CI, .98–1.25; see Figure 2).

Table 1

Data collected from included meta-analysis studies

		n	*%*
Intervention			
	ET	38	55
	CPT	24	35
	EMDR	4	6
	SMT	3	4
Instrument			
	CAPS	31	45
	PCL	28	41
	Other	10	14
Sample			
	Min range	5	
	Max range	1888	
Allocation			
	Random	23	33
	Non-random	46	67
Analysis			
	ITT	29	42
	Completer	36	52
Setting			
	Inpatient	12	17
	Outpatient	45	65
Modality			
	Individual	40	58
	Group	14	20
	Combination	12	17
No. of sessions			
	Mean	14	
	Min range	1	
	Max range	47	
No. of trauma focused sessions			
	Mean	7.5	
	Min range	0	
	Max range	13	
Pre-treatment symptom severity (%)			
	Mean	64	
	Min range	42	
	Max range	81	
ES (Hedges g)			
	Mean	1.1	
	Min range	-.46	
	Max range	3.1	

Note. Intervention: ET = Exposure therapy; CPT = Cognitive processing therapy; EMDR = Eye movement and reprocessing therapy; SMT = Stress management therapy. Instrument: CAPS = Clinician-Administered PTSD Scale; PCL = PTSD Checklist. Analysis: ITT = Intent-to-treat analysis. Modality:

Individual = Individual therapy; Group = Group therapy; Combination = Group therapy combined with individual therapy.

Univariate predictors

The predictive utility of several categorical variables was examined by means of subgroup analyses (Table 2 and Figure 3). Interventions that solely consisted of a group-only therapy format fared significantly worse compared with interventions that consisted of-or included-individual psychotherapy (g = .63 vs. g = 1.22; p<.001). The individual therapy format did not differ significantly from a combination (individual and group) format (g = 1.17 vs. g = 1.40; p = .26). The results demonstrated significant differences (p < .001) between treatment interventions, with CPT (g = 1.33) and ET (g = 1.06) yielding greater effect sizes than EMDR (g = .38) and SMT (g = .16). These results show that patients treated with CPT or ET had greater PTSD symptom reductions compared to those treated with EMDR and SMT. As expected, non-random treatment allocation was associated with a higher effect size compared to random treatment allocation (g = 1.27 vs. g = .68; p < .001), showing that patients that were randomly allocated to a guideline recommended PTSD intervention experienced fewer treatment gains (i.e., lower effect size) compared to patients that participated in observational studies. There were no significant group differences regarding type of treatment delivery, treatment setting, intent-to treat vs. completer analyses, measurement instrument and measurement method.

Meta-regression analyses (Table 3) identified the number of trauma focused sessions (β = .51; p < .001) as a positive predictor, indicating that each subsequent trauma focused session further decreased PTSD symptom severity. PTSD symptom severity did not predict treatment outcome. After visual inspection of the pre-treatment symptom severity scatterplot, a quadratic expression between symptom severity and treatment outcome was added to the linear expression.

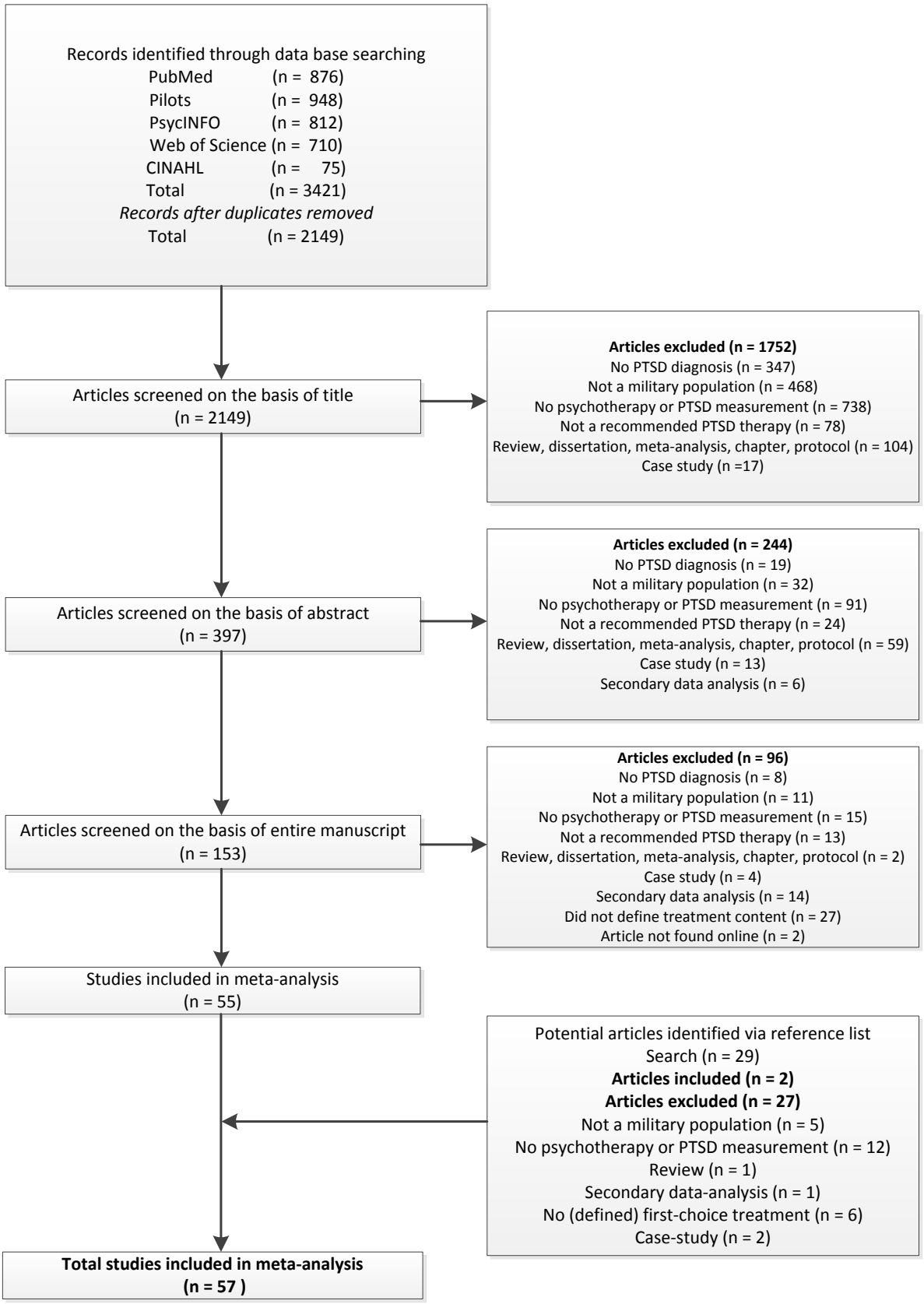

Figure 1. *Flowchart study selection.*

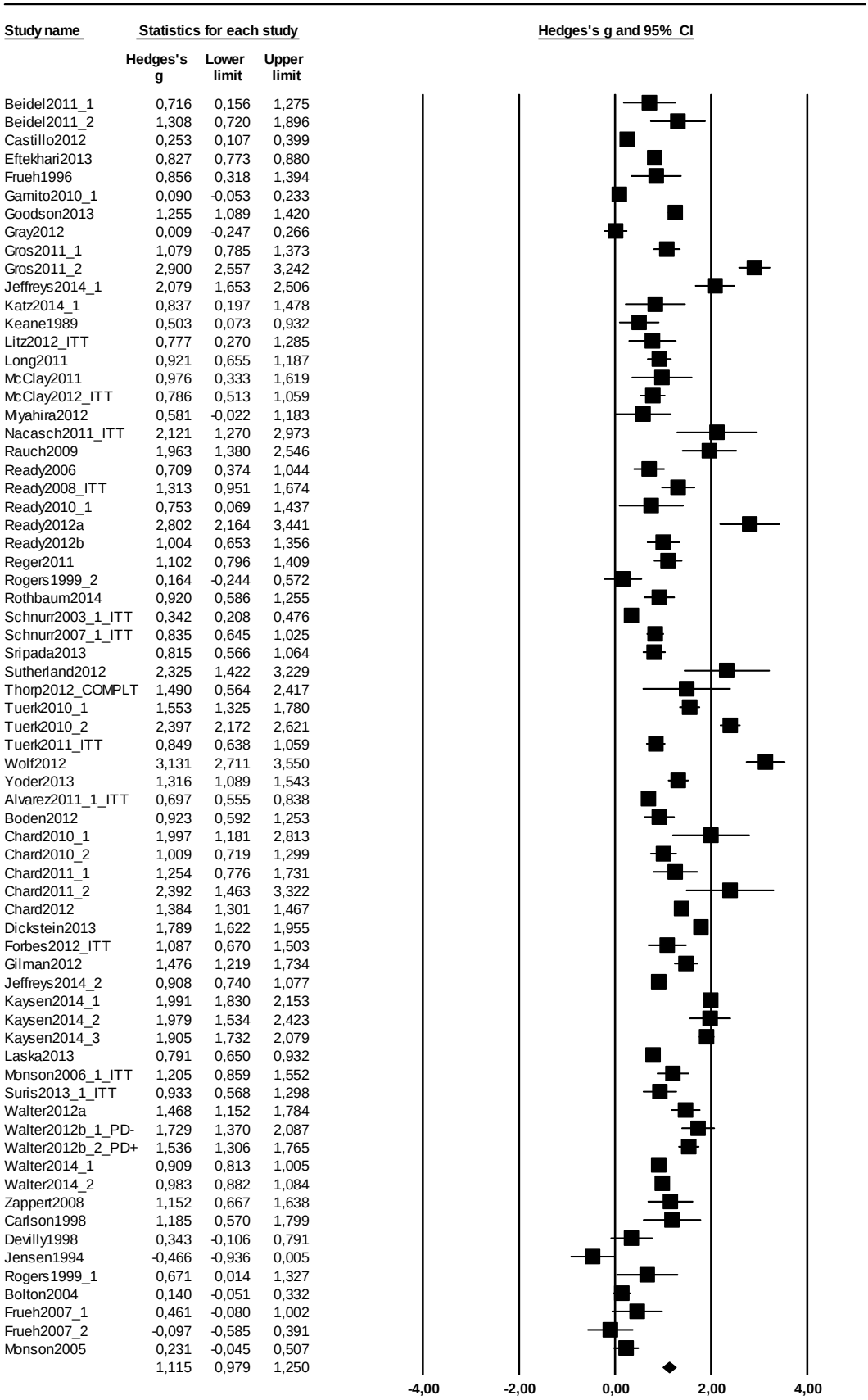

Figure 2. *Forest plot for PTSD treatment efficacy (pre vs. post)*

The quadratic regression expression of pre-treatment severity ($\beta = -.29$; $p = .01$) negatively predicted treatment outcome, indicating that patients with relatively low and high PTSD symptom severity levels benefited less from treatment than patients with moderate symptom severity levels. Demographic data and the number of treatment sessions did not predict treatment outcome.

Multivariate predictors

The significant univariate predictors were further assessed whilst controlling for interference from confounding study characteristics variables. Treatment allocation was the only significant predictor and therefore the only study characteristic we controlled for (Table 4). Therapy format proved a significant categorical predictor in the previous subgroup analysis. It was dummy coded (group-only vs. individual or combination therapy format) and reanalysed as a continuous predictor. This enabled us to compare the effects of therapy format on treatment outcome with other continuous predictors and control for confounding variables. The same strategy was employed for treatment type. Each intervention was dummy coded against ET as reference group.

Multivariate meta-regression analyses revealed the number of trauma focused sessions ($\beta = .40$; $p < .01$) as a positive predictor of treatment effect, meaning that each subsequent trauma focused sessions decreased PTSD symptoms (i.e., increased treatment effect size). Group-only therapy format ($\beta = -.40$; $p < .001$) was a negative treatment predictor, indicating that patients treated in a group therapy format benefitted less from therapy than patients treated in an individual therapy format or in a combination (individual and group) format. The quadratic expression of pre-treatment PTSD symptom severity ($\beta = -.29$; $p < .01$) was a negative outcome predictor, illustrating that patients with relatively low and high PTSD symptom severity levels experienced less symptom decrease compared to patients with moderate severity levels (Figure 4). The SMT intervention ($\beta = -.26$; $p < .05$) negatively predicted treatment outcome compared to ET (dummy reference group), indicating that patients that were treated with SMT experienced less PTSD symptom reduction compared to ET therapy. EMDR ($\beta = -.12$; $p = .26$) no longer predicted treatment outcome after controlling for allocation, indicating that EMDR was equally effective as ET (dummy reference group) in reducing PTSD symptoms.

Heterogeneity, publication bias and sensitivity analysis

There was evidence of heterogeneity (p(Q) = .00) with a high dispersion of the observed variance (I^2 = 96%). These findings validated the usage of the random-effects model and the search for covariates to explain the observed dispersion. The Egger test did not indicate a possible publication bias (t = 1.38, df = 67, p(1-tailed) = .09). Sensitivity analysis showed that exclusion of n = 20 (29%) studies that were judged to run a risk of bias did not impact the study results. The sensitivity analyses were completed by recalculating the pooled effect outcomes after removal of any one study from the total meta-analysis to examine the influence of each individual study on the overall effect estimate, the highest and lowest pooled effect sizes ranged between 1.14 [95% CI, 1.00–1.27] and 1.08 [95% CI, .95–1.22]. This indicated that the influence of each individual study on the pooled effect size was small.

Table 2

Univariate subgroup analyses

Variables		*p*	Mean ES	n
Treatment characteristics				
Intervention		.001		
	CPT		1.33	23
	Exposure		1.06	38
	EMDR		.38	4
	SMT		.16	3
Treatment Setting		.70		
	Outpatient		1.10	45
	Inpatient		1.20	12
Treatment Modality		.01		
	Combination†		1.40	11
	Individual therapy		1.17	41
	Group therapy		.63	14
Treatment Delivery		.16		
	Face to face		1.14	57
	Internet/Telehealth		.82	3
	Virtual reality		.73	8
Study characteristics				
Allocation		.001		
	Non-Random		1.27	46
	Random		.68	23
Analysis		.96		
	Completer		1.09	36
	Intent-to-Treat		1.08	29
PTSD Instrument		.17		
	CAPS		1.19	31
	PCL		1.07	28
	OTHER		.75	10
Measurement method		.22		
	Questionnaire		1.00	35
	Interview		1.18	34

Note. n = Number of studies. Mean ES = Mean effect size (Hedges g)
† Combination therapy = Group and individual therapy combined.

Table 3

Univariate regression analyses

Variables	β	R^2	n
Patient characteristics			
Age	-.17	3%	67
Male gender	.05	3%	65
Caucasian	-.05	0%	57
Afro-American	.03	0%	48
Hispanic	.25	6%	32
Divorced	-.29	8%	24
Unemployed	.12	2%	25
Veteran status	.10	1%	66
Pre-treatment symptom severity	.06	0%	67
Pre-treatment symptom severity^2	-.29*	8%	67
Treatment characteristics			
No. of sessions	.19	4%	68
No. of trauma focused sessions	.51**	26%	43

Note. Age = Age in years; Male gender = % of males versus females; Caucasian = % belonging to a Caucasian ethnicity; Afro-American = % belonging to an Afro-American ethnicity; Hispanic = % belonging to a Hispanic ethnicity; Divorced = % divorced; Unemployed = % unemployed; Veteran status = % veterans versus active duty; Pre-treatment symptom severity = Pre-treatment PTSD symptom severity based on total questionnaire score expressed as a %; No. of sessions = Number of therapy sessions; No. of trauma focused sessions = Number of trauma focused therapy sessions ; R^2= Explained variance; n = Number of studies.

* $p < .05$.

** $p < .001$.

Table 4

Multivariate regression analyses of significant univariate predictors with 'treatment allocation' as covariate

Variables	β	R^2	ΔR^2	n
Patient characteristics				
Pre-treatment symptom severity[2]	-.29**	27%	9%	67
Treatment characteristics				
Group therapy format	-.40***	35%	17%	66
No. of trauma-focus sessions	.40**	37%	19%	43
CPT vs. Exposure	.17	23%	5%	68
EMDR vs. Exposure	-.12	21%	3%	68
SMT vs. Exposure	-.26**	27%	9%	68

Note. No. of trauma focused sessions = Number of trauma focused therapy sessions. Group therapy format = Dummy coded variable group versus individual therapy and combination therapy. Pre-treatment symptom severity = Pre-treatment PTSD symptom severity based on total questionnaire score expressed as a %. CPT vs. Exposure, EMDR vs. Exposure and SMT vs. Exposure are dummy variables of the categorical variable 'Intervention'. R^2= explained variance. ΔR^2 = the change in R^2 values after subtracting explained variance from control variable 'Allocation'. n = Number of studies.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

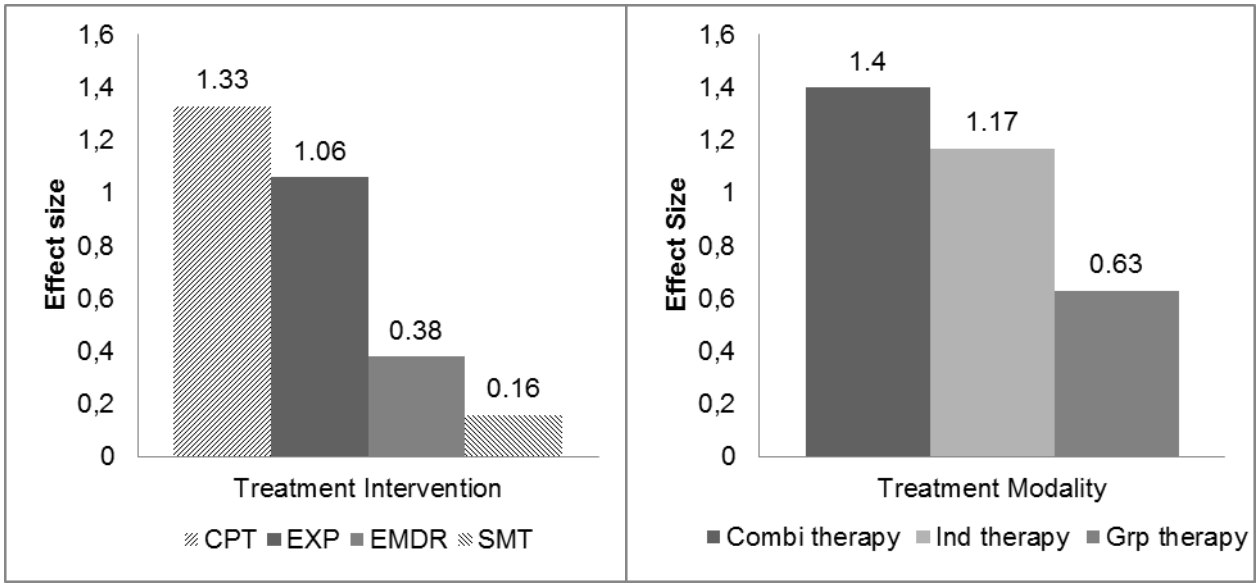

Figure 3. *Univariate analyses of treatment effect size (Hedges' g) for treatment interventions and treatment modalities*

Discussion

The present meta-analysis investigated PTSD psychotherapy outcome predictors for veterans and soldiers. An individual or combination (group and individual) therapy format, (prolonged) ET and CPT interventions as well as the number of trauma focused therapy sessions predicted increased treatment effectiveness. In contrast, group-only therapy, EMDR and SMT interventions, negatively impacted treatment effectiveness. EMDR was however no longer associated with decreased treatment effectiveness after controlling for a random or non-random treatment allocation. High and low pre-treatment PTSD severity levels predicted lower treatment gains compared with moderate pre-treatment PTSD severity levels (Figure 4).

SMT interventions were less effective compared to ET and CPT interventions, whilst the results for EMDR were mixed compared to ET and CPT interventions. SMT might be less effective because it does not particularly target maladaptive trauma related cognitions, or activate

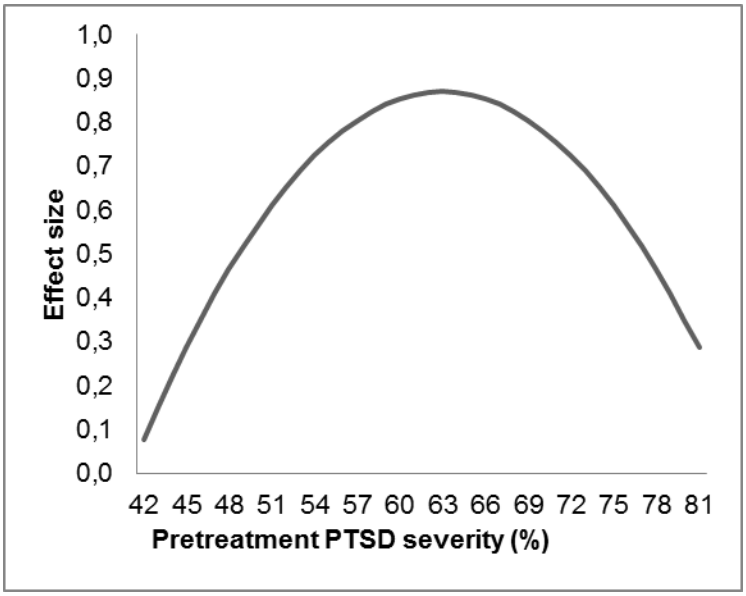

Figure 4. *Graph of quadratic regression of pre-treatment PTSD symptom severity level as percentages on effect size (Hedges' g), whilst controlling for 'treatment allocation'*

fear memory structures that allow for habituation and modification of the pathological fear structures. Both ET and CPT are based on cognitive and emotional processing theories (Ehlers & Clark, 2000; Rauch & Foa, 2006), using proven therapy elements, such as exposure. It is presently unclear why EMDR might be less effective than ET and CPT. Unlike exposure therapies, EMDR therapy uses free association techniques that often only briefly access details of traumatic memories, instead of repetitive exposure to traumatic memories. Experimental studies showed that the underlying mechanism of EMDR did not seem to be based on habituation (e.g., Leer, Engelhard, Altink, & Van den Hout, 2013), and would therefore be less suited for promoting habituation and symptom reduction compared exposure-based therapies (McGuire, Lee, & Drummond, 2014; Rogers & Silver, 2002). Alternatively, the inferior EMDR results might be attributed to study design characteristics. Non-random allocations are known to overestimate effect sizes (Schulz, Chalmers, Hayes, & Altman, 1995), whereas all EMDR studies used a 'superior' random allocation design. After controlling for treatment allocation, EMDR no longer predicted a negative treatment outcome compared to ET. Therefore, EMDR might be as effective as ET and CPT. It is recommended to test both hypotheses mentioned above using well-

designed and controlled studies that directly compare EMDR with CPT and ET for veterans and soldiers.

Group therapy is a popular and recommended treatment format for traumatized veterans (The management of post-traumatic stress Working Group, 2010), despite insufficient evidence regarding its efficacy (IOM, 2008). The present meta-analysis demonstrated that a group-only format performed significantly worse than an individual or combined treatment format. It is expected that group size limits the amount of exposure time to one's own traumatic experiences. Most patients did not receive more than one or two personal exposure sessions within group therapy and spent the majority of exposure time listening to the traumatic stories of fellow veterans. Listening to the traumatic content of others might be less effective in activating and habituating one's own traumatic memories. Another explanation could be that within-group tensions or sociodynamics deter from the expected therapy results (Battegay, 1977). For example, anger-a common issue among veterans with PTSD-can provoke counter-aggression from other group members, and discussions with the group leader that challenge the therapeutic progress (Stone, 2009). Traumatic experiences that evoke intense feelings of shame or guilt are also expected to be problematic for patients in a group format because they make patients become self-conscious, feel exposed, or fear judgement instead from their peers (Lee, Scragg, & Turner, 2001). Shame or guilt-ridden patients must likely overcome higher anxiety thresholds before feeling sufficiently safe to share their thoughts, feelings and experiences in group therapy compared to individual therapy.

A combination therapy format was found to be as effective as an individual-only format. All combination therapy programmes provided individual trauma focused therapy, unlike the group-only formats that offered collective trauma focused therapy. The combination formats often used the group therapy component to target other non-trauma focused themes, such as providing psychoeducation, social support, or emotional-regulation to address social isolation, impaired social functioning, and anger management issues. These issues can have detrimental effects for PTSD treatment outcome (Evans et al., 2009, 2010; Forbes et al., 2002, 2003, 2008; Lloyd et al., 2014; Owens et al., 2008). We believe group therapy might augment trauma focused therapy if used in conjunction with individual trauma focused therapy. These combination formats had the highest combined effect size, though no significant difference in effect size was found with the individual formats that reported a somewhat lower combined effect size.

Interested readers are referred to the supplementary table (Appendix B) for an overview of the therapy format of each study.

The present results bridge the gap between conflicting findings regarding pre-treatment symptom severity (Forbes et al., 2003; Perconte & Griger, 1991). At moderate severity levels, patients appeared to receive the most benefit from recommended therapies, whilst low and high severity levels predicted lower treatment gains. Relatively low severity levels might reflect a state of underengagement that does not sufficiently activate the fear structure to enable optimal habituation and PTSD symptom reduction (Rauch & Foa, 2006). Conversely, patients with progressively severe symptoms become increasingly overwhelmed (overengagement) by the fear-related emotional intensity of their traumatic memories, and are unable to voluntary cognitively inhibit and disengage from re-experiencing threatening intrusive memories (Aupperle, Melrose, Stein, & Paulus, 2012; Rubin, Boals, & Berntsen, 2008). The emotional intensity obstructs habituation to decrease anxiety levels, whilst the distracting nature of threatening stimuli could impair attention regulation and performance at the cost of therapeutic suggestions (Aupperle et al., 2012). Alternatively, increasing severity levels could cause a gradual loss in adaptive abilities (Davidson et al., 2012; Moore, Varra, Michael, & Simpson, 2010), resulting in mental defeat, which is a negative outcome predictor (Ehlers et al., 1998; Kleim & Ehlers, 2009). Higher PTSD severity levels are also indicative of multiple life and (post-) deployment stressors among military personnel (Smid, Kleber, Rademaker, Van Zuiden, & Vermetten, 2013). Multiple (traumatic) stressors suggest a cumulative burden on survivors that complicates treatment compared to single traumatic events. Previous traumatic events moreover sensitised survivors to respond more strongly to subsequent stressors that impair recovery.

Unlike the total number of sessions, only the number of trauma focused sessions patients received predicted treatment improvement. These results contribute to the growing evidence that PTSD interventions need to focus on the traumatic content in order to be the most effective (e.g., Bisson, Roberts, Andrew, Cooper, & Lewis, 2013). It also highlights the importance of treatment attendance to decrease PTSD symptoms. Treatment attendance was previously identified by Tarrier, Sommerfield, Pilgrim, and Faragher (2000) as one of the strongest predictors of lower PTSD treatment gains.

The different modes of delivery appeared equally effective as face-to-face therapy. The demographic variables age, gender, ethnicity, marital, work, and military status, did not appear to

play a part in PTSD treatment efficacy in soldiers and veterans, suggesting that recommended PTSD interventions are equally effective across these demographic groups. Though it must be noted that ethnicity was operationalised for only three major minority groups in the United States and in a manner that might not grasp the dynamics surrounding the concept of ethnicity, such as the phase of cultural adaptation (e.g., Knipscheer & Kleber, 2006).

Strengths and limitations

The present study is the first to gather predictive information from recommended PTSD interventions. The meta-analyses were in accordance with PRISMA guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009); we performed a thorough search that minimised publication and language bias, and assessed the quality of each included study to increase the reliability of the results. Medication use is a common practice for veterans with PTSD with over 65% receiving SSRI/SNRIs (Abrams, Lund, Bernardy, & Friedman, 2013). This number roughly reflects the percentage on medication (75%) in the included meta-analysis studies and strengthens the generalisability of our findings for the clinical practice. Medication use was not investigated in the present study due to insufficient reported data. In general, medication use can be expected to have a small positive augmenting effect on treatment compared to a large psychotherapy effect on treatment outcome (Watts et al., 2013). The present study has a number of limitations. Our meta-analysis is mainly based on findings among veterans from the U.S.A. The possibility of generalizing our results to other countries remains an issue for future research. Furthermore, all meta-analyses risk ecological fallacy and the current study is not exempt from this risk (Reade, Delaney, Bailey, & Angus, 2008). The exploratory nature of the present study did not correct for multiple hypothesis testing and could risk type-I errors because it was considered more important to detect possible predictors instead of using stringent criteria that may fail to detect significant predictors. We did not examine follow-up data because only 18 studies provided data. The loss of more than two thirds of the available studies was considered an unacceptable loss in statistical power. The quality of the included studies varied, but was considered adequate based on a quality assessment; the results were robust after performing the sensitivity analysis excluding low quality studies. Only four studies examined EMDR and three studies examined SMT for veterans with PTSD, which could obscure the results. Nevertheless, the findings did not encourage SMT interventions for traumatized veterans and did not provide clear indications regarding the

suitability of EMDR. It should be noted that SIT is a specific form of SMT that has been recommended by the VA-DoD guidelines (The management of post-traumatic stress Working Group, 2010), but has not been sufficiently studied for veterans and soldiers with PTSD.

Clinical Implications and Conclusion

Veterans are best served using individual-based, or a combination of individual-based and group-based psychotherapy, to target PTSD. Group-only therapy formats should not be used to target PTSD. Exposure-based therapies, such as (prolonged) ET and CPT, are preferred above SMT. Though we might err on the side of caution, our results do not yet support EMDR as a recommended therapy for veterans (see also Albright & Thyer, 2010; IOM guidelines, 2008).

Patients with relatively low and high PTSD symptom severity levels appear at greater risk of treatment stagnation. This finding stresses the importance for therapists to maintain a proper therapeutic window: a psychological midpoint between inadequate and overwhelming activation of trauma related emotion during treatment (Briere & Scott, 2014). There are no interventions that specifically target high levels of PTSD severity, however, these levels are indicative of greater and more diverse impairment (Wolf et al., 2014). Currently, most PTSD experts recommend phase-based or sequenced therapy approaches that target a diversity (e.g., personality changes) of symptoms that clinically correlate with PTSD and that are often referred to as complex PTSD (e.g., Cloitre et al., 2012).Whether such approaches are more effective than immediate trauma focused treatment remains a matter of debate. These findings highlight the need to develop interventions that target this poor outcome group since these patients place a considerable cost and burden on the health care system in terms of ongoing needs for care, as well as associated disability benefits and work productivity loss (Engel et al., 1999; Sayer et al., 2010; Wald & Taylor, 2009).

Current advances in magnetic resonance imaging (MRI) scan abilities combined with longitudinal study designs allow researchers to connect psychoneurobiological information to treatment outcome (e.g., Kennis et al., 2015). There is definitely a need to examine the neurobiological pathways of high symptomatology patients against moderate and low symptomatology patients for a better understanding of the neural underpinnings of treatment resistant veterans. Therapists are further advised to discuss the beneficial effects of treatment

attendance during trauma focused therapy and discuss the dangers of therapy avoidance regarding decreases in treatment gains.

In conclusion, the current results were derived from a veteran and active military population and this should be taken into account when generalising beyond the current PTSD population. Nonetheless, the identified predictors may play an important role with respect to the enhancement of psychotherapies among other traumatised populations that face violent traumatic events and likely receive similar interventions in comparable therapeutic environments (e.g., police officers and victims of violent crimes). We urge researchers to test the identified predictors in other trauma populations in order to optimise recommended PTSD psychotherapies.

Acknowledgements

We would like to thank Professor Dr. Joop Hox for his meta-analytical advice and Gerko Vink (MSc) for his valuable instructions concerning the application of missing imputation techniques in meta-analytic studies.

References

Abrams, T. E., Lund, B. C., Bernardy, N. C., & Friedman, M. J. (2013). Aligning clinical practice to PTSD treatment guidelines: Medication prescribing by provider type. *Psychiatric Services, 64,* 142–148. http://dx.doi.org/10.1176/appi.ps.201200217.

Albright, D. L., & Thyer, B. (2010). Does EMDR reduce post-traumatic stress disorder symptomatology in combat veterans? *Behavorial Interventions, 25,* 1–19. http://dx.doi.org/10.1002/bin.295.

Altman, D. G. (2001). Systematic reviews of evaluations of prognostic variables. *British Medical Journal, 323,* 224–228. http://dx.doi.org/10.1136/bmj.323.7306.224.

American Psychiatric Association (1994). *Diagnostic and statistical manual of mental health disorders* (4th ed.). Washington DC: Author.

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Aupperle, R. L., Melrose, A. J., Stein, M. B., & Paulus, M. P. (2012). Executive function and PTSD: Disengaging from trauma. *Neuropharmacology, 62,* 686–694. http://dx.doi.org/10.1016/j.neuropharm.2011.02.008.

Australian Centre for Posttraumatic Mental Health (ACPMH) (2007). *Australian guidelines for the treatment of adults with acute stress disorder and posttraumatic stress disorder*. Melbourne, Victoria: ACPMH.

Barlow, D. H., Bullis, J. R., Comer, J. S., & Ametaj, A. A. (2013). Evidence-based psychological treatments: An update and a way forward. *Annual Review of Clinical Psychology, 9,* 1–27. http://dx.doi.org/10.1146/annurev-clinpsy-050212-185629.

Battegay, R. (1977).Möglichkeiten und Gefahren der Gruppenpsychotherapie [Possibilities and dangers of group psychotherapy]. *Zeitschrift für Klinische Psychologie Psychiatrie und Psychotherapie, 25*(1), 52–63.

Belsher, B. E., Tiet, Q. Q., Garvert, D. W., & Rosen, C. S. (2012). Compensation and treatment: Disability benefits and outcomes of U.S. veterans receiving residential PTSD treatment. *Journal of Traumatic Stress, 25,* 494–502. http://dx.doi.org/10.1002/jts.21747.

Benish, S., Imel, Z., & Wampold, B. (2008). The relative efficacy of bona fide psychotherapies for treating post-traumatic stress disorder: A meta-analysis of direct comparisons. *Clinical Psychology Review, 28,* 746–758. http://dx.doi.org/10.1016/j.cpr.2007.10.005.

Bisson, J. I., Roberts, N. P., Andrew, M., Cooper, R., & Lewis, C. (2013). Psychological therapies for chronic post-traumatic stress disorder (PTSD) in adults. *Cochrane Database of Systematic Reviews, 12,* 1–241. http://dx.doi.org/10.1002/14651858.CD003388.pub4.

Boden, M. T., Bernstein, A., Walser, R. D., Bui, L., Alvarez, J., & Bonn-Miller, M. O. (2012a). Changes in facets of mindfulness and posttraumatic stress disorder treatment outcome. *Psychiatry Research, 200,* 609–613. http://dx.doi.org/10.1016/j.psychres.2012.07.011.

Boden, M. T., Kimerling, R., Jacobs-Lentz, J., Bowman, D., Weaver, C., Carney, D., … Trafton, J. A. (2012b). Seeking safety treatment for male veterans with a substance use disorder and post-traumatic stress disorder symptomatology. *Addiction, 107,* 578–586. http://dx.doi.org/10.1111/j.1360-0443.2011.03658.x.

Borenstein, M., Hedges, L.V., Higgins, J. P. T., & Rothstein, H. R. (2009). *Introduction to metaanalysis.* Cornwall: John Wiley & Sons.

Bradley, R., Greene, J., Russ, E., Dutra, L., & Westen, D. (2005). A multidimensional meta-analysis of psychotherapy for PTSD. *American Journal of Psychiatry, 162,* 214–227.

Briere, J. N., & Scott, C. (2014). Emotional processing. In J. N. Briere,& C. Scott (Eds.), *Principles of trauma therapy: A guide to symptoms, evaluation, and treatment* (pp. 165–195). California: Sage.

Cloitre, M., Courtois, C.A., Ford, J. D., Green, B. L., Alexander, P., Briere, J., et al. (2012). *The ISTSS expert consensus treatment guidelines for complex PTSD in adults.* Retrieved from: http://www.istss.org/AM/Template.cfm?Section=ISTSS_ Complex_PTSD_ Treatment_Guidelines&Template=/CM/ContentDisplay. cfm&ContentID=5185

Congress of the United States (CBO) (2012). *The Veterans Health Administration's treatment of PTSD and traumatic brain injury among recent combat veterans.* Washington, DC: Congressional Budget Office.

Davidson, J., Stein, D. J., Rothbaum, B. O., Pedersen, R., Szumski, A., & Baldwin, D. S. (2012). Resilience as a predictor of treatment outcome in patients with posttraumatic stress disorder treated with venlafaxine extended release or placebo. *Journal of*

Psychopharmacology, 26, 778–783. http://dx.doi.org/10.1177/0269881111413821.

Ehlers, A., Bisson, J., Clark, D., Creamer, M., Pilling, S., Richards, D., et al. (2010). Do all psychological treatments really work the same in posttraumatic stress disorder? *Clinical Psychology Review, 30,* 269–276. http://dx.doi.org/10.1016/j.cpr.2009.12.001.

Ehlers, A., & Clark, D. M. (2000). A cognitive model of posttraumatic stress disorder. *Behaviour Research and Therapy, 38,* 319–345.

Ehlers, A., Clark, D. M., Dunmore, E., Jaycox, L., Meadows, E., & Foa, E. B. (1998). Predicting response to exposure treatment in PTSD: The role of mental defeat and alienation. *Journal of Traumatic Stress, 11(*3), 457–471.

Engel, C., Ursano, R., Magruder, C., Tartaglione, R., Jing, Z., Labbate, L. A., & Debakey (1999). Psychological conditions diagnosed among veterans seeking Department of Defense Care for Gulf War-related health concerns. *Journal of Occupational & Environmental Medicine, 41*(5), 384–392.

Engelhard, I. M., Van den Hout, M. A.,Weerts, J., Arntz, A., Hox, J. J. C. M., & McNally, R. (2007). Deployment-related stress and trauma in Dutch soldiers returning from Iraq. *British Journal of Psychiatry, 191*(2), 140–145.

Evans, L., Cowlishaw, S., Forbes, D., Parslow, R., & Lewis, V. (2010). Longitudinal analyses of family functioning in veterans and their partners across treatment. *Journal of Consulting and Clinical Psychology, 78,* 611–622.http://dx.doi.org/10.1037/a0020457.

Evans, L., Cowlishaw, S., & Hopwood, M. (2009). Family functioning predicts outcomes for veterans in treatment for chronic posttraumatic stress disorder. *Journal of Family Psychology, 23*(4), 531–539. http://dx.doi.org/10.1037/a0015877.

Fontana, A., Rosenheck, R., & Desai, R. (2012). Comparison of treatment outcomes for veterans with posttraumatic stress disorder with and without comorbid substance use/dependence. *Journal of Psychiatric Research, 46,* 1008–1014. http://dx.doi.org/10. 1016/j.jpsychires.2012.05.004.

Forbes, D., Creamer, M., Allen, N., Elliott, P., McHugh, T., Debenham, P., et al. (2002). The MMPI-2 as a predictor of symptom change following treatment for posttraumatic stress disorder. *Journal of Personality Assessment, 79,* 321–336. http://dx.doi.org/10. 1207/S15327752JPA7902_13.

Forbes, D., Creamer, M., Hawthorne, G., Allen, N., & McHugh, T. (2003). Comorbidity of

symptom change after treatment in combat-related posttraumatic stress disorder. *The Journal of Nervous and Mental Distress, 191,* 93–99. http://dx.doi.org/10.1097/01.NMD.0000051903.60517.98.

Forbes, D., Parslow, R., Creamer, M., Allen, N., McHugh, T., & Hopwood, M. (2008). Mechanisms of anger and treatment outcome in combat veterans with posttraumatic stress disorder. *Journal of Traumatic Stress, 21,* 142–149. http://dx.doi.org/10.1002/jts.20315.

Forbes, D., Parslow, R., Fletcher, S., McHugh, T., & Creamer, M. (2010). Attachment style in the prediction of recovery following group treatment of combat veterans with post-traumatic stress disorder. *Journal of Nervous and Mental Disease, 198,* 881–884. http://dx.doi.org/10.1097/NMD.0b013e3181fe73fa.

Ford, J. D., & Kidd, P. (1998). Early childhood trauma and disorders of extreme stress as predictors of treatment outcome with chronic posttraumatic stress disorder. *Journal of Traumatic Stress, 11*(4), 743–761.

Goodson, J., Helstrom, A., Halpern, J. M., Ferenschak, M. P., Gillihan, S. J., & Powers, M. B. (2011). Treatment of posttraumatic stress disorder in U.S. combat veterans: A meta-analytic review. *Psychological Reports, 2,* 573–599. http://dx.doi.org/10.2466/02.09.15.16.PR0.109.5.573-599.

Institute of Medicine (IOM) (2008). *Treatment of posttraumatic stress disorder: An assessment of the evidence.* Washington, DC: The National Academies Press.

Institute of Medicine (IOM) (2014). *Treatment for posttraumatic stress disorder in military and veteran populations: Final assessment.* Washington, DC: National Academy of Sciences. Retrieved from http://iom.nationalacademies.org/~/media/Files/Report%20Files/2014/PTSD-II/PTSD-II-RB.pdf.

International Society for Traumatic Stress Studies (ISTSS) (2009). *Effective treatments for PTSD: Practice guidelines from the International Society for Traumatic Stress Studies.* New York: Guilford Press.

Johnson, D. R., & Lubin, H. (1997). Treatment preferences of Vietnam veterans with posttraumatic stress disorder. *Journal of Traumatic Stress, 10*(3), 391–405.

Kennis, M., Van Rooij, S. J., Tromp, D. P., Fox, A. S., Rademaker, A. R., Kahn, R. S., et al. (2015). Treatment outcome-related white matter differences in veterans with

posttraumatic stress disorder. *Neuropsychopharmacology*, 1–9. http://dx.doi.org/10.1038/npp.2015.94.

Kitchiner, N. J., Roberts, N., Wilcox, D., & Bisson, J. (2012). Systematic review and meta-analyses of psychosocial interventions for veterans of the military. *European Journal of Psychotraumatology, 3,* 19267. http://dx.doi.org/10.3402/ejpt.v3i0.19267.

Kleim, B. & Ehlers, A. (2009). Evidence for a curvilinear relationship between posttraumatic growth and posttrauma depression and PTSD in assault survivors. *Journal of Traumatic Stress, 22,* 45–52. http://dx.doi.org/10.1002/jts.20378.

Knipscheer, J. W., & Kleber, R. J. (2006). The relative contribution of posttraumatic and acculturative stress to subjective mental health among Bosnian refugees. *Journal of Clinical Psychology, 62,* 339–353. http://dx.doi.org/10.1002/jclp.20233.

Lee, D. A., Scragg, P., & Turner, S. (2001). The role of shame and guilt in traumatic events: A clinical model of shame-based and guilt-based PTSD. *British Journal of Medical Psychology, 74,* 451–466.

Leer, A., Engelhard, I. M., Altink, A., & Van den Hout, M. A. (2013). Eye movements during recall of aversive memory decreases conditioned fear. *Behaviour Research and Therapy, 51,* 633–640. http://dx.doi.org/10.1016/j.brat.2013.07.004.

Lloyd, D., Nixon, R. D. V., Varker, T., Elliott, P., Perry, D., Bryant, R. A., et al. (2014). Comorbidity in the prediction of Cognitive Processing Therapy treatment outcomes for combat-related posttraumatic stress disorder. *Journal of Anxiety Disorders, 28,* 237–240. http://dx.doi.org/10.1016/j.janxdis.2013.12.002.

McGuire, T. M., Lee, C.W., & Drummond, P.D. (2014). Potential of eye movement desensitization and reprocessing therapy in the treatment of post-traumatic stress disorder. *Psychology Research and Behavior Management, 7,* 273–283. http://dx.doi. org/10.2147/PRBM.S52268.

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine, 6*(6), e1000097. http://dx.doi.org/10.1371/journal.pmed1000097.

Moons, K. G. M., Altman, D. G., Vergouwe, Y., & Royston, P. (2009a). Prognosis and prognostic research: Application and impact of prognostic models in clinical practice. Research Methods & Reporting, 338, 1487–1490. http://dx.doi.org/10.1136/bmj.b606.

Moons, K. G. M., Royston, P., Vergouwe, Y., Grobbee, D. E., & Altman, D. G. (2009b). Prognosis and prognostic research: What, why, and how? *Research Methods & Reporting, 338,* 1317–1320. http://dx.doi.org/10.1136/bmj.b375.

Moore, S. A., Varra, A.A., Michael, S. T., & Simpson, T. L. (2010). Stress-related growth, positive reframing, and emotional processing in the prediction of post-trauma functioning among veterans in mental health treatment. *Psychological Trauma: Theory, Research, Practice, and Policy, 2*(2), 93–96. http://dx.doi.org/10.1037/a0018975.

National Institute for Clinical Excellence (NICE) (2005). *Post-traumatic stress disorder (PTSD). The management of PTSD in adults and children in primary and secondary care.* London: National Institute for Clinical Excellence.

National Institute for Health and Clinical Excellence (NICE) (2009). *The guidelines manual.* London: National Institute for Health and Clinical Excellence.

Owens, G. P., Chard, K. M., & Cox, T. A. (2008). The relationship between maladaptive cognitions, anger expression, and posttraumatic stress disorder among veterans in residential treatment. *Journal of Aggression, Maltreatment & Trauma, 17,* 439–452. http://dx.doi.org/10.1080/10926770802473908.

Perconte, S. T., & Griger, M. L. (1991). Comparison of successful, unsuccessful, and relapsed Vietnam veterans treated for posttraumatic stress disorder. *Journal of Nervous and Mental Disease, 179,* 558–562.

Pietrzak, R. H., Whealin, J. M., Stotzer, R. L., Goldstein, M.B., & Southwick, S.M. (2011). An examination of the relation between combat experiences and combat-related posttraumatic stress disorder in a sample of Connecticut OEF-OIF Veterans. *Journal of Psychiatric Research, 45,* 1579–1584. http://dx.doi.org/10.1016/j.jpsychires.2011.07.010.

Price, M., Gros, D. F., Strachan, M., Ruggiero, K. J., & Acierno, R. (2013). Combat experiences, pre-deployment training, and outcome of exposure therapy for post-traumatic stress disorder in Operation Enduring Freedom/Operation Iraqi Freedom veterans. *Clinical Psychology and Psychotherapy, 20,* 277–285. http://dx.doi.org/10.1002/cpp.1768.

Rauch, S., & Foa, E. (2006). Emotional processing theory (EPT) and exposure therapy for PTSD. *Journal of Contemporary Psychotherapy, 36,* 61–65. http://dx.doi.org/10.1007/s10879-006-9008-y.

Reade, M. C., Delaney, A., Bailey, M. J., & Angus, D. C. (2008). Bench-to-bedside review: Avoiding pitfalls in critical care meta-analysis-funnel plots, risk estimates, types of heterogeneity, baseline risk and the ecologic fallacy. *Critical Care, 12,* 220. http://dx.doi.org/10.1186/cc6941.

Richardson, J. D., Contractor, A. A., Armour, C., Cyr, K., Elhai, J.D., & Sareen, J. (2014). Predictors of long-term treatment outcome in combat and peacekeeping veterans with military-related PTSD. *The Journal of Clinical Psychiatry, 75,* e1299–e1305. http://dx.doi.org/10.4088/JCP.13m08796.

Richardson, L. K., Frueh, B. C., & Acierno, R. (2010). Prevalence estimates of combat-related post-traumatic stress disorder: Critical review. *The Royal Australian and New Zealand College of Psychiatrists, 44,* 4–19. http://dx.doi.org/10.3109/00048670903393597.

Rogers, S., & Silver, S. M. (2002). Is EMDR an exposure therapy? A review of trauma protocols. *Journal of Clinical Psychology, 58*(1), 43–59.

Rooney, K., Hunt, C., Humphreys, L., Harding, D., Mullen, M., & Kearney, J. (2007). Prediction of outcome for veterans with post-traumatic stress disorder using constructs from the transtheoretical model of behaviour change. *Australian and New Zealand Journal of Psychiatry, 41,* 590–597. http://dx.doi.org/10.1080/00048670701392825.

Rubin, D. C., Boals, A., & Berntsen, D. (2008). Memory in posttraumatic stress disorder: Properties of voluntary and involuntary, traumatic and non-traumatic autobiographical memories in people with and without PTSD symptoms. *Journal of Experimental Psychology: General, 137,* 591–614. http://dx.doi.org/10.1037/a0013165.

Sayer, N. A., Noorbaloochi, S., Frazier, P., Carlson, K., Gravely, A., & Murdoch, M. (2010). Reintegration problems and treatment interests among Iraq and Afghanistan combat veterans receiving VA medical care. *Psychiatric Services, 61,* 589–597. http://dx.doi.org/10.1176/appi.ps.61.6.589.

Schulz, K. F., Chalmers, I., Hayes, R. J., & Altman, D. G. (1995). Empirical evidence of bias dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *Journal of the American Medical Association Psychiatry, 273*(5), 408–412.

Smid, G. E., Kleber, R. J., Rademaker, A. R., Van Zuiden, M., & Vermetten, E. (2013). The role of stress sensitization in progression of posttraumatic distress following deployment.

Social Psychiatry and Psychiatric Epidemiology, 48, 1743–1754. http://dx.doi.org/10.1007/s00127-013-0709-8.

Steindl, S. R., Young, R., Creamer, M., & Crompton, D. (2003). Hazardous alcohol use and treatment outcome in male combat veterans with posttraumatic stress disorder. *Journal of Traumatic Stress, 16*(1), 27–34.

Stone, W. N. (2009). Frustration, anger, and the significance of alter-ego transferences in group psychotherapy. In W. Stone (Ed.), *Contributions of self psychology to group psychotherapy: Selected papers* (pp. 107–122). London: Karnac books.

Tarrier, N., Sommerfield, C., Pilgrim, H., & Faragher, B. (2000). Factors associated with outcome of cognitive-behavioural treatment of chronic post-traumatic stress disorder. *Behaviour Research and Therapy, 38,* 191–202. http://dx.doi.org/10.1016/S0005-7967(99)00030-3.

The management of post-traumatic stress Working Group (2004). *VA/DoD clinical guidelines for the management of post-traumatic stress.* Department of Veterans Affairs, Department of Defense.

The management of post-traumatic stress Working Group (2010). *VA/DoD clinical practice guideline for management of post-traumatic stress.* Update of 2004 guideline. Department of Veterans Affairs, Department of Defense.

Vink, G., Frank, L. E., Pannekoek, J., & Van Buuren, S. (2014). Predictive mean matching imputation of semicontinuous variables. *Statistica Neerlandica, 68,* 61–90. http://dx.doi.org/10.1111/stan.12023.

Wald, J., & Taylor, S. (2009). Work limitations in employed persons seeking treatment for chronic posttraumatic stress disorder. *Journal of Traumatic Stress, 18,* 312–315. http://dx.doi.org/10.1002/jts.20430.

Walter, K. H., Kiefer, S. L., & Chard, K. M. (2012). Relationship between posttraumatic stress disorder and postconcussive symptom improvement after completion of a posttraumatic stress disorder/traumatic brain injury residential treatment program. *Rehabilitation Psychology, 57,* 13–17. http://dx.doi.org/10.1037/a0026254.

Wampold, B. E., Imel, Z. E., Laska, K. M., Benish, S., Miller, S. D., Flückiger, C., … Budge, S. (2010). Determining what works in the treatment of PTSD. *Clinical Psychology Review, 30,* 923-933. doi:10.1002/jclp.20683

Watts, B. V., Schnurr, P. P., Mayo, L., Young-Xu, Y., Weeks, W. B., & Friedman, M. J. (2013). Meta-analysis of the efficacy of treatments for posttraumatic stress disorder. *Journal of Clinical Psychiatry, 74,* 541–550. http://dx.doi.org/10.4088/JCP.12r08225.

Wilson, D. B. (2005). *Meta-analysis macros for SPSS.* Retrieved July 1, 2013 from: http://mason.gmu.edu/~dwilsonb/ma.html

Wolf, E. J., Miller, M. W., Kilpatrick, D., Resnick, H. S., Badour, C. L., Marx, B. P., et al. (2014). ICD-11 complex PTSD in U.S. national and veteran samples: Prevalence and structural associations with PTSD. *Clinical Psychological Science, 3,* 215-219. doi:10.1177/2167702614545480

Appendix A

Reference list of studies included in the meta-analysis

Alvarez, J., McLean, C., Harris, A. H. S., Rosen, C. S., Ruzek, J. I., & Kimerling, R. (2011). The comparative effectiveness of cognitive processing therapy for male veterans treated in VHA posttraumatic stress disorder residential rehabilitation program. *Journal of Consulting and Clinical Psychology, 79*, 590–599. doi:10.1037/a0024466

Beidel, D. C., Frueh, B. C., Uhde, T. W., Wong, N., & Mentrikoski, J. M. (2011). Multicomponent behavioral treatment for chronic combat-related posttraumatic stress disorder: A randomized controlled trial. *Journal of Anxiety Disorders,* 25, 224-231. doi:10.1016/j.janxdis.2010.09.006

Boden, M. T., Bernstein A., Walser, R. D., Bui, L., Alvarez, J., & Bonn-Miller, M. O. (2012). Changes in facets of mindfulness and posttraumatic stress disorder treatment outcome. *Psychiatry Research 200*, 609-613. doi:10.1016/j.psychres.2012.07.011

Bolton, E. E., Lambert, J. F., Wolf, E. J., Raja, S., Varra, A. A., & Fisher, L. M. (2004) Evaluating a cognitive-behavioral group treatment program for veterans with posttraumatic stress disorder. *Psychological Services, 1*(2), 140-146.

Carlson, J. G., Chemtob, C. M., Rusnak, K., Hedlund, N. L., & Muraoka, M. (1998). Eye movement and reprocessing (EMDR) treatment for combat-related posttraumatic stress disorder. *Journal of Traumatic Stress, 11*(1), 3-24.

Castillo, D. T., C'de Baca, J., Oualls, C., & Bornovalova, M. A. (2012). Group exposure therapy treatment for post-traumatic stress disorder in female veterans. *Military Medicine, 177*, 1486-1491. doi:10.7205/MILMED-D-12-00186

Chard, K. M., Ricksecker, E. G., Healy, E. T., Karlin, B. E., & Resick, P. A. (2012). Dissemination and experience with cognitive processing therapy. *Journal of Rehabilitation Research & Development, 49*, 667-678. doi:org/10.1682/JRRD.2011.10.0198

Chard, K. M., Schumm, J. A., McIlvain, S. M., Bailey, G. W., & Parkinson, R. B. (2011). Exploring the efficacy of a residential treatment program incorporating cognitive processing therapy-cognitive for veterans with PTSD and traumatic brain injury. *Journal of Traumatic Stress, 24*, 347-351. doi:10.1002/jts.20644

Chard, K. M., Schumm, J. A., Owens, G. P., & Cottingham, S. M. (2010). A comparison of OEF and OIF veterans and Vietnam veterans receiving cognitive processing therapy. *Journal of Traumatic Stress, 23*, 25-32. doi:10.1002/jts.20500.

Devilly G. J., Spence S. H., & Rapee, R. M. (1998). Statistical and reliable change with eye movement desensitization and reprocessing: Treating trauma within a veteran population. *Behavior Therapy, 29*(3), 435-455.

Dickstein, B. D., Walter, K. H., Schumm, J. A., & Chard, K. M. (2013). Comparing response to cognitive processing therapy in military veterans with subthreshold and threshold posttraumatic stress disorder. *Journal of Traumatic Stress, 26,* 703-709. doi:10.1002/jts.21869

Eftekhari, A., Ruzek, J. I., Crowley, J. J., Rosen, C. S., Greenbaum, M. A., & Karlin, B. E. (2013). Effectiveness of national implementation of prolonged exposure therapy in Veterans Affairs care. *Journal of the American Medical Association Psychiatry, 70,* 949-955. doi:10.1001/jamapsychiatry.2013.36

Forbes, D., Lloyd, D., Nixon, R. D. V., Elliott, P., Varker, T., Perry, D., … Creamer, M. (2012). A multisite randomized controlled effectiveness trial of cognitive processing therapy for military-related posttraumatic stress disorder. *Journal of Anxiety Disorders, 26,* 442-452. doi:10.1016/j.janxdis.2012.01.006

Frueh, B. C., Monnier, J., Yim, E., Grubaugh, A. L., Hamner, M., & Knapp, R. G. (2007). A randomized trial of telepsychiatry for posttraumatic stress disorder. *Journal of Telemedicine and Telecare, 13,* 142-147.

Frueh, B. C., Turner, S. M., Beidel, D. C., Mirabella, R. F., & Jones, W. J. (1996). Trauma management therapy: A preliminary evaluation of a multicomponent behavioral treatment for chronic combat-related PTSD. *Behaviour Research and Therapy, 34*, 533-543. doi.org/10.1016/0005-7967(96)00020-4

Gamito, P., Oliveira, J., Rosa, P., Morais, D., Duarte, N., Oliveira, S., & Saraiva, T. (2010). PTSD elderly war veterans: A clinical controlled pilot study. *Cyberpsychology, Behavior, and Social Networking*, *13*(1), 43-48.

Gilman, R., Schumm, J. A., & Chard, K. M. (2012). Hope as a change mechanism in the treatment of posttraumatic stress disorder. *Psychological Trauma: Theory, Research, Practice, and Policy, 4,* 270-277. doi:10.1037/a0024252

Goodson, J. T., Lefkowitz, C. T., Helstrom, A. W., & Gawrysiak, M. J. (2013). Outcomes of prolonged exposure therapy for veterans with posttraumatic stress disorder. *Journal of Traumatic Stress, 26,* 419-425. doi:10.1002/jts.21830

Gray, M. J., Schorr, Y., Nash, W., Lebowitz, L., Amidon, A., Lansing, A., … Litz, B. T. (2012). Adaptive disclosure: An open trial of a novel exposure-based intervention for service members with combat-related psychological stress injuries. *Behavior Therapy, 43*, 407-415. doi:10.1016/j.beth.2011.09.001

Gros, D. F., Yoder, M., Tuerk, P. W., Lozano, B. E., & Acierno, R. (2011). Exposure therapy for PTSD delivered to veterans via telehealth: Predictors of treatment completion and outcome and comparison to treatment delivered in person. *Behavior Therapy, 42,* 276-283. doi:10.1016/j.beth.2010.07.005

Jeffreys, M. D., Reinfelda, C., Nairb, P. V., Garciaa, H. A., Mata-Galana, E., & Rentza, T. O. (2014). Evaluating treatment of posttraumatic stress disorder with cognitive processing therapy and prolonged exposure therapy in a VHA specialty clinic. *Journal of Anxiety Disorders, 28,* 108-114. doi:org/10.1016/j.janxdis.2013.04.010

Jensen, J. A. (1994). An investigation of eye movement desensitization and reprocessing (EMD/R) as a treatment for posttraumatic stress disorder (PTSD) symptoms of Vietnam combat veterans. *Behavior Therapy, 25,* 2311-2326.

Katz, L. S., Douglas, S., Zaleski, K., Williams, J., Huffman, C., & Cojucar, G. (2014). Comparing holographic reprocessing and prolonged exposure for women veterans with sexual trauma: A pilot randomized trial. *Journal of Contemporary Psychotherapy, 44,* 9-19. doi:10.1007/s10879-013-9248-6

Kaysen, D., Schumm, J., Pedersen, E. R., Seim, R. W., Bedard-Gilligan, M., & Chard, K. M. (2014). Cognitive Processing Therapy for veterans with comorbid PTSD and alcohol use disorders. *Addictive Behaviors, 39,* 420-427. doi:org/10.1016/j.addbeh.2013.08.016

Keane, T. M., Fairbank, J. A., Caddell, J. M., & Zimering, R. T. (1989) Implosive (flooding) therapy reduces symptoms of PTSD in Vietnam combat veterans. *Behavior Therapy, 20,* 245-260.

Laska, K. M., Smith, T. L., Wislocki, A. P., Minami, T., & Wampold, B. E. (2013). Uniformity of evidence-based treatments in practice? Therapist effects in the delivery of cognitive processing therapy for PTSD. *Journal of Counseling Psychology, 60,* 31-41. doi:10.1037/a0031294

Litz, B. T., Salters-Pedneault, K., Steenkamp, M. M., Hermos, J. A., Bryant, R. A., Otto, M. W., & Hofmann, S. G. (2012). A randomized placebo-controlled trial of D-cycloserine and exposure therapy for posttraumatic stress disorder. *Journal of Psychiatric Research, 46,* 1184-1190. doi:10.1016/j.jpsychires.2012.05.006

Long, M. E., Hammons, M. E., Davis, J. L., Frueh, B. C., Khan, M. M., Elhai, J. D., & Teng, E. J. (2011). Imagery rescripting and exposure group treatment of posttraumatic nightmares in Veterans with PTSD. *Journal of Anxiety Disorders, 25,* 531-535. doi:10.1016/j.janxdis.2010.12.007

McClay, R. N., Wood, D. P., Webb-Murphy, J. A., Spira, J. L., Wiederhold, M. D., Pyne, J. M., & Wiederhold, B. K. (2011). A randomized, controlled trial of virtual reality-graded exposure

therapy for post-traumatic stress disorder in active duty service members with combat-related post-traumatic stress disorder. *Cyberpsychology, Behavior, and Social Networking, 14,* 223-229. doi:10.1089/cyber.2011.0003

Miyahira, S. D., Folen, R. A., Hoffman, H. G., Garcia-Palacios, A., Spira, J. L., & Kawasaki, M. (2012). The effectiveness of VR exposure therapy for PTSD in returning warfighters. *Studies in Health Technology and Informatics, 181,* 128-132. doi:10.3233/978-1-61499-121-2-128

Monson, C. M., Rodriguez, B. J., & Warner, R. (2005). Cognitive-Behavioral Therapy for PTSD in the real world: Do interpersonal relationships make a real difference? *Journal of Clinical Psychology, 61*(6), 751-761.

Monson, C. M., Schnurr, P. P., Resick, P. A., Friedman, M. J., Young-Xu, Y., & Stevens, S. P. (2006). Cognitive processing therapy for veterans with military-related posttraumatic stress disorder. *Journal of Consulting and Clinical Psychology, 74,* 898-907. doi:10.1037/0022-006X.74.5.898

Nacasch, N., Foa, E. B., Huppert, J. D., Tzur, D., Fostick, L., Dinstein, Y., … Zohar, J. (2010). Prolonged exposure therapy for combat- and terror-related posttraumatic stress disorder: A randomized control comparison with treatment as usual. *Journal of Clinical Psychiatry, 72,* 1174-1180. doi:10.4088/JCP.09m05682blu

Rauch, S. A. M., Defever, E., Favorite, T., Duroe, A., Garrity, C., Martis, B., & Liberzon, I. (2009). Prolonged exposure for PTSD in a Veterans Health Administration PTSD clinic. *Journal of Traumatic Stress, 22,* 60-64. doi:10.1002/jts.20380

Ready, D. J., Gerardi, R. J., Backscheider, A. G., Mascaro, N., & Rothbaum, B. A. (2010). Comparing virtual reality exposure therapy to present-centered therapy with 11 U.S. Vietnam veterans with PTSD. *Cyberpsychology and Behavior Social Network, 13*(1), 49–54.

Ready, D. J., Pollack S., Rothbaum, B. A., & Alarcon, R. D. (2006). Virtual reality exposure for veterans with posttraumatic stress disorder. *Journal of Aggression, Maltreatment & Trauma, 12,* 199-220. doi:10.1300/J146v12n01_11

Ready, D. J., Sylvers, P., Worley, V., Butt, J., Mascaro, N., & Bradley, B. (2012b). The impact of group-based exposure therapy on the PTSD and depression of 30 combat veterans. *Psychological Trauma: Theory, Research, Practice, and Policy, 4,* 84-93. doi:10.1037/a0021997

Ready, D. J., Thomas, K. R., Worley, V., Backscheider, A. G., Harvey, L. A. C., Baltzell, D., & Rothbaum, B. O. (2008). A field test of group based exposure therapy with 102 veterans with war-related posttraumatic stress disorder. *Journal of Traumatic Stress, 21,* 150-157. doi:10.1002/jts.20326

Ready, D. J., Vega, E. M., Worley, V., & Bradley, B. (2012a). Combining group-based exposure therapy with prolonged exposure to treat U.S. Vietnam veterans with PTSD: A case study. *Journal of Traumatic Stress, 25,* 574-577. doi:10.1002/jts.21734

Reger, G. M., Holloway, K. M., Candy, C., Rothbaum, B. O., Difede, J., Rizzo, A. A., & Gahm, G. A. (2011). Effectiveness of virtual reality exposure therapy for active duty soldiers in a military mental health clinic. *Journal of Traumatic Stress, 24,* 93-96. doi:10.1002/jts.20574

Rogers, S., Silver, S. M., Goss, J., Obenchain, J., Willis, A., & Whitney, R. L. (1999). A single session, group study of exposure and eye movement desensitization and reprocessing in treating posttraumatic stress disorder among Vietnam war veterans: Preliminary Data. *Journal of Anxiety Disorders, 13*(1-2), 119-130.

Rothbaum, B. O., Price, M., Jovanovic, T., Norrholm, S. D., Gerardi, M., Dunlop, B., … Ressler, K. J. (2014). A randomized, double-blind evaluation of d-cycloserine or alprazolam combined with virtual reality exposure therapy for posttraumatic stress disorder in Iraq and Afghanistan war veterans. *American Journal of Psychiatry, 171,* 640-648. doi:10.1176/appi.ajp.2014.13121625

Schnurr, P. P., Friedman, M. J., Engel, C. C., Foa, E. B., Shea, M. T., Chow, B. K., … Bernardy, N. (2007). Cognitive behavioral therapy for posttraumatic stress disorder in women – a randomized controlled trial. *Journal of the American Medical Association, 297*(8), 820-830.

Schnurr, P. P., Friedman, M. J., Foy, D. W., Shea, M. T., Hsieh, F. Y., Lavori, P. W., … Bernardy, N. (2003). Randomized trial of trauma-focused group therapy for posttraumatic stress disorder: results from a Department of Veterans Affairs cooperative study. *Archives of General Psychiatry, 60*(5), 481-489.

Sripada, R. K., Rauch, S. A. M., Tuerk, P. W., Smith, E., Defever, A. M., Mayer, R. A., … Venners, M. (2014). Mild traumatic brain injury and treatment response in prolonged exposure for PTSD. *Journal of Traumatic Stress, 26,* 369-375. doi:10.1002/jts.21813

Surís, A., Link-Malcolm, J., Chard, K., Ahn, C., & North, C. (2013). A randomized clinical trial of cognitive processing therapy for veterans with PTSD related to military sexual trauma. *Journal of Traumatic Stress, 26,* 28-37. doi:10.1002/jts.21765

Sutherland, R. J., Mott, J. M., Lanier, S. H., Williams, W., Ready, D. J., & Teng, E. J. (2012). A pilot study of a 12-week model of group-based exposure therapy for veterans with PTSD. *Journal of Traumatic Stress, 25,* 150-156. doi:10.1002/jts.21679

Thorp, S. R., Stein, M. B., Jeste, D. V., Patterson, T. L., & Wetherell, J. L. (2012). Prolonged exposure therapy for older veterans with posttraumatic stress disorder: A pilot study. *American Association for Geriatric Psychiatry, 20,* 276-280. doi:10.1097/JGP.0b013e3182435ee9

Tuerk, P. W., Yoder, M., Grubaugh, A., Myrick, H., Hamner, M., & Acierno, R. (2011). Prolonged exposure therapy for combat-related posttraumatic stress disorder: An examination of treatment effectiveness for veterans of the wars in Afghanistan and Iraq. *Journal of Anxiety Disorders 25,* 397-403. doi:10.1016/j.janxdis.2010.11.002

Tuerk, P. W., Yoder, M., Ruggiero, K. J., Gros, D. F., & Acierno, R. (2010). A pilot study of prolonged exposure therapy for posttraumatic stress disorder delivered via telehealth technology. *Journal of Traumatic Stress, 23,* 116-123. doi:10.1002/jts.20494

Walter, K. H., Bolte, T. A., Owens, G. P., & Chard, K. M. (2012a). The impact of personality disorders on treatment outcome for veterans in a posttraumatic stress disorder residential treatment program. *Cognitive Therapy and Research, 36,* 576-584. doi:10.1007/s10608-011-9393-8

Walter, K. H., Kiefer, S. L., & Chard, K. M. (2012b). Relationship between posttraumatic stress disorder and postconcussive symptom improvement after completion of a posttraumatic stress disorder/traumatic brain injury residential treatment program. *Rehabilitation Psychology, 57,* 13-17. doi:10.1037/a0026254

Walter, K. H., Varkovitzky, R. L., Owens, G. P., Lewis, J., & Chard, K. M. (2014). Cognitive Processing Therapy for veterans with posttraumatic stress disorder: A comparison between outpatient and residential treatment. *Journal of Consulting and Clinical Psychology, 82,* 551-561. doi:http://dx.doi.org/10.1037/a0037075

Wolf, G. K., Strom, T. Q., Kehle, S. M., & Eftekhari, *A.* (2012). A preliminary examination of prolonged exposure therapy with Iraq and Afghanistan veterans with a diagnosis of posttraumatic stress disorder and mild to moderate traumatic brain injury. *Journal of Head Trauma Rehabilitation, 27,* 26-32. doi:10.1097/HTR.0b013e31823cd01f

Yoder, M., Lozano, B., Center, K. B., Miller, A., Acierno, R., & Tuerk, P. W. (2013). Effectiveness of prolonged exposure for PTSD in older veterans. *The International Journal of Psychiatry in Medicine, 45,* 111-124. doi:http://dx.doi.org/10.2190/PM.45.2.b

Zappert, L. N., & Westrup, D. (2008). Cognitive processing therapy for posttraumatic stress disorder in a residential treatment setting. *Psychotherapy: Theory, Research, Practice, Training, 45,* 361-376. doi:10.1037/0033-3204.45.3.361

Appendix B

Supplementary table data collected from included meta-analysis studies

Authors	Intervention	Instrument	sample (N)	Allocation	Analysis	Setting	Modality	No of sessions	No. of trauma focused sessions	Pre-treatment symptom severity (%)	ES (Hedges g)
Alvarez et al. (2011)	CPT	PCL	104	NON-RANDOM	ITT	IN	GRP	14	N.I.	75.4	.71
Beidel et al. (2011)	ET	CAPS	14	RANDOM	COMPL	OUT	COMBI	29	-	62.4	.72
Beidel et al. (2011)	ET	CAPS	16	RANDOM	COMPL	OUT	COMBI	29	-	66.6	1.31
Boden et al. (2012)	CPT	PCL	48	NON-RANDOM	COMPL	IN	GRP	14	N.I.	72.9	.92
Bolton et al. (2004)	SMT	PCL	62	NON-RANDOM	COMPL	-	GRP	-	0	76.3	.14
Carlson et al. (1998)	EMDR	M-PTSD	10	RANDOM	ITT	OUT	IND	12	11	67.1	1.16
Castillo et al. (2012)	ET	PCL	88	NON-RANDOM	ITT	OUT	GRP	6	-	70.2	.25
Chard et al. (2010I)	CPT	CAPS	51	NON-RANDOM	-	OUT	IND	12	10	52.9	2.00
Chard et al. (2010)	CPT	CAPS	50	NON-RANDOM	-	OUT	IND	12	12	48.9	1.01
Chard et al. (2011)	CPT	CAPS	28	NON-RANDOM	COMPL	IN	COMBI	28	N.I.	55.3	1.25
Chard et al. (2011)	CPT	CAPS	14	NON-RANDOM	COMPL	IN	COMBI	28	N.I.	59.8	2.39
Chard et al. (2012)	CPT	PCL	374	NON-RANDOM	COMPL	-	-	12	-	75.4	1.38
Devilly et al. (1998)	EMDR	M-PTSD	12	RANDOM	COMPL	OUT	IND	2	2	68.8	.34
Dickstein et al. (2013)	CPT	PCL	483	NON-RANDOM	ITT	OUT	IND	12	7	70.3	1.79
Eftekhari et al. (2013)	ET	PCL	1888	NON-RANDOM	ITT	-	-	9	-	74.4	.83
Forbes et al. (2012)	CPT	CAPS	30	RANDOM	ITT	OUT	IND	12	9	55.5	1.03

Frueh et al. (1996)	ET	CAPS	11	NON-RANDOM	COMPL	OUT	COMBI	29	-	60.6	.86
Frueh et al. (2007)	SMT	PCL	21	RANDOM	ITT	OUT	GRP	14	0	73.4	.46
Frueh et al. (2007)	SMT	PCL	17	RANDOM	ITT	OUT	GRP	14	0	78.8	-.10
Gamito et al. (2010)	ET	CAPS	5	RANDOM	-	OUT	GRP	12	-	42.1	.09
Gilman et al. (2012)	CPT	CAPS	164	NON-RANDOM	-	IN	COMBI	25	N.I.	56.4	1.48
Goodson et al. (2013)	ET	PCL	115	NON-RANDOM	ITT	OUT	IND	11	9	75.2	1.25
Gray et al. (2012)	ET	PCL	44	NON-RANDOM	COMPL	OUT	IND	6	5	70.7	.78
Gros et al. (2011)	ET	PCL	37	NON-RANDOM	COMPL	OUT	IND	12	11	74.4	1.08
Gros et al. (2011)	ET	PCL	27	NON-RANDOM	COMPL	OUT	IND	12	11	73.5	2.9
Jeffreys et al. (2014)	ET	PCL	128	NON-RANDOM	COMPL	-	IND	13	5	66.7	2.08
Jeffreys et al. (2014)	CPT	PCL	268	NON-RANDOM	COMPL	-	-	12	-	75.9	.91
Jensen et al. (1994)	EMDR	Other	13	RANDOM	COMPL	-	IND	3	2	44	-.46
Katz et al. (2014)	ET	PCL	15	RANDOM	COMPL	OUT	IND	10	-	77.9	.84
Kaysen et al. (2014)	CPT	CAPS	272	NON-RANDOM	ITT	OUT	IND	10	9	49.2	1.99
Kaysen et al. (2014)	CPT	CAPS	57	NON-RANDOM	ITT	OUT	IND	8	7	51.1	1.98
Kaysen et al. (2014)	CPT	CAPS	207	NON-RANDOM	ITT	OUT	IND	9	8	50.5	1.91
Keane et al. (1989)	ET	Other	11	RANDOM	ITT	OUT	IND	14	13	-	.50
Laska et al. (2013)	CPT	PCL	192	NON-RANDOM	COMPL	-	IND	12	11	71.1	.79
Litz et al. (2012)	ET	CAPS	13	RANDOM	ITT	OUT	IND	6	4	54	.78
Long et al. (2011)	ET	PCL	33	NON-RANDOM	COMPL	OUT	GRP	6	-	80.8	.92
McClay (2012)	ET	PCL	42	NON-RANDOM	ITT	OUT	IND	10	7	67.6	.79
McClay et al. (2011)	ET	CAPS	10	RANDOM	ITT	OUT	IND	10	4	61.4	.87

Miyahira et al. (2012)	ET	CAPS	10	RANDOM	COMPL	-	IND	10	9	53.1	.55
Monson et al. (2005)	CBT	Other	45	NON-RANDOM	COMPL	-	GRP	21	-	-	.23
Monson et al. (2006)	CPT	CAPS	30	RANDOM	ITT	OUT	IND	12	11	56.4	1.21
Nacasch et al. (2011)	ET	PSS-I	15	RANDOM	ITT	OUT	IND	11	9	72.7	1.91
Rauch et al. (2009)	ET	Other	10	NON-RANDOM	COMPL	OUT	IND	13	12	71	1.96
Ready et al. (2006)	ET	CAPS	14	NON-RANDOM	COMPL	OUT	IND	14	13	53.4	.71
Ready et al. (2008)	ET	CAPS	102	NON-RANDOM	ITT	OUT	GRP	34	-	66.7	1.21
Ready et al. (2010)	ET	CAPS	6	RANDOM	COMPL	OUT	IND	10	9	64.6	.75
Ready et al. (2012a)	ET	PSS-I	8	NON-RANDOM	ITT	OUT	COMBI	22	-	64.2	2.80
Ready et al. (2012b)	ET	PCL	28	NON-RANDOM	COMPL	OUT	GRP	32	-	75.9	1.00
Reger et al. (2011)	ET	PCL	24	NON-RANDOM	COMPL	OUT	COMBI	7	5	71.7	1.10
Rogers et al. (1999)	EMDR	IES22	6	RANDOM	COMPL	IN	IND	1	1	42.4	.63
Rogers et al. (1999)	ET	IES22	6	RANDOM	COMPL	IN	IND	1	1	46.6	.16
Rothbaum et al. (2014)	ET	CAPS	53	RANDOM	COMPL	-	IND	6	5	60.7	.92
Schnurr et al. (2003)	ET	CAPS	180	RANDOM	ITT	OUT	GRP	30	-	59.1	.34
Schnurr et al. (2007)	ET	CAPS	141	RANDOM	ITT	OUT	IND	10	7	57.1	.84
Sripada et al. (2013)	ET	PCL	51	NON-RANDOM	ITT	OUT	IND	10	9	70.6	.81
Surís et al. (2013)	CPT	CAPS	52	RANDOM	ITT	OUT	IND	12	9	62.6	.93
Sutherland et al. (2012)	ET	CAPS	10	NON-RANDOM	ITT	-	GRP	24	-	59.1	2.27
Thorp et al. (2012)	ET	CAPS	8	NON-RANDOM	COMPL	OUT	IND	12	11	68.8	1.43
Tuerk et al. (2010)	ET	PCL	9	NON-RANDOM	COMPL	OUT	IND	10	9	71.8	1.55
Tuerk et al. (2010)	ET	PCL	29	NON-RANDOM	COMPL	OUT	IND	10	9	71.4	2.40

Tuerk et al. (2011)	ET	PCL	65	NON-RANDOM	ITT	OUT	IND	7	6	74.2	.85
Walter et al. (2012a)	CPT	CAPS	53	NON-RANDOM	COMPL	IN	COMBI	25	N.I.	57.7	1.73
Walter et al. (2012a)	CPT	CAPS	104	NON-RANDOM	COMPL	IN	COMBI	25	N.I.	55.6	1.54
Walter et al. (2012b)	CPT	CAPS	28	NON-RANDOM	COMPL	IN	COMBI	47	N.I.	54.9	1.47
Walter et al. (2014)	CPT	CAPS	514	NON-RANDOM	ITT	OUT	IND	8	7	49.4	.91
Walter et al. (2014)	CPT	CAPS	478	NON-RANDOM	ITT	IN	COMBI	24	N.I.	55	.98
Wolf et al. (2012)	ET	PCL	10	NON-RANDOM	COMPL	-	IND	13	13	81.4	3.13
Yoder et al. (2013)	ET	PCL	66	NON-RANDOM	ITT	OUT	IND	11	10	74.3	1.32
Zappert et al. (2008)	CPT	PCL	18	NON-RANDOM	COMPL	IN	GRP	12	N.I.	51.6	1.15

Note. Intervention: ET = Exposure therapy; CPT = Cognitive processing therapy; EMDR = Eye movement and reprocessing therapy; SMT = Stress management therapy. Analysis: COMPL = Completer analysis; ITT = Intent-to-treat analysis. Setting: In = Inpatient; OUT = Outpatient. Modality: IND = Individual therapy; GRP = Group therapy; COMBI = Group therapy and individual therapy combined. N.I. = Not investigated.

Appendix C

Supplementary table study quality assessment

Authors	Representativeness study population	Loss of follow-up data	Prognostic variables adequately measured	Outcome of interest adequately measured	Confounders appropriately accounted for	Overall Risk of bias
Alvarez (2011)	M	L	L	M	L	**M**
Beidel (2011)	M	M	L	L	L	**M**
Beidel (2011)	L	L	L	L	L	**L**
Boden (2012)	M	H	L	L	L	**H**
Bolton (2004)	M	H	H	L	M	**H**
Carlson (1998)	L	L	L	L	L	**L**
Castillo (2012)	L	L	L	L	L	**L**
Chard (2010)	L	L	L	L	L	**L**
Chard (2011)	M	M	L	L	L	**M**
Chard (2012)	H	H	M	L	L	**H**
Devilly (1998)	M	H	L	L	L	**H**
Dickstein (2013)	L	L	L	L	L	**L**
Eftekhari (2013)	L	L	L	L	L	**L**
Forbes (2012)	L	M	L	L	L	**L**
Frueh (1996)	M	M	L	L	L	**M**
Frueh (2007)	L	M	L	L	L	**L**
Gamito (2010)	L	L	L	L	L	**L**
Gilman (2012)	L	L	L	L	L	**L**
Goodson (2013)	L	L	L	L	L	**L**
Gray (2012)	M	M	L	L	L	**M**
Gros (2011)	L	H	L	L	L	**H**
Jeffreys (2014)	H	H	L	L	L	**H**
Jensen (1994)	H	H	L	L	L	**H**
Katz (2014)	H	M	L	L	L	**H**
Kaysen (2014)	M	L	L	L	L	**L**
Keane (1989)	M	L	L	L	M	**M**
Laska (2013)	M	H	L	L	L	**H**
Litz (2012)	M	L	L	L	M	**M**
Long (2011)	M	H	L	L	L	**H**
McClay (2011)	L	L	L	L	M	**L**
McClay (2012)	M	M	M	L	M	**M**
Miyahira (2012)	H	H	M	L	M	**H**

Monson (2005)	M	H	M	L	L	**H**
Monson (2006)	L	L	L	L	L	**L**
Nacasch (2011)	M	L	L	L	L	**L**
Rauch (2009)	L	H	L	L	M	**H**
Ready (2006)	M	M	M	L	M	**M**
Ready (2008)	L	L	L	L	L	**L**
Ready (2010)	L	L	L	L	M	**L**
Ready (2012a)	M	L	L	L	L	**L**
Ready (2012b)	M	L	L	L	M	**M**
Reger (2011)	H	L	L	L	L	**H**
Rogers (1999)	M	L	M	L	L	**M**
Rothbaum (2014)	L	M	L	L	L	**L**
Schnurr (2003)	L	L	L	L	L	**L**
Schnurr (2007)	L	M	L	L	L	**L**
Sripada (2013)	L	L	L	L	L	**L**
Suris (2013)	M	L	L	L	M	**M**
Sutherland(2012)	L	L	L	L	L	**L**
Thorp (2012)	M	M	L	L	L	**M**
Tuerk (2010)	L	M	L	L	L	**L**
Tuerk (2011)	L	L	L	L	L	**L**
Walter (2012a)	L	L	L	M	L	**L**
Walter (2012b)	M	H	L	L	L	**H**
Walter (2014)	L	M	L	L	L	**L**
Wolf (2012)	L	H	L	L	M	**H**
Yoder (2013)	L	L	L	L	L	**L**
Zappert (2008)	M	H	L	L	L	**H**

Note. L = Low risk of bias; M = Moderate risk of bias; H = High risk of bias.

Chapter 3

Predicting post-traumatic stress disorder treatment response in refugees: Multilevel analysis

Published as:

Haagen, J. F. G., Heide, F., Mooren, T. M., Knipscheer, J. W., & Kleber, R. J. (2017). Predicting post-traumatic stress disorder treatment response in refugees: Multilevel analysis. *British Journal of Clinical Psychology, 56*(1), 69-83. doi:10.1111/bjc.12121

Abstract

Given the recent peak in refugee numbers and refugees' high odds of developing post-traumatic stress disorder (PTSD), finding ways to alleviate PTSD in refugees is of vital importance. However, there are major differences in PTSD treatment response between refugees, the determinants of which are largely unknown. This study aimed at improving PTSD treatment for adult refugees by identifying PTSD treatment response predictors. A prospective longitudinal multilevel modelling design was used to predict PTSD severity scores over time. We analysed data from a randomized controlled trial with pre-, post-, and follow-up measurements of the safety and efficacy of eye movement desensitization and reprocessing and stabilization in asylum seekers and refugees suffering from PTSD. Lack of refugee status, comorbid depression, demographic, trauma related and treatment-related variables were analysed as potential predictors of PTSD treatment outcome. Treatment outcome data from 72 participants were used. The presence ($B = 6.5$, $p = .03$) and severity ($B = 6.3$, $p < .01$) of a pre-treatment depressive disorder predicted poor treatment response and explained 39% of the variance between individuals. Refugee patients who suffer from PTSD and severe comorbid depression benefit less from treatment aimed at alleviating PTSD. Results highlight the need for treatment adaptations for PTSD and comorbid severe depression in traumatized refugees, including testing whether initial targeting of severe depressive symptoms increases PTSD treatment effectiveness.

Acknowledgment contribution authors

Designed research: Ter Heide, Mooren, Kleber

Performed research: Haagen, Ter Heide

Analysed data: Haagen

Wrote the paper: Haagen, Ter Heide, Knipscheer, Kleber

Introduction

Armed conflict and political oppression disrupt lives and force many to flee their home country to look for protection elsewhere. In 2015, forced migration resulted in almost 20 million refugees and asylum seekers worldwide, 3 million of whom resettled in Western countries, and over 1 million new arrivals in asylum application (UN High Commissioner for Refugees (UNHCR), 2015). Pre-migration experiences of physical and psychological violence in their home country, losing home and loved ones, the stresses of forced migration, and post-migration ordeals (e.g., poor socioeconomic status, financial and legal [asylum] insecurities, acculturation issues, daily hassles) may cause or amplify severe psychological distress in refugees and increase their odds of developing posttraumatic stress disorder (PTSD; American Psychiatric Association (APA), 2013; Bogic, Njoku, & Priebe, 2015; Chu, Keller, & Rasmussen, 2013; Knipscheer & Kleber, 2006; Li, Liddell, & Nickerson, 2016; Slobodin & De Jong, 2015; Steel et al., 2009). These circumstances likely contribute to the elevated PTSD prevalence rates of 5–31% among refugees (Fazel, Wheeler, & Danesh, 2005; Lambert & Alhassoon, 2015; Steel et al., 2009), compared to general-population prevalence rates in North America of 4–7% (Kessler, Chiu, Demler, Merikangas, & Walters, 2005), and European rates of 0–7% (Burri & Maercker, 2014). PTSD is known to heavily interfere with refugees' ability to function as individuals, as well as in their families, communities, and society as a whole (Söndergaard &Theorell, 2004). Finding ways to alleviate the burden of PTSD in refugees is therefore of great importance.

Trauma focused psychotherapy is an effective treatment strategy for refugees with PTSD (Lambert & Alhassoon, 2015). Lambert and Alhassoon reported a large overall treatment effect (g = 0.91) for trauma focused therapy, although there is great variability in the effect sizes between studies with both very small (g = 0.1) and large (g = 2.4) treatment effects. These heterogeneous treatment effects may be attributed to patient characteristics (differences between study samples), design variations (e.g., choice of questionnaire, intervention and randomization, number of sessions, and control condition used to calculate treatment effect size), and methodological issues (e.g., sample size; Lambert & Alhassoon, 2015; Slobodin & De Jong, 2015). Despite the overall efficacy, a large proportion of treated refugees (18–54%) show no improvement after PTSD treatment (e.g., Stenmark, Guzey, Elbert, Holen, 2014; Ter Heide,

Mooren, Van de Schoot, De Jongh, & Kleber, 2016), highlighting the complexities of PTSD psychotherapy with people from refugee backgrounds.

To optimize treatment response, outcome research would profit from the identification of markers that distinguish between treatment responders and non-responders. Factors that may predict the outcome of PTSD treatment in a range of trauma-affected populations include PTSD onset, childhood trauma, trauma severity, and initial reactions to trauma (Steinert, Hofmann, Leichsenring, & Kruse, 2015). Only a small number of studies however directly examined predictors of treatment response in refugees. One demographic variable (male gender; Stenmark et al., 2014), one migration-related variable (lack of refugee status; Raghavan, Rasmussen, Rosenfeld, & Keller, 2013), two trauma related variables (abduction history, Betancourt et al., 2012; offender status, Stenmark, Catani, Neuner, Elbert, & Holen, 2013), one coping variable (lack of a firm belief system; Brune et al., 2002), one treatment variable (the number of trauma focused treatment sessions; Lambert & Alhassoon, 2015), and two clinical variables (comorbid depression, Silove, Manicavasagar, Coello, & Aroche, 2005; poorer pre-intervention mental health, Van Wyk, Schweitzer Brough, Vromans, & Murray, 2012) have been found to predict poor treatment response.

In addition to these variables, other variables are often clinically assumed to influence treatment response. Differences in refugee treatment response may be explained by ongoing psychosocial stressors (Miller & Rasmussen, 2010). For example, uncertainty about a refugee status (i.e., having a formal refugee status vs. seeking a formal refugee status as an asylum seeker), accompanied by the fear of forced return to the home country, may reverse any beneficial treatment effects (McFarlane & Kaplan, 2012), whilst status obtainment improved treatment outcome (Raghavan et al., 2013). Language difficulties and the need for an interpreter may also clinically be assumed to diminish treatment response (Miller, Martell, Pazdirek, Caruth, & Lopez, 2005; National Institute for Clinical Excellence [NICE], 2005). Furthermore, the number and nature (civilian, political, veteran) of refugees' traumatic experiences may influence treatment response. Different experiences may have different contextual meanings that could complex symptom constellations and affect treatment outcome (Nickerson, Bryant, Silove, & Steel, 2011). Political activists are regularly subjected to imprisonment for opposing, criticizing, or participating in political activities against the government. They are more likely to face isolation, and physical and mental torture. Unlike political activists, veterans are former members

of a State's armed forces; they are more often exposed to combat situations. Civilian refugees, on the other hand, are not active members of the government or any group in conflict with the government. Such experiences shape the social perspective in which PTSD recovery takes place.

The aim of the study was to examine treatment outcome predictors in a sample of treated refugees and asylum seekers with PTSD. The term 'refugee' is used throughout the article to refer to both refugees and asylum seekers. The goal was to investigate novel prospective outcome predictors as well as to replicate previous refugee treatment outcome predictor findings. We conducted a multilevel analysis of PTSD treatment outcome data of adult refugees who participated in a randomized controlled trial (RCT). Multilevel analysis is an advanced statistical method, well suited for analysing longitudinal data with multiple dependent outcomes. Following the available evidence, we hypothesized that pre-treatment PTSD severity, comorbid depression, lack of refugee status, language difficulties (i.e., need for an interpreter during therapy), the number and nature of traumatic events, male gender, fewer psychotherapy sessions, and treatment dropout would predict poorer treatment response.

Methods

Study design

We analysed data from a RCT that compared the safety and efficacy eye movement desensitization and reprocessing (EMDR) and stabilization in asylum seekers and refugees suffering from PTSD. EMDR is a trauma focused intervention in which a focus on traumatic memories is combined with an attention-demanding task (Shapiro, 2001). Stabilization therapy focuses on building psychosocial skills and competencies, to better cope with or control traumatic distress, improve emotion-regulation, and improve relational skills (Cloitre et al., 2012). The trial was performed at two locations of a Dutch specialist psychotrauma treatment and research centre, Foundation Centrum '45. Both interventions provided 12 hours of treatment contact, divided over nine sessions in the EMDR condition and 12 sessions in the stabilization condition. Participants completed an assessment at the start of treatment, post-treatment, and at 3-month follow-up. Both treatments were shown to be safe and limitedly efficacious, and no differences in outcomes

between treatments were found. For a comprehensive report of study design and outcome, see Ter Heide et al. (2016).

Sample

The sample consisted of 72 treatment-seeking adult refugees and asylum seekers who met the DSM-IV-TR diagnostic criteria for PTSD, 36 of whom were assigned to EMDR and 36 to stabilization. Six participants (17%) in the EMDR and 8 (22%) participants in the stabilization condition prematurely terminated treatment. Participants in both conditions benefited equally from treatment (EMDR $\beta = .44$ vs. stabilization $\beta = .48$, $p > .05$). There were no differences in pre-treatment demographic or clinical variables between the two conditions, except that patients in the EMDR condition were more likely to be male (83% vs. 61%; $\chi^2 = 4.4$, $p < .05$). Table 1 provides an overview of the sample characteristics. The APA ethical standards were followed in the conduct of the study which was approved by the medical ethics committee of the University of Leiden (reference number: OND1324839; ISRCTN20310201). An informed consent was required before patients were included in the study.

Outcome measure

The Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995) served as the primary outcome measure at each measurement interval. It consists of 17 items used to diagnose PTSD according to DSM-IV. Frequency and severity of symptoms are rated on two 5-point Likert scales ranging from 0 (absent) to 4 (extreme), resulting in a score range of 0–136. The CAPS has good psychometric properties across a variety of clinical populations (Weathers, Keane, & Davidson, 2001), including refugees (Charney & Keane, 2007). The internal consistency in the present sample was good (Cronbach's $\alpha = .86$).

Predictive measures

The Hopkins Symptom Checklist (HSCL-25) is a screening instrument for anxiety and depression, which has been designed especially for use with traumatized refugees (Mollica, Wyshak, De Marneffe, Khuon, & Lavelle, 1987). The current study used the depression section of the instrument to assess pre-treatment depression severity. This section consists of 15 items that are rated on a 4-point Likert scale ranging from 1 (not at all) to 4 (extreme). Internal

consistency of the depression subscale in the present sample was excellent (Cronbach's $\alpha = .91$). The presence or absence of a DSM-IV diagnosis of comorbid major depressive disorder was routinely assessed at intake by a trained clinician and was also examined as a predictor of treatment outcome.

Data analysis

Independent-samples t-tests and chi-square (X^2) comparisons were used to examine possible differences between patients per condition, after which longitudinal multilevel modelling (MLM) was used to predict PTSD severity scores over time. Longitudinal MLM enables the identification of variables that predict the variance within persons (time level) and between persons (individual level). We calculated the intraclass correlation (ICC) statistic to determine which proportion of the total variance is located at each of these levels (Hruschka, Kohrt, & Worthman, 2005). The level-1 variables consisted of PTSD symptom severity at each assessment and included the assessment itself (time). The pre-treatment assessment was considered time = 0. Each subsequent assessment increased the time variable by 1. Level-2 variables consisted of the between-individual variables to predict changes in the slope of time. MLM does not assume independence between outcome observations nor between the residuals and errors (Graham, 2009). It is better suited than ANOVA repeated measures to deal with assumptions of sphericity, unbalanced data, sampling hierarchy, and missing data, and it increases statistical power beyond ANOVA designs (Hruschka et al., 2005). Classic standard errors were used because robust standard errors may be biased in samples with <100 patients (Hox & Maas, 2001).

To enhance sample size, CAPS severity scores were imputed. We created 10 imputation data sets using predictive mean matching (PMM) and imputed 15% of the post-treatment and 13% of the follow-up CAPS scores. There were no missings in the level-2 data (i.e., individual predictor data), except for one person with a missing pre-treatment HSCL-25 (depression) score. PMM is a recommended multiple imputation technique to increase the reliability of the results (Vink, Frank, Pannekoek, & Van Buuren, 2014). To preserve the multilevel structure of the data and, consequently, precise estimates, a partitioned PMM was used (Vink, Lazendic, & Van Buuren, 2015). Missing data were considered missing at random (MAR) if patients dropped out of treatment without notification, due to travel distance, or due to increase in suicidal ideations.

Participants who discontinued treatment for treatment-related reasons were considered not missing at random (NMAR). All NMAR cases had complete data at all measurement intervals.

Table 1

Pre-treatment demographic and clinical characteristics

Sample Characteristics		*n(%)*	*mean(SD)*
Pre-treatment			
Age in years			41.5(11.3)
Years in the Netherlands[i]			9.4(5.2)
Region of origin	Europe	8(11)	
	Asia	20(28)	
	Africa	19(26)	
	Middle East	25(35)	
Gender	Male	52(72)	
Education	No education/ Primary school	19(26)	
	Secondary school or higher	53(74)	
Marital Status	Single/ Divorced / Widow	36(50)	
Refugee status	Temporary / Permanent permit	59(82)	
	Pending / Rejected	13(18)	
Number of experienced PTEs			12(5.0)
Type of experienced PTEs	Murder of friends/family	54(75)	
	Combat situation	48(67)	
	Physical torture[ii]	46(66)	
	Imprisonment[ii]	44(63)	
	Serious injury[i]	39(55)	
	Rape or sexual abuse[ii]	16(23)	
Refugee background	Civilian	30(42)	
	Political	17(24)	
	Veteran	10(14)	
Comorbid depressive disorder		46(64)	
Symptom severity levels	PTSD severity		76.5(18.1)
	Depression severity[i]		2.9(.56)
Post-treatment			
Interpreter presence		40(56)	
Number of sessions T1-T2			10.7(2.8)
Treatment dropout		14(19)	

Note. PTE's = potentially traumatic events. [i] $n = 71$,[ii] $n = 70$. PTSD severity was measured with the CAPS. Depression severity was measured with the HSCL-25.

A stepwise multilevel model was constructed. Longitudinal intercept-only multilevel models tend to overestimate the variance at the time level (within-subject) and underestimate it at the subject level (Hox, 2010). To offer a more realistic model, the time variable was included in the intercept-only model ($CAPS_{ti} = \beta_{00} + \beta_{10}*TIME_{ti} + r_{0i} + r_{1i}*TIME_{ti} + e_{ti}$). First, the intercept-only model with a fixed-effects time component was compared with the intercept-only model with a random-effects time component, to test whether there were individual trajectories between patients in treatment response (random slope), or whether all patients had a similar trajectory (fixed slope). Full maximum likelihood estimates enabled comparisons between the different fit models. A chi-square test based on the difference in deviance between models enabled assessment of the best model fit. The best fit model was chosen as the baseline model. Second, each univariate predictor variable (pre-treatment PTSD severity, comorbid depression diagnosis and severity, refugee status, interpreter presence during therapy, the number and nature of traumatic events, gender, number of psychotherapy sessions, and treatment dropout) was added to the baseline model to test whether these variables predicted PTSD severity change via the time slope. During this step, we controlled for any possible effects from treatment condition and location (Centre 1 and Centre 2) by adding them to the baseline model. As no difference in efficacy between treatments was found in the RCT, we combined patient data of both conditions to increase predictive power. This strategy is recommended, providing treatment condition is added to the model as a control variable (Moons, Royston, Vergouwe, Grobbee, & Altman, 2009). Third, all significant and control predictors were added to the baseline model and simultaneously analysed in a final multilevel model. We also tested for moderator effects between significant treatment predictors and treatment condition to ascertain whether these predictors influenced each condition differently. The proportion of explained variance (R^2) was calculated for the final model (Hox, 2010). SPSS (version 22; IBM Corp., Armonk, NY, USA) was used to examine possible differences between patients per condition and to generate the imputation data sets. All multilevel analyses (including imputation analyses) were performed in HLM (version 7) software (Scientific Software International, Skokie, IL, USA).

Results

The results section offers a step-by-step overview of the identification process of predictors. Table 2 consists of a correlation matrix of the principal continuous predictors and PTSD outcome measures at each time measurement interval.

Baseline model

The ICC of the fixed time slope baseline model was 0.57, meaning that 57% of the variance of CAPS outcome scores was explained by differences between individuals at the group level. The remaining 43% of the variance was explained by differences within each subject, indicating the extent to which the CAPS scores of an individual tended to vary over time.

We compared the fixed linear time slope baseline model with a random time slope (Table 3). The random time slope model had a significant better fit compared to the fixed linear slope model ($\chi^2 = 14.1$; $p < .001$). This indicated the presence of unexplained between-subject variation in PTSD symptom severity over time and permitted the search for individual characteristics (predictors) to explain this variability. The baseline model showed an average PTSD symptom severity of 75 CAPS points at pre-treatment and a significant 3-point decrease in PTSD symptoms per time interval ($B = 3.0$, $p < .05$).

Baseline model with predictors

The control variables condition and location were added to the baseline model. Each predictor was subsequently added to the 'baseline plus control variables' model in a separate multilevel analysis. Each separate multilevel model has a different average symptom decrease because part of the decrease is explained by the unique predictors in each model.

Mean pre-treatment depression severity ($B = 6.0$, $SE = 2.4$, $p = .02$) predicted poor PTSD treatment response over time. The model had an average PTSD symptom decrease of 22.9, meaning that for each 1-point increase in HSCL depression score (to a maximum of 4), the PTSD CAPS symptom decrease would be 6 points less, with a maximum of 24 points. Patients with maximum depression severity scores would experience a small increase in PTSD severity at post-

treatment and follow-up. This indicated that patients with progressively severe levels of depression had progressively less PTSD symptom reduction over time.

Table 2

Correlation matrix

		1	2	3	4	5	6
PTSD severity pre-treatment	1	1					
PTSD severity posttreatment	2	.61**	1				
PTSD severity follow-up	3	.47**	.70**	1			
Depression diagnosis pre-treatment	4	.20	.25	.23	1		
Depression severity pre-treatment	5	.56**	.36**	.47**	.06	1	
Number of sessions received	6	.06	-.04	-.14	-.12	-.01	1

Note. Dropout: 0 = Treatment completer, 1 = Dropout. Location: 0 = Centre 1, 1 = Centre 2. Condition: 0 = EMDR, 1 = Stabilization.

PTSD severity was measured with the CAPS. Depression severity was measured with the HSCL-25.

*$p < .05$. ** $p < .01$

Table 3

Hierarchical multilevel regression analyses predicting PTSD treatment outcome (N = 72)

Parameter	Baseline Fixed Time model (fixed Time slope)		Baseline random time model (random time slope)		Multivariate model		Moderator model	
	B	**S.E.(B)**	***B***	**S.E.(B)**	***B***	**S.E.(B)**	***B***	**S.E.(B)**
	Fixed effects							
Intercept	75.0***	2.2	75.0***	2.2	75.***	2.2	75.***	2.2
Level 1 (CAPS severity score at T1, T2, T3)								
Time	-3.0*	1.4	-3.0*	14	-29.9***	7.9	-48.5**	17.4
Level 2 (Characteristics)								
Location					6.4*	2.8	5.8*	2.8
Condition					.51	2.6	18.1	14.7
Dep severity					6.3**	2.3	9.4*	3.7
Dep diagnosis					6.5*	2.9	8.4†	4.3
Dep severity X Condition							-5.2	4.8
Dep diagnosis X Condition							-3.4	5.4
	Random parameters							
σ^2_e (s.d.)	232.4 (15.2)		189.7 (13.8)		190.2 (13.8)		190.1 (13.6)	
σ^2_u0 (s.d.)	306.1 (17.5)***		186.6 (13.7)***		185.9 (13.6)***		186.1 (13.6)***	
σ^2_u1 (s.d.)			42.7 (6.5)**		30.5 (5.5)*		27.8 (5.3)*	
-2 log likelihood ratio	1904.8		1890.7		1877.0		1875.0	

Note. CAPS = Clinician-Administered PTSD Scale; Dep = Depression; PTSD = post-traumatic stress disorder. Location: 0 = Centre 1, 1 = Centre 2; Condition: 0 = EMDR, 1 = Stabilization. Fit difference between baseline models: $\chi^2(14.1, df = 2, p < .001)$; fit difference between baseline random time model and multivariate model $\chi^2(13.7, df = 4, p < .01)$; fit difference between multivariate model and multivariate model with moderators $\chi^2(2.0, df = 2, p > .05)$.

* $p < .05$; ** $p < .01$; *** $p < .001$ † $p < .06$

Similarly, a diagnosis of major depressive disorder also proved predictive of poor treatment response (B = 6.0, SE = 3.0, p = .05). The average PTSD symptom decrease in this model was 10.7 points, indicating that patients with a major depressive disorder improved less than patients without a major depressive disorder. None of the other predictors (pre-treatment PTSD severity, refugee status, interpreter presence during therapy, the number and nature of traumatic events, gender, number of psychotherapy sessions, and treatment dropout) were significant.

Multivariate model

The multivariate model (Table 3) included all significant and control predictors in the MLM analysis. The equation was as follows:

$$CAPS = \beta_{00} + \beta_{10}*TIME + \beta_{11}*CONDITION*TIME + \beta_{12}*LOCATION*TIME + \beta_{13}*DEPRESSION\ DIAGNOSIS*TIME + \beta_{14}*DEPRESSION\ SEVERITY*TIME + r_0 + r_1 + e$$

The average PTSD severity decreased by 29.9 points over time. This average slope represents patients with neither depression symptoms nor a diagnosis (best case scenario). For each 1-point increase in pre-treatment depression severity, symptom reduction would be 6.3 points less (SE = 2.3, $p < .01$). Patients with a pre-treatment major depressive diagnosis had 6.5 points less PTSD symptom reduction over time (SE = 2.9, p = .03). These findings indicate that worst-case scenario, patients with the maximum depression severity score of 4 and a depressive diagnosis, would experience, on average an increase of 3.6 PTSD severity points between pre-treatment and follow-up. Figure 1 shows four different possible trajectories for patients, based on the presence of a depressive disorder and minimum and maximum depression severity.

The multivariate model was further expanded with two moderator variables (Depression diagnosis x Condition and Depression severity x Condition) to examine whether depression impacted treatment outcome differently for EMDR and stabilization (Table 3). There were no significant moderation effects ($p > .05$) and the expanded model did not provide a better fit ($p > .05$), indicating that depression severity and diagnosis exerted similar effects on treatment outcome for both interventions. Based on these results, the multivariate model without moderators was considered the final model.

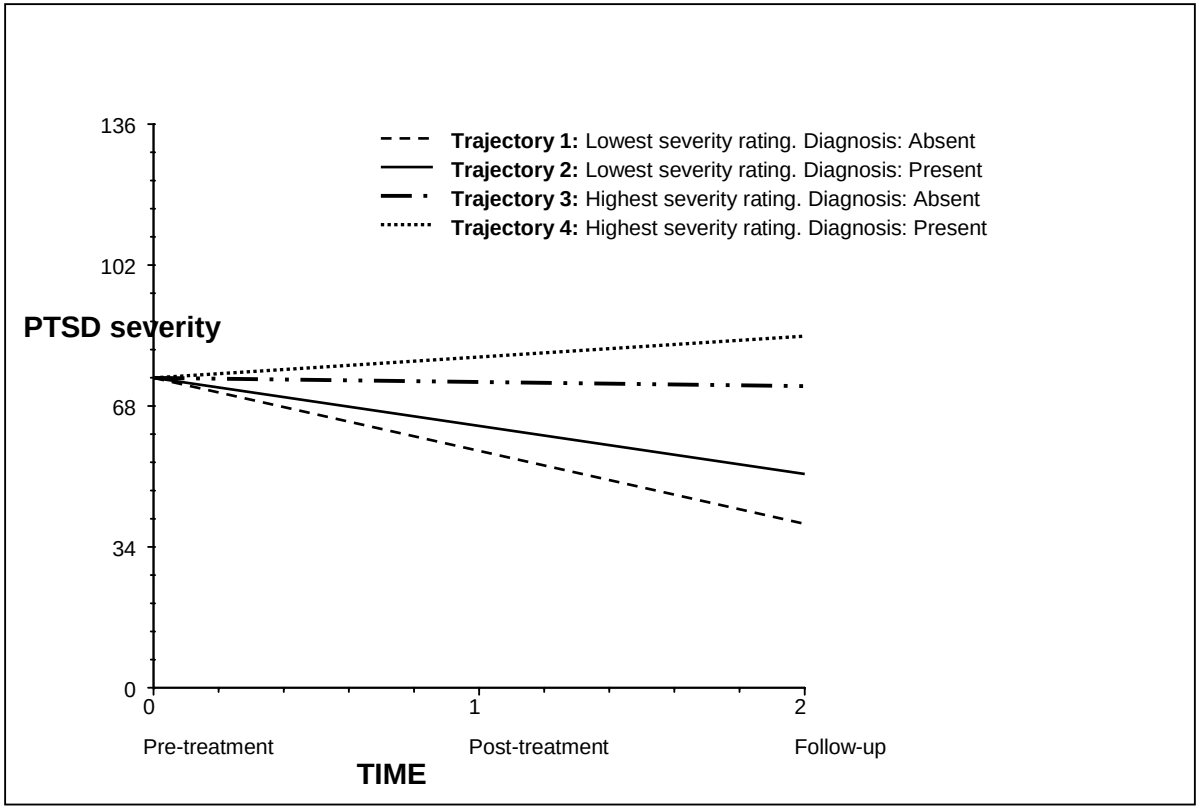

Figure 1. *Four treatment trajectories over time*

Note. The post-traumatic stress disorder (PTSD) severity score (y-axis) was measured with the Clinician-Administered PTSD Scale (CAPS). Depression severity was measured with the HSCL-25. The severity rating ranged from 1 (lowest) to 4 (highest). A comorbid depression diagnosis was either Absent (i.e., no comorbid disorder) or Present (i.e., a comorbid disorder).

The final model explained 39% of the variance between individuals. In sum, the change in PTSD severity scores at post-treatment and follow-up was mostly (57%) the result of individual differences between patients. A sizeable portion (39%) of these differences was explained by the presence and severity of comorbid depression.

Discussion

This study aimed to explain variations in treatment response in an RCT for refugee patients suffering from PTSD. Using multilevel regression analysis at multiple time intervals, the present study identified pre-treatment depressive symptom severity and a diagnosis of depressive disorder as predictors of poor PTSD treatment response. None of the other examined variables predicted treatment response.

Major depressive disorder is frequently associated with PTSD (Buhmann, 2014; Keller, Feeny, & Zoellner, 2014). There is consistent cross-sectional evidence of greater symptom severity, higher disability levels, and poorer functioning among PTSD patients with comorbid depression compared to patients with PTSD only (Bedard-Gilligan et al., 2015; Momartin, Silove, Manicavasagar, & Steel, 2004). Despite this evidence, only one study has considered comorbid depression as a predictor of poor treatment outcome (Silove et al., 2005). Comorbid depression did predict poor PTSD treatment response and premature treatment termination in non-refugee samples, such as traumatized civilians (Bryant, Moulds, Guthrie, Dang, & Nixon, 2003; Taylor et al., 2001) and childhood sexual abuse victims (McDonagh et al., 2005).

The mechanisms through which depression limits psychological recovery are still largely unknown. Angelakis and Nixon (2015) offer several explanations based on emotional processing theory. The first explanation is that successful treatment depends on the modification of traumatic memory structures that underlie emotions, via activation (engagement) of the fear structure through exposure and subsequent habituation. Patients are thus able to emotionally process traumatic memories. An inability to fully experience emotional affect (emotional numbing) in depressed patients may lead to underactivation (underengagement) of the fear structure. Alternatively, depressive patients may be more prone to use trans-diagnostic avoidance strategies present in both PTSD and depression, such as rumination and overgeneralizing

traumatic memories, which inhibit the full experience of negative emotions. The second explanation is that a greater accessibility of negative autobiographical memories as a result of depression inhibits emotional disengagement from negative trauma content during exposure. This would result in a contrary reaction in which depressive patients become overwhelmed by the emotional intensity of the traumatic memories (overengagement) and successful habituation is prevented.

Angelakis and Nixon based their hypotheses on the assumption that PTSD treatment involves exposure to traumatic memories. Because not all PTSD interventions – for example stabilization – target traumatic memories, we propose alternative hypotheses. In refugee patients with comorbid depression and PTSD, loss and grief may be at the heart of their pathology. The violent loss of friends and family members is a common occurrence among refugees. Refugee patients who experienced a traumatic loss were five times more likely to develop comorbid depression besides PTSD compared to refugee patients without traumatic loss (Momartin et al., 2004). Whilst PTSD development was primarily related to exposure to life-threatening situations (Momartin et al., 2004), comorbid depression development was related to exposure to significant losses (Kersting et al., 2009). Loss may be a major cause of depression, a core aspect of refugee functioning that demands attention besides PTSD, and may require different treatment strategies. We found no evidence for the predictive value of variables that are traditionally seen as indicative of treatment response in traumatized refugees, including psychosocial stressors (lack of refugee status, language difficulties [need for an interpreter during therapy], nature of the traumatic events), the number of traumatic stressors, gender, and PTSD symptom severity.

Measuring *changes in refugee status* after treatment instead of pre-treatment status may be a more sensitive method to determine the impact of a (lack of) refugee status on treatment outcome. Drozdek, Kamperman, Tol, Knipscheer, and Kleber (2013) reported improved treatment outcome among refugees who gained a refugee status during therapy and argue that removal of status uncertainty increases recovery in the short term; however, a growing awareness of the challenges in rebuilding a future in the host society may again limit these beneficial effects in the long term.

Strengths and limitations

The use of group averages risks masking positive and negative effects between subgroups because it does not account for individual differences in treatment (Moynihan, Henry, & Moons, 2014). Predictor research enables clinicians to identify (non)responders and tailor interventions to optimize response (Riley et al., 2013). The present study is one of the first to examine comorbid depression as a predictor of poor PTSD treatment response in refugees. We used multiple measurements and employed multilevel analysis to better represent the nested data for each individual compared to traditional (ANOVA) methods. The present study examined a severely traumatized patient sample and used an RCT design with few exclusion criteria. Current findings may be applicable to other treatment populations who suffered multiple traumatic events and display high depression comorbidity.

There are also limitations. The present study examined multiple predictors but did not correct for multiple testing and could risk reporting false positives. Due to the lack of predictive studies, a more exploratory analysis was deemed more useful for the detection of possible predictors that would otherwise remain undiscovered if a strictly *a priori* method were used. The current findings need to be replicated. Comorbid depression might have a different effect on alternative PTSD treatments besides EMDR and stabilization, and may not be generalizable to other modalities of PTSD treatment, although the present study moderator analysis showed an equally disruptive effect for two very distinct. The non-significant findings need to be interpreted with caution given the sample size and complexity of the analyses.

Conclusions

Comorbid depression was found to predict poor treatment response. The disorder is highly prevalent among refugees with PTSD (Momartin et al., 2004). In accordance with PTSD NICE (2005) treatment guidelines, we recommend initially targeting severe depression (which will also likely lower PTSD symptoms; Keller et al., 2014), and then only commencing complementary PTSD treatment after alleviation of severe depressive symptoms. There is, however, no evidence available as to whether this sequential approach to treating PTSD and severe depression is superior to treatment of PTSD alone or to a combined PTSD and depression treatment approach

(Angelakis & Nixon, 2015). Clinicians and researchers are urged to examine the impact of treatment timing on PTSD treatment effectiveness for patients with severe comorbid depression.

A sole focus on PTSD for traumatized refugees may fall short in the presence of severe comorbidity (Buhmann, 2014), and may oversimplify complex problems (Briggs & Macleod, 2006). Therapists are recommended to carefully discuss patient needs and whether these primarily focus on PTSD, depression, or perhaps grief. Although an assessment of patient needs is essential in any treatment, it is considered especially so in refugee populations (Summerfield, 1999).

Psychosocial factors that are traditionally assumed to limit treatment response in traumatized refugees, such as lack of refugee status or need for an interpreter, were not found to predict treatment response. These factors warrant further attention regarding their impact on treatment and may imply that practitioners need not refrain from offering psychotherapy for PTSD in refugees based on the assumption that asylum seekers and refugees with little fluency show little treatment response.

In sum, there are major individual differences in treatment response between refugees. The present study identified the presence and severity of a comorbid major depressive disorder as predictors for poor PTSD outcome in traumatized refugees. These results highlight the need for alternative treatment strategies for PTSD and comorbid severe depression in traumatized refugees, including testing whether initial targeting of severe depressive symptoms and only commencing PTSD treatment after reducing depression severity to more moderate levels is more effective than initial PTSD treatment or targeting PTSD and severe depression simultaneously. Future research should determine which approach is superior to alleviate the psychological burden of trauma and displacement in refugees.

Practitioner Points

- There are differences in post-traumatic stress disorder (PTSD) treatment response between traumatized refugees.
- Comorbid depressive disorder and depression severity predict poor PTSD response.
- Refugees with PTSD and severe depression may not benefit from PTSD treatment.
- Targeting comorbid severe depression before PTSD treatment is warranted.
- This study did not correct for multiple hypothesis testing.
- Comorbid depression may differentially impact alternative PTSD treatments.

Acknowledgement

We thank Prof. Dr. Ivan Komproe for his statistical advice.

References

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: Author.

Angelakis, S., & Nixon, R. D. (2015). The comorbidity of PTSD and MDD: Implications for clinical practice and future research. *Behaviour Change, 32,* 1–25. doi:10.1017/bec.2014.26

Bedard-Gilligan, M., Duax Jakob, J. M., Doane, L. S., Jaeger, J., Eftekhari, A., Feeny, N., & Zoellner, L. A. (2015). An investigation of depression, trauma history, and symptom severity in individuals enrolled in a treatment trial for chronic PTSD. *Journal of Clinical Psychology, 71,* 725–740. doi:10.1002/jclp.22163

Betancourt, T. S., Newnham, E. A., Brennan, R. T., Verdeli, H., Borisova, I., Neugebauer, R., . . . Bolton, P. (2012). Moderators of treatment effectiveness for war-affected youth with depression in northern Uganda. *The Journal of Adolescent Health, 51,* 544–550. doi:10.1016/j.jadohealth.2012.02.010

Blake, D. D., Weathers, F. W., Nagy, L. M., Kaloupek, D. G., Gusman, F. D., Charney, D. S., & Keane, T. M. (1995). The development of a clinician-administered PTSD scale. *Journal of Traumatic Stress, 8,* 75–90. doi:10.1002/jts.2490080106

Bogic, M., Njoku, A., & Priebe, S. (2015). Long-term mental health of war-refugees: A systematic literature review. *BMC International Health and Human Rights, 15,* 29. doi:10.1186/s12914-015-0064-9

Briggs, L., & Macleod, A. S. (2006). Demoralisation – a useful conceptualisation of non-specific psychological distress among refugees attending mental health services. *The International Journal of Social Psychiatry, 52,* 512–524. doi:10.1177/0020764006066832

Brune, M., Haasen, C., Krausz, M., Yagdiran, O., Bustos, E., & Eisenman, D. P. (2002). Belief systems as coping factors for traumatized refugees: A pilot study. *European Psychiatry, 17*(8), 451–458.

Bryant, R. A., Moulds, M. L., Guthrie, R. M., Dang, S. T., & Nixon, R. D. (2003). Imaginal exposure alone and imaginal exposure with cognitive restructuring in treatment of posttraumatic stress disorder. *Journal of Consulting and Clinical Psychology, 71,* 706–712. doi:10.1037/0022-006X.71.4.706

Buhmann, C. B. (2014). Traumatized refugees: Morbidity, treatment and predictors of outcome. *Danish Medical Journal, 61,* B4871.

Burri, A., & Maercker, A. (2014). Differences in prevalence rates of PTSD in various European countries explained by war exposure, other trauma and cultural value orientation. *BMC Research Notes, 7,* 407. doi:10.1186/1756-0500-7-407

Charney, M. E., & Keane, T. M. (2007). Psychometric analyses of the Clinician-Administered PTSD Scale (CAPS)–Bosnian translation. *Cultural Diversity & Ethnic Minority Psychology, 13,* 161–168. doi:10.1037/1099-9809.13.2.161

Chu, T., Keller, A. S., & Rasmussen, A. (2013). Effects of post-migration factors on PTSD outcomes among immigrant survivors of political violence. *Journal of Immigrant and Minority Health, 15,* 890–897. doi:10.1007/s10903-012-9696-1

Cloitre, M., Courtois, C. A., Ford, J. D., Green, B. L., Alexander, P., Briere, J., . . . Van der Hart, O. (2012). *The ISTSS expert consensus treatment guidelines for complex PTSD in adults.* Retrieved from http://www.istss.org/ISTSS_Main/media/Documents/ComplexPTSD.pdf

Drožđek, B., Kamperman, A. M., Tol, W. A., Knipscheer, J. W., & Kleber, R. J. (2013). Is legal status impacting outcomes of group therapy for posttraumatic stress disorder with male asylum seekers and refugees from Iran and Afghanistan? *BMC Psychiatry, 13,* 148. doi:10.1186/1471-244X-13-148

Fazel, M., Wheeler, J., & Danesh, J. (2005). Prevalence of serious mental disorder in 7000 refugees resettled in western countries: A systematic review. *The Lancet, 365,* 1309–1314. doi:10.1016/S0140-6736(05)61027-6

Graham, J. W. (2009). Missing data analysis: Making it work in the real world. *Annual Review of Psychology, 60,* 549–576. doi:10.1146/annurev.psych.58.110405.085530

Hox, J. J. (2010). *Multilevel analysis: Techniques and application* (2nd ed.). New York, NY: Routledge.

Hox, J. J., & Maas, C. J. (2001). The accuracy of multilevel structural equation modeling with pseudobalanced groups and small samples. *Structural Equation Modeling, 8,* 157–174. doi:10.1207/S15328007SEM0802_1

Hruschka, D. J., Kohrt, B. A., & Worthman, C. M. (2005). Estimating between- and within-individual variation in cortisol levels using multilevel models. *Psychoneuroendocrinology, 30,* 698–714. doi:10.1016/j.psyneuen.2005.03.002

Keller, S. M., Feeny, N. C., & Zoellner, L. A. (2014). Depression sudden gains and transient depression spikes during treatment for PTSD. *Journal of Consulting and Clinical Psychology, 82,* 102–111. doi:10.1037/a0035286

Kersting, A., Kroker, K., Horstmann, J., Ohrmann, P., Baune, B. T., Arolt, V., & Suslow, T. (2009). Complicated grief in patients with unipolar depression. *Journal of Affective Disorders, 118,* 201–204. doi:10.1016/j.jad.2009.01.033

Kessler, R. C., Chiu, W. T., Demler, O., Merikangas, K. R., & 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,* 617–627. doi:10.1001/archpsyc.62.6.617

Knipscheer, J. W., & Kleber, R. J. (2006). The relative contribution of posttraumatic and acculturative stress to subjective mental health among Bosnian refugees. *Journal of Clinical Psychology, 62,* 339–353. doi:10.1002/jclp.20233

Lambert, J. E., & Alhassoon, O. M. (2015). Trauma focused therapy for refugees: Meta-analytic findings. *Journal of Counseling Psychology, 62*, 28–37. doi:10.1037/cou0000048

Li, S. S. Y., Liddell, B. J., & Nickerson, A. (2016). The relationship between post-migration stress and psychological disorders in refugees and asylum seekers. *Current Psychiatry Reports, 18,* 82. doi:10.1007/s11920-016-0723-0

McDonagh, A., Friedman, M., McHugo, G., Ford, J., Sengupta, A., Mueser, K., . . . Descamps, M. (2005). Randomized trial of cognitive-behavioral therapy for chronic posttraumatic stress disorder in adult female survivors of childhood sexual abuse. *Journal of Consulting and Clinical Psychology, 73,* 515–524. doi:10.1037/0022-006X.73.3.515

McFarlane, C. A., & Kaplan, I. (2012). Evidence-based psychological interventions for adult survivors of torture and trauma: A 30-year review. *Transcultural Psychiatry, 49,* 539–567. doi:10.1177/ 1363461512447608

Miller, K. E., Martell, Z. L., Pazdirek, L., Caruth, M., & Lopez, D. (2005). The role of interpreters in psychotherapy with refugees: An exploratory study. *American Journal of Orthopsychiatry, 75,* 27–39. doi:10.1037/0002-9432.75.1.27

Miller, K. E., & Rasmussen, A. (2010). War exposure, daily stressors, and mental health in conflict and post-conflict settings: Bridging the divide between trauma focused and

psychosocial frameworks. *Social Science & Medicine, 70,* 7–16. doi:10.1016/j.socscimed.2009.09.029

Mollica, R. F., Wyshak, G., De Marneffe, D., Khuon, F., & Lavelle, J. (1987). Indochinese versions of the Hopkins Symptom Checklist-25: A screening instrument for the psychiatric care of refugees. *The American Journal of Psychiatry, 144,* 497–500. doi:10.1176/ajp.144.4.497

Momartin, S., Silove, D., Manicavasagar, V., & Steel, Z. (2004). Comorbidity of PTSD and depression: Associations with trauma exposure, symptom severity and functional impairment in Bosnian refugees resettled in Australia. *Journal of Affective Disorders, 80,* 231–238. doi:10.1016/S0165-0327(03)00131-9

Moons, K. G., Royston, P., Vergouwe, Y., Grobbee, D. E., & Altman, D. G. (2009). Prognosis and prognostic research: What, why, and how? *British Medical Journal, 338,* b375. doi:10.1136/ bmj.b375

Moynihan, R., Henry, D., & Moons, K. G. (2014). Using evidence to combat overdiagnosis and overtreatment: Evaluating treatments, tests, and disease definitions in the time of too much. *PLoS Medicine, 11,* e1001655. doi:10.1371/journal.pmed.1001655

National Institute for Clinical Excellence (NICE) (2005). *Post-traumatic stress disorder: The management of PTSD in adults and children in primary and secondary care*. Wiltshire, UK: Gaskell and the British Psychological Society.

Nickerson, A., Bryant, R. A., Silove, D., & Steel, Z. (2011). A critical review of psychological treatments of posttraumatic stress disorder in refugees. *Clinical Psychology Review, 31,* 399–417. doi:10.1016/j.cpr.2010.10.004

Raghavan, S., Rasmussen, A., Rosenfeld, B., & Keller, A. S. (2013). Correlates of symptom reduction in treatment-seeking survivors of torture. *Psychological Trauma: Theory, Research, Practice, and Policy, 5,* 377–383. doi:10.1037/a0028118

Riley, R. D., Hayden, J. A., Steyerberg, E. W., Moons, K. G., Abrams, K., Kyzas, P. A., . . . Hemingway, H. (2013). Prognosis Research Strategy (PROGRESS) 2: Prognostic factor research. *PLoS Medicine, 10,* e1001380. doi:10.1371.journal/pmed.1001380

Shapiro, F. (2001). *Eye movement desensitization and reprocessing: Basic principles, protocols and procedures.* New York, NY: Guilford Press.

Silove, D., Manicavasagar, V., Coello, M., & Aroche, J. (2005). PTSD, depression, and acculturation. *Intervention, 3*(1), 46–50.

Slobodin, O., & De Jong, J. T. V. M. (2015). Mental health interventions for traumatized asylum seekers and refugees: What do we know about their efficacy? *International Journal of Social Psychiatry, 61,* 17–26. doi:10.1177/0020764014535752

Söndergaard, H. P., & Theorell, T. (2004). Language acquisition in relation to cumulative posttraumatic stress disorder symptom load over time in a sample of resettled refugees. *Psychotherapy & Psychosomatics, 73,* 320–323. doi:10.1159/000078849

Steel, Z., Chey, T., Silove, D., Marnane, C., Bryant, R. A., & Van Ommeren, M. (2009). Association of torture and other potentially traumatic events with mental health outcomes among populations exposed to mass conflict and displacement: A systematic review and meta-analysis. *JAMA, 302,* 537–549. doi:10.1001/jama.2009.1132

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. Nordic Journal of Psychiatry, 69,* 483–496. doi:10.3109/08039488.2015.1005023

Stenmark, H., Catani, C., Neuner, F., Elbert, T., & Holen, A. (2013). Treating PTSD in refugees and asylum seekers within the general health care system. A randomized controlled multicenter study. *Behaviour Research and Therapy, 51,* 641–647. doi:10.1016/j.brat.2013.07.002

Stenmark, H., Guzey, I. C., Elbert, T., & Holen, A. (2014). Gender and offender status predicting treatment success in refugees and asylum seekers with PTSD. *European Journal of Psychotraumatology, 5,* 20803. doi:10.3402/ejpt.v5.20803

Summerfield, D. (1999). A critique of seven assumptions behind psychological trauma programmes in war-affected areas. *Social Science & Medicine, 48*(10), 1449–1462.

Taylor, S., Fedoroff, I. C., Koch, W. J., Thordarson, D. S., Fecteau, G., & Nicki, R. M. (2001). Posttraumatic stress disorder arising after road traffic collisions: Patterns of response to cognitive–behavior therapy. *Journal of Consulting and Clinical Psychology, 69,* 541–551. doi:10.1037/0022-006X.69.3.541

Ter Heide, F. J. J., Mooren, T. M., Van de Schoot, R., De Jongh, A., & Kleber, R. J. (2016). Eye movement desensitisation and reprocessing therapy v. stabilisation as usual with refugees:

Randomised controlled trial. *The British Journal of Psychiatry, 209,* 311–318. doi:10.1192/ bjp.bp.115.167775

UN High Commissioner for Refugees (UNHCR) (2015). *UNHCR global report 2015.* Retrieved from http://www.unhcr.org/gr15/index.xml

Van Wyk, S., Schweitzer, R., Brough, M., Vromans, L., & Murray, K. (2012). A longitudinal study of mental health in refugees from Burma: The impact of therapeutic interventions. *The Australian and New Zealand Journal of Psychiatry, 46,* 995–1003. doi:10.1177/0004867412443059

Vink, G., Frank, L. E., Pannekoek, J., & Van Buuren, S. (2014). Predictive mean matching imputation of semicontinuous variables. *Statistica Neerlandica, 68,* 61–90. doi:10.1111/stan.12023

Vink, G., Lazendic, G., & Van Buuren, S. (2015). Partitioned predictive mean matching as a multilevel imputation technique. *Psychological Test and Assessment Modeling, 57*(4), 577–597.

Weathers, F. W., Keane, T. M., & Davidson, J. R. (2001). Clinician-administered PTSD scale: A review of the first ten years of research. *Depression and Anxiety, 13*(3), 132–156.

Chapter 4

The legitimacy of trauma focused psychotherapy in clinical settings: Conveying evidence into practice and practice into evidence for veterans with PTSD

Submitted as:

Haagen, J. F. G., Knipscheer, J. W., & Kleber, R. J. (2017). The legitimacy of trauma focused psychotherapy in clinical settings: Conveying evidence into practice and practice into evidence for veterans with PTSD.

Abstract

Recent evidence questions the superiority of trauma focused over non-trauma focused treatment for veterans with PTSD. The present study compared the effectiveness of trauma focused versus non-trauma focused treatment for veterans with PTSD and examined prior treatment experiences as a negative treatment outcome predictor. Using a prospective multisite cohort design, patients received an assortment of trauma and non-trauma focused interventions. The sample consisted of 79 predominantly male veterans with PTSD. After six months of treatment, 64 (81%) veterans were available for follow-up. Treatment response was measured by posttraumatic reactions symptom reduction with the IES-R. The main analyses consisted of multiple regression and ANOVA analyses, supplemented with effect sizes and reliable change calculations. In terms of significance testing, non-trauma focused treatment was equally effective as trauma focused treatment ($p > .05$). Effect size calculations and reliable change rates, however, favored trauma focused treatment approaches. Non-trauma focused approaches reported minimal to medium treatment effect sizes versus medium to large effect sizes for trauma focused approaches. One-third of the patients receiving non-trauma focused approaches reported reliable clinical worsening during treatment, whereas reliable clinical worsening was almost non-existent for patients receiving trauma focused approaches. Prior PTSD treatment experiences predicted nonresponse ($\beta = -.28$, $p < .05$) highlighting the role of treatment expectancies in therapeutic recovery. These findings appear to favor current PTSD treatment guidelines that recommend trauma focused psychotherapies as a first-choice approach but also highlight the potential role of common factors, such as treatment expectancies, on recovery.

Keywords: PTSD, combat, treatment, prospective, predict, effectiveness.

Acknowledgment contribution authors

Designed research: Haagen, Knipscheer, Kleber

Performed research: Haagen

Analysed data: Haagen

Wrote the paper: Haagen, Knipscheer, Kleber

Introduction

Do the patients that we study in scientific research fit the profile of the patients that we treat in clinical practice? According to Corrigan and Hull (2015), knowledge derived from posttraumatic stress disorder (PTSD) treatment studies does not adequately reflect clinical practice because complex symptom manifestations are largely left outside the scope of research. If research does not reflect clinical practice, it may threaten the generalizability of results and question the validity of guideline recommendations regarding the preferential status of certain empirically-supported PTSD interventions.

All PTSD treatment guidelines base their recommendations on the empirical results of treatment studies (Australian Centre for Posttraumatic Mental Health [ACPMH], 2013; Institute of Medicine [IoM], 2008; International Society for Traumatic Stress Studies [ISTSS], 2009; National Institute for Health and Clinical Excellence [NICE], 2009; The management of post-traumatic stress Working Group [VA-DoD], 2010). The study quality plays an important factor in determining the weight and direction of PTSD treatment recommendations. Evidence from randomized controlled trials (RCT) is considered superior and leading compared to non-randomized controlled trial designs (ACPMH, 2013; IoM, 2008; VA-DoD, 2010). Some PTSD guidelines base their recommendations exclusively on RCT results (IoM, 2008). RCT designs are considered superior because of their ability to reach the highest levels of internal validity and their ability to make causal inferences. To reach such levels of internal validity, RCT designs use randomization methodologies, generally focus on a specific intervention involving a fixed number of sessions, a specific population or pathology, strictly standardized treatment procedures, and rigorously trained clinicians to ensure treatment is delivered as intended with therapist idiosyncrasy minimized (Starcevic, 2003). The use of randomization, in particular, is praised as a methodological approach to minimize selection bias by equalizing the influence of external factors on outcome between comparison conditions (Viera & Bangdiwala, 2007).

RCT studies deliver a fundamental contribution to the field of psychotherapy in separating the wheat from the chaff (i.e., the establishment of empirically-validated interventions). There may not be an alternative design on par with the RCT to reach the highest level of internal validity in psychotherapy research. However, RCT results do not however necessarily match clinical reality because optimal research circumstances do not reflect practical

work circumstances. This concern has been acknowledged by PTSD guidelines (ACPMH, 2013; VA-DoD, 2010).

RCTs tend to impose study restrictions that exclude complicating or severe (comorbid) symptom presentations. A decade ago 30% of all treatment-seeking PTSD patients were excluded from randomized psychotherapy trials (Bradley, Greene, Russ, Dutra, & Westen, 2005). According to these meta-analysis findings, 46% of the patients with a suicide risk, 46% with a dependency, and 62% with a serious comorbidity were excluded from trial participation. A recent meta-analysis demonstrated that exclusion criteria remain a risk for the external validity of RCTs (Leeman et al., 2017). Three-quarters (75%) of the PTSD participants with a substance use disorder were excluded from RCT treatment studies. RCT designs may have progressed during the last decade to be more inclusive, it remains likely that a significant proportion of patients continue to be excluded from RCT studies.

RCT studies are moreover dependent on the willingness of patients to participate, which introduces a volunteer or self-selection bias of motivated patients. Furthermore, restrictions on the number of sessions and duration allow for studying only a short span of the total treatment period. The average PTSD psychotherapy trial lasted three months between pre- and posttreatment (unpublished data Haagen et al., 2015), whilst 80% of the veterans with PTSD are still in treatment after four years of psychotherapy (Congress of the United States, 2012).

RCTs often require stringent standardization and adherence to treatment procedures, which proved to be extremely difficult in - and not corresponding with - clinical practice (Starcevic, 2003). A stringent manualized approach may also interference with self-correcting processes between patients and clinicians (e.g., trying alternative approaches), and clinician spontaneity to enhance treatment outcome (Seligman, 1995).

Last, it is argued that RCT psychotherapy designs do not allow for proper randomization - the most fundamental tool to minimize bias - because blinded randomization is not possible (Starcevic, 2003). Patients and clinicians are aware of the treatment condition in which they partake and may be biased as a result of this knowledge by their (selection) preferences or expectations, despite randomization.

If the empirical evidence does not reflect clinical practice, it may endanger the validity of best-practice guideline recommendations. One such recommendation, the preferential use of trauma focused treatment, has become a key debate issue. Several researchers provided empirical

evidence of its superiority above non-trauma focused interventions (Bisson, Roberts, Andrew, Cooper, & Lewis, 2013; Ehlers et al., 2010; Gerger, Munder, Gemperli et al., 2014). Other researchers, however, demonstrated that PTSD psychotherapies were equally efficacious in promoting recovery through non-specific treatment mechanisms, such as treatment expectancies and therapeutic alliance (Benish, Impel, & Wampold, 2008; Wampold et al., 2010).

In a bid to unite the contrasting evidence regarding the superiority of trauma focused treatment versus non-trauma focused treatment, Gerger, Munder, and Barth (2014) examined patient complexity as a moderator of treatment outcome. Their meta-analysis indicated the superiority of trauma focused therapy for less complicated PTSD patients. Trauma focused treatment, however, proved only slightly superior for more complex psychotrauma populations, including combat veterans. Veterans with PTSD are considered difficult-to-treat. A sizeable proportion (30-50%) does not improve after psychotherapy and veterans benefit less from psychotherapy compared to other PTSD populations (Bradley et al., 2005; Goodson et al., 2011; Steenkamp et al., 2015). Veterans often experienced repeated and interpersonal combat-related traumatic events, manifest a range of complex symptom manifestations that may complicate PTSD treatment or result in RCT study exclusion. An overview of complicating factors has been provided in a meta-analysis by Haagen, Smid, Knipscheer, and Kleber (2015). A recent veteran meta-analysis concluded that trauma and non-trauma focused interventions were equally effective for veterans, though this meta-analysis was hampered by the small number of included studies (Steenkamp, Litz, Hoge, & Marmar, 2015). These outcomes question the legitimacy of current PTSD treatment guidelines that recommend trauma focused therapy above non-trauma focused alternatives for veterans. A legitimacy that is founded on the medical model of psychotherapy that specifies that specific treatment components (such as exposure), produce specific-effects that are responsible for most of the effectiveness of PTSD treatment (Wampold & Impel, 2015, p. 28).

The medical model emphasis the importance of the type of intervention in promoting recovery. Besides examining treatment specific-effects (e.g., a trauma-focus vs. non-trauma-focus), another approach would be to shift that emphasis to address the role of non-specific effects on PTSD treatment outcome to understand what promotes therapeutic recovery. Non-specific effects revolve around common factors present in most psychotherapies (Wampold et al., 2016), and treatment expectancies are considered to be one of the key pillars. Positive

treatment expectancies predicted PTSD treatment improvement (Delsignore & Schnyder, 2007; Price et al., 2015), and may be central to therapeutic recovery (Budge & Wampold, 2015). Treatment expectancies are based on learning experiences (Benedetti, 2008; Colloca & Benedetti, 2006). As such, prior PTSD treatment experiences may be viewed as a failed attempts among treatment-seeking patients that instill negative treatment expectancies for future interventions.

The present study aims to examine the effectiveness of trauma focused (systematic exposure to traumatic memories) versus non-trauma focused-treatment approaches for treatment-seeking veterans with PTSD. It was hypothesized that, in accordance with the medical model of psychotherapy, veterans with PTSD would demonstrate greater symptom improvement for trauma focused approaches compared to non-trauma focused approaches. We also hypothesized that prior treatment experience was a negative treatment outcome predictor. In line with the criticism of Corrigan and Hull (2015) regarding the possible unrepresentativeness of RCTs for clinical practice, the current study examined a cohort of veterans without any study or treatment restrictions. The current study is not meant to substitute results from RCT studies but adds insights based on a study design that promotes the highest levels of external validity. The results may support guideline development in making critical appraisals in their recommendations.

Method

Design

The current study used a prospective observational multisite cohort design. Three Dutch specialized treatment centers participated: Foundation Centre ’45, the Military Mental Healthcare Centre, and the Psychotrauma Centre Zuid-Nederland. The medical-ethical committee of the Utrecht University Medical Centre granted the study exemption from ethical approval because the assessments were part of standard diagnostic procedures, routine outcome monitoring, and because the study did not influence treatment procedures (case number 12-535/C). Patients were informed that their data could be used for scientific purposes and were provided with the opportunity to object, though none did.

Sample

The sample consisted of 79 treatment-seeking veterans (73%) and active duty (27%) soldiers with almost exclusively (96%) diagnostician established combat-related PTSD. The majority served in Afghanistan (37%), Bosnia-Hercegovina (27%), or Lebanon (19%). Over half of the veterans had no prior PTSD treatment experiences (57%). After six months of treatment 64 (81%) patients received a follow-up measure. The remaining 15 (19%) patients were not measured due to (early) successful treatment completion before follow-up (*n* = 5, 6%), premature dropout (*n* = 4, 5%), unwillingness or unavailability for follow-up (*n* = 3, 5%), and reasons unknown (*n* = 3, 4%). Table 1 provides an overview of the sample characteristics and Figure 1 provides a flowchart of the study process.

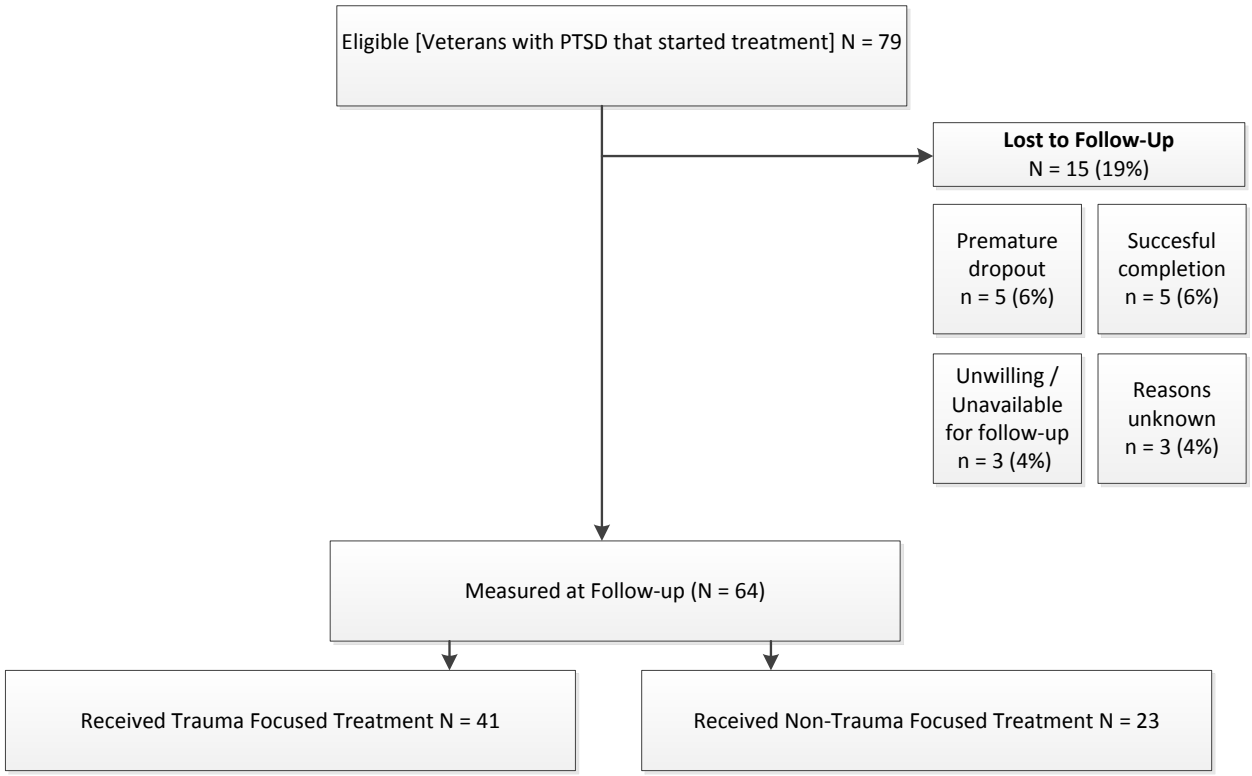

Figure 1. *Participant flowchart*

Treatment

The present study assumed that trauma focused interventions would deliver stronger treatment effects compared to non-trauma focused interventions. Veteran PTSD treatment data were split between trauma focused and non-trauma focused interventions (in accordance with the medical model of psychotherapy hypothesis). Besides the type of therapy, it was assumed that non-specific factors present in all psychotherapies would impact treatment outcome (Wampold, Ahn, & Coleman, 2001). Veteran PTSD treatment data were pooled, irrespective of the specific intervention in accordance with models that emphasize the importance of non-specific effects above the type of therapy (Wampold et al., 2016). The present study took a practical approach to examining mechanisms of change present or absent in a range of individual psychotherapies.

Psychotherapy took place in three different settings (outpatient, day treatment, and inpatient). All psychotherapeutic interventions targeted PTSD or PTSD related pathology. Two-thirds of the 64 patients who received a follow-up (n = 42, 65%) received at least one trauma focused session, with an average of 6.1 trauma focused sessions. Empirically supported trauma focused therapy consisted of either eye movement and reprocessing therapy (EMDR) (Bisson et al., 2013), exposure therapy (Bisson et al., 2013), narrative exposure therapy (Robjant & Fazel, 2010), or brief eclectic psychotherapy for PTSD (Gersons & Schnyder, 2013). Only sessions that reported explicit systematic exposure to traumatic memories in the electronic patient dossiers, and reported a general assessment of functioning (SUD) score at the start and end the exposure session, were considered trauma focused sessions. The remaining one-third (35%) of the sample received non-trauma focused treatment, consisting of cognitive behavioral therapy (without systematic exposure to traumatic memories), eclectic therapy, or patient-centered therapy.

Measures

The Dutch Impact of Event Scale-Revised (IES-R; Kleber & De Jong, 1998; Weiss & Marmar, 1996) measures the psychological impact of traumatic events. Respondents reported how often they experienced symptoms of intrusions, avoidance, and hyperarousal in the past seven days. The 22 items are closely linked to the PTSD symptoms as described in the DSM-IV-TR and rated on a 5-point Likert scale ranging from 0 (*not at all*) to 4 (*extremely*). The sum score ranges from 0-88. The IES-R is considered a psychometrically sound measure for clinical and research

purposes with a 6-month test-retest reliability of .94 (Weiss & Marmar, 1996). The IES-R reliability in the present study was considered excellent (Cronbach's $\alpha = .93$). Demographic and treatment data were collected during the first pre-treatment measurement and after the follow-up measurement (Table 1).

Table 1

Demographic and treatment data

Characteristics		Total sample		TF sample		non-TF sample	
Demographics		*n*(%)	*M*(*SD*)	*n*(%)	*M*(*SD*)	*n*(%)	*M*(*SD*)
Age	Years		40.0(10.3)		39.5(10.2)		40.5(9.9)
Gender	Male	76(96)		40(98)		22(96)	
Educational Level	High school	4(5)		2(5)		2(9)	
	Lower Secondary Education	32(41)		15(37)		9(41)	
	Higher Secondary Education	32(41)		21(51)		6(27)	
	Higher Vocational/Academic	10(13)		3(7)		5(23)	
Marital Status	Married	34(43)		18(44)		11(48)	
	Cohabitating	21(27)		11(27)		7(30)	
	Single	16(20)		8(20)		5(22)	
	Divorced	5(6)		3(7)		0(0)	
Employment Status	Full-time Employed	39(49)		18(44)		13(56)	
	Part-time Employed	1(1)		0(0)		1(4)	
	Disabled	28(35)		19(46)		6(26)	
	Unemployed	10(13)		4(10)		3(13)	
Treatment Centre	Foundation Centre '45	53(67)		28(68)		16(70)	
	Military Mental Health Care Utrecht	17(22)		10(24)		4(17)	
	Psychotrauma Centre Zuid-Nederland	9(11)		3(7)		3(13)	
Comorbid Diagnosis	Major Depressive Disorder	33(42)		17(41)		9(39)	
	Substance Disorder	26(33)		17(41)		5(22)	
	Number of Disorders		1.4(1.4)		1.6(1.5)		1.2(1.1)
Treatment Data (*n* = 64)							
Trauma focused Treatment	Received Trauma focused Treatment	41(64)		41(100)		0(0)	
	Number of Trauma focused Sessions			6.1(4.8)		0(0)	
Prior PTSD treatment experience		26(43)		17(41)		9(39)	
Posttraumatic symptoms severity	IES-R		57.5(15.2)		60.7(14.1)		53.0(14.5)
Treatment Setting	Outpatient	34(53)		22(54)		12(52)	
	Day Treatment	10(16)		2(5)		8(35)	
	Inpatient	18(28)		17(41)		1(4)	
	Combination	2(3)		0(0)		2(9)	

Note: IES-R = Impact of Events Scale Revised. TF = Trauma focused. Total sample *n* = 79; TF sample *n* = 41; non-TF sample *n* = 23.

Procedure

Veterans with a suspected DSM-IV-TR PTSD diagnosis (American Psychiatric Association, 2000) completed the pre-treatment diagnostic assessment that consisted of a set of questionnaires related to psychological problems, coping strategies, and psychopathology symptoms that included PTSD. The measurements were primarily used for diagnostic and treatment evaluation purposes. Patients with a formal DSM-IV-TR PTSD diagnosis, diagnosed by a psychotherapist or psychiatrist, were eligible for a follow-up assessment after six months of psychotherapy. Treatment outcome was measured with self-reported PTSD symptom severity at pre-treatment and follow-up. All data were collected between January 2013 and June 2015.

Statistical analysis

All analyses were performed with SPSS version 22. Independent *t*-tests and cross tabulation comparisons were performed between trauma focused and non-trauma focused participants, and between study completers and those with no follow-up. The main analyses consisted of (hierarchical) regression analyses that examined the effects of the number of trauma focused sessions and prior treatment experience on treatment outcome. All regression analyses controlled for pre-treatment posttraumatic symptom severity, treatment location, treatment setting, and the number of psychotherapy sessions. IES-R change scores were used as the dependent variable. We used SPSS bootstrap (5000 samples) for the regression analyses to compensate for any lack of normality and gain more accurate statistical estimates. Bootstrap estimates the properties of the sample distribution from the sample data and is a more robust method for inferring standard errors, confidence intervals, and significance tests (Field, 2009).

The use of change scores has been criticized as unreliable or prone to bias resulting from regression to the mean, though many objections have been refuted (Allison, 1990; Edwards, 2001). Change scores deliver acceptable and corresponding results to alternative regression methods in most cases (Dalecki & Willits, 1991). The multiple regression analysis controlled for pre-treatment PTSD symptom severity to adjust for possible effects due to the association between pre-post scores and pre-treatment scores (Dalecki & Willits, 1991). To limit any possible shortcomings of change scores we chose not to rely exclusively on change scores and also examined treatment outcome differences using mixed design ANOVAs as an alternative method. Instead of PTSD change scores, pre-treatment and follow-up posttraumatic symptom severity

scores were used as the dependent variables. For the ANOVA comparison analyses, trauma focused treatment was operationalized as having received at least one systematic exposure-based psychotherapy session versus no trauma focused sessions.

Regression and ANOVA analyses are based on statistical significance. Statistical significance is not a direct indicator of the size of the effect, but a function of sample size, effect size and p-level (Ferguson, 2009). Potential non-significant findings may be a power issue requiring large samples and can be misleading. To determine the practical significance of both approaches, the Reliable Change Index (RCI) rates of recovery and treatment effect sizes were calculated. The RCI ascertains the portion of patients who showed a statistical reliable change in posttraumatic reactions symptom severity (IES-R) scores at follow-up. The RCI was calculated using the pre- and posttreatment IES-R severity scores and standard deviations, IES-R test-retest reliability scores ($\alpha = .94$; Weiss & Marmar, 1996), and a 95% confidence interval (Jacobson and Truax, 1991). Whereas "effect sizes are resistant to sample size influence, and thus provide a truer measure of the magnitude of effect between variables" (Ferguson, 2009, p. 532). The ANOVA effect sizes were reported as uncorrected eta squared (η^2) and corrected omega squared (ω^2) effect sizes, according to Lakens (2013). An eta squared and omega squared effect size of .01 was considered small, .06 medium, and .14 large (Field, 2009).

Results

Completers vs. dropouts analyses

The dropout percentages in the present study (19%) matched the PTSD treatment dropout percentages for veterans (18%) and the general population (20%) (Bradley et al., 2005; Imel, Laska, Jakupcak, & Simpson, 2013). There were no significant differences ($p > .05$) between study completers and treatment dropouts in terms of age or posttraumatic severity responses, though there was a trend of higher pre-treatment posttraumatic severity responses for dropouts ($M = 70.2$, $SD = 7.4$ vs. $M = 57.6$, $SD = 14.5$; $t(69) = -1.9$, $p = .06$). Those who successfully completed treatment before follow-up and as a result also dropped out of the study, had lower posttraumatic severity responses compared to study completers ($M = 42.0$, $SD = 19.3$ vs. $M =$

57.6, *SD* = 14.5; *t*(69) = -2.3, *p* = .03). There were no differences between study completers and those unwilling or unavailable for follow-up (*p* > .05).

Trauma focused vs. non-trauma focused interventions

Group Differences. Independent *t*-tests and cross tabulation comparisons revealed no significant (*p* > .05) group differences on the following pretreatment demographic and clinical variables: age, gender, education level, marital and employment status, treatment center, prior PTSD treatment experiences, the presence of a comorbid depressive disorder, substance disorder, or the number of disorders. Independent *t*-tests did reveal near-significantly (*p* = .05) elevated pre-treatment posttraumatic severity responses for veterans that received trauma focused therapy compared to veterans that received non-trauma focused therapy (*M* = 60.7, *SD* = 14.1 vs. *M* = 53.0, *SD* = 14.5). Cross tabulation comparisons revealed that veterans in both conditions were as likely to have received outpatient therapy (54% vs. 52%), veterans that received trauma focused interventions were more likely inpatient patients (41% vs. 4%), whereas non-trauma focused veterans more likely day treatment patients (35% vs. 5%).

Regression and ANOVA Analyses. The number of trauma focused sessions did not predict treatment outcome (β = .10, *p* = .55) while controlling for multiple centre locations and number of psychotherapy sessions. These results indicate that veterans with PTSD benefitted equally from psychotherapy irrespective of the number of trauma focused psychotherapy sessions. The mixed ANOVA analyses confirmed the regression findings (Table 2). There was a medium treatment effect over time for the total sample (ω^2 = .051, *p* = .04), indicating patients on average significantly reduced their posttraumatic symptomatology during therapy. The amount of symptom reduction was similar for those who received trauma focused and those who received non-trauma focused psychotherapy (*p* = .67). Veterans that were treated with non-trauma focused approaches experienced an average symptom decrease from posttraumatic severity responses decreased from M_{pre} = 53.0 (*SD* = 14.5) to M_{post} = 48.5 (*SD* = 21.7). Veterans treated with trauma focused approaches experienced an average posttraumatic symptom decrease of M_{pre} = 60.7 (*SD* = 14.1) to M_{post} = 53.8 (*SD* = 20.8).

Recovery Rates and Effect sizes. According to the RCI calculations, an IES-R change score of 11 points or higher reflected a reliable change. Patients who received non-trauma

focused approaches were more likely to deteriorate (30% vs. 2%), less likely to remain unchanged (39% vs. 71%), and equally likely to achieve improvement (30% vs. 27%), compared to patients who received trauma focused approaches, $\chi^2(2)= 11.8$, $p < .01$.

The effect size of each approach differed. Non-trauma focused approaches demonstrated a small negative treatment effect ($\omega^2 = -.009$). The negative treatment effect is contrary to the reported average posttraumatic severity reduction for non-trauma focused approaches. It is likely the result of the omega squared bias correction method for small sample sizes. The uncorrected eta squared (η^2) effect size, which risks overestimation of the effect size, indicated a small to medium positive treatment effect of .034. Trauma focused treatment approaches reported a medium to large corrected effect size for trauma focused approaches ($\omega^2 = .102$). The uncorrected eta squared η^2 effect size corresponded with a large effect size of .13.

Prior PTSD treatment experiences

Group Differences. Group differences (Table 3) revealed that previously treated patients received considerably more psychotherapy sessions ($M = 35.4$ vs. $M = 16.4$, $p < .001$), were as likely to receive trauma focused treatment ($\chi^2(1)= .00$, $p > .05$), received an equal amount - if not more - trauma focused sessions ($M = 7.0$ vs. 5.2, $p = .22$), and were more likely to receive inpatient treatment (78% vs. 22%) instead of outpatient treatment (19% vs. 81%) compared to first-timers ($\chi^2 = p < .01$). Previously treated PTSD patients had slightly higher average pre-treatment posttraumatic severity responses compared to treatment first timers in the ($M = 59$, $SD = 13$ vs. $M = 56$, $SD = 16$, $p = .03$).

Regression and ANOVA Analyses. Prior PTSD treatment experiences predicted negative treatment outcome ($\beta = -.32$, $p < .05$), indicating that previously treated patients fared worse in therapy. The mixed ANOVA analyses (Table 2; Figure 2) supported the regression findings: previously treated veterans benefitted less from therapy compared to PTSD treatment first timers ($p = .055$). Though the p-value failed to reach significance by a hair, it can be considered an important effect as previously treated patients on average did not respond to therapy ($\omega^2 = -.024$; $M_{pre} = 59$; $M_{post}= 60$), whereas first timers reported medium to large positive treatment effects ($\omega^2 = .122$, $M_{pre} = 56$, $M_{post}= 46$).

Table 2

Mixed design ANOVA: PTSD treatment outcome between and within-subjects

Dependent variable: PTSD	*df*	*Type III*	*MS*	*F*	*p*
Trauma focused (*n* = 64)					
Within-Subjects					
Time	1	956.6	956.6	4.4	.04
Time X Trauma focused	1	40.7	40.7	.19	.67
Error	62	13456.0	217.0		
Between Subjects					
Trauma focused	1	1221.9	1221.9	2.8	.10
Error	62	26841.2	432.9		
Prior Treatment (*n* = 61)					
Within-Subjects					
Time	1	600.2	600.2	3.1	.09
Time X Prior Treatment	1	753.0	753.0	3.8	.06
Error	59	11560.0	195.9		
Between Subjects					
Prior Treatment	1	2162.6	2162.6	5.1	.03
Error	59	24929.1	422.5		

Note: Trauma focused considers 0 exposure sessions versus at least 1 exposure session. Recommended Trauma focused Dose considered 0 exposure sessions, versus one or more exposure

Hierarchical regression model with trauma focused versus non-trauma focused interventions and prior PTSD treatment experiences

To test the previous findings relative to each other, we simultaneously analyzed the predictors in a hierarchical regression model. In step 1 of the model the control variables pre-treatment posttraumatic severity responses, treatment location, setting, and total number of sessions were included, and during step 2 the variables of interest. The final model (Table 4) provided similar outcomes in terms of significance and in the size of effects (regression coefficients) compared to the previous analyses. The number of trauma focused sessions and treatment setting did not

predict treatment outcome ($p > .05$), demonstrating no differences in treatment effect between trauma and non-trauma focused treatment. Prior PTSD treatment experiences continued to be a negative outcome predictor ($\beta = -.28$, $p < .05$). The covariates predicted 28% of the variance whereas the number of trauma focused sessions and prior PTSD treatment experiences predicted an additional 7% of the total explained variance of PTSD treatment outcome. The total explained variance was $R^2 = 35\%$.

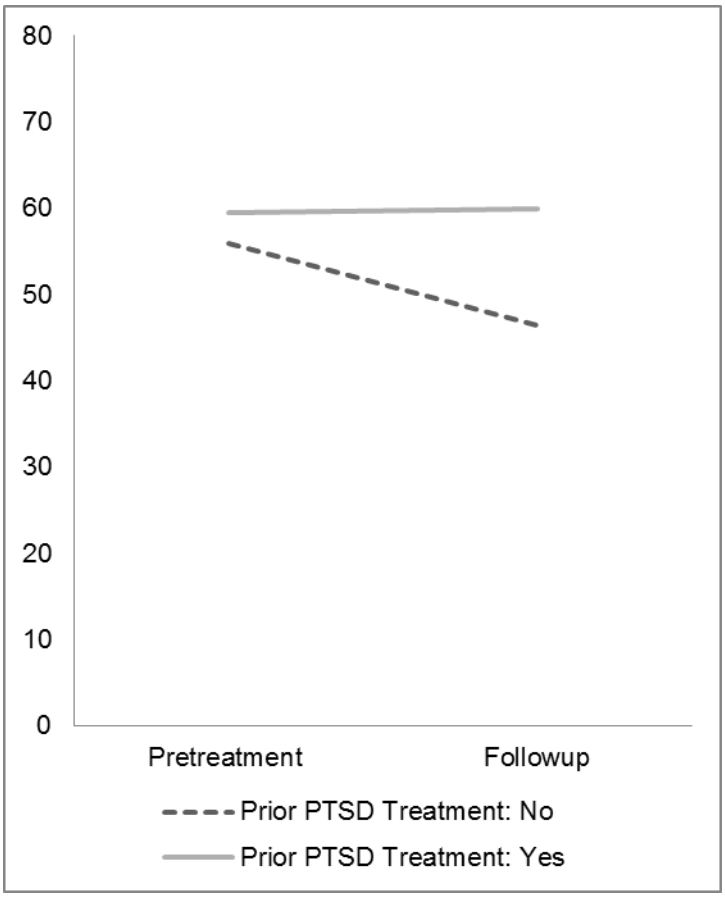

Figure 2. *Treatment outcome based on prior PTSD treatment*

Table 3

Sample characteristics between prior treatment and no prior treatment

		1.No Prior *n* = 35 (57%)	2.Prior PTSD *n* = 26 (43%)	χ^2	*df*	*t*	*p*
Age		40.0(9.7)	40.9(10.2)		59	.35	.73
Number of Sessions		16.4(10.4)	35.4(23.5)		58	3.8	.00
Received TF Treatment		22(65%)	17(65%)	.00	1		.96
Number of TF Sessions*		5.2(4.5)	7.0(4.5)		37	-1.2	.22
Pre-treatment symptom severity	IES-R	59.5(13.2)	56.0(16.3)		59	.93	.36
Comorbidity	Number of Comorbid Disorders	1.1(1.2)	2.0(1.5)		59	2.6	.01
	Major Depressive Disorder (*n*, %)	48%	52%	1.7	1		.19
	Substance Abuse Disorder (*n*, %)	64%	36%	6.0	2		.05
	Substance Dependence Disorder	14%	86%				
Setting	Outpatient (*n*, %)	81%	19%	16.5	2		.00
	Day Treatment (*n*, %)	44%	56%				
	Inpatient (*n*, %)	22%	78%				

Note. p = two-tailed. One patient was excluded from the *t*-test analysis on Number of sessions due to missing data. Two patients were excluded from the setting cross tab analysis because they received treatment in multiple settings. *Number of trauma focused (TF) Sessions only considered patients that received a trauma focused approach.

Table 4

Hierarchical multiple regression analysis predicting PTSD treatment outcome between pre-treatment and follow-up

Predictor		B(SE)	CI(B)	β	F	ΔR^2
Step 1					4.0**	28%
	Location A	-15.9(8.0)	[-32.1, -.47]	-.31		
	Location B	-23.2(8.0)	[-38,0, -7.1]	-.39**		
	Total Sessions	-.34(.17)	[-.65, .02]	-.35*		
	Setting	-4.7(5.9)	[-16.8, 6.9]	-.11		
	PTSD Severity	.59(.18)	[.25, .97]	.45**		
Step 2					3.9**	7%
	TF Sessions	.63(.54)	[-.35, 1.8]	.15		
	Prior Treatment	-10.8(5.3)	[-22.7, -1.8]	-.28*		
Total R^2	35%**					
n	57					

Note. Four patients were excluded due to missing data on prior PTSD treatment predictor and two patients that received treatment both in- and outpatient setting. Bootstrapping was used to estimate the SE, CI, and significant tests. Location A and B are dummy variables for treatment locations, Setting is a dummy variable for outpatient (score 0) or inpatient (score 1). Total Sessions = The total number of psychotherapy sessions received. PTSD Severity = Pre-treatment posttraumatic symptom severity. TF Sessions = The total number of trauma focused sessions received. Prior Treatment is a dummy variable of no prior PTSD treatment received (score 0) or prior treatment received (score 1). * $p < .05$. ** $p < .01$.

Discussion

The present study investigated the effectiveness of trauma focused treatment approaches compared to non-trauma focused treatment approaches for veterans with PTSD. Both approaches proved equally effective in reducing posttraumatic stress reactions in terms of significance testing. A closer inspection, however, displayed differences between both approaches. Trauma

focused approaches demonstrated a larger treatment effect size and less reliable symptom worsening. Also, prior PTSD treatment experiences was a negative treatment outcome predictor.

Eligibility of trauma focused treatment

In terms of significance testing, both trauma focused and non-trauma focused approaches were equally effective. However, the required numbers to detect a small treatment superiority effect between trauma focused and non-trauma focused approaches with a power of .80 and significance criterion of .05 would require a sample size of at least 394 persons. Such large numbers were beyond the scope of the present study, as well as 90% of all existing guideline recommended veteran PTSD treatment studies (see Haagen et al., 2015, Appendix B). Significance testing alone may not always be the most informative factor to guide clinical practice. (RCI) Recovery rates and treatment effect sizes were investigated as alternative sources of information less depended on sample size (Ferguson, 2009).

Effect sizes demonstrated a minimal to medium treatment effect size for non-trauma focused approaches and a medium to large treatment effect size for trauma focused approaches (depending on the effect size correction method). The difference in treatment effect appeared to be related to a greater reliable symptom exacerbation (30%) in non-trauma focused interventions, compared to trauma focused interventions (2%). As such, the present findings correspond with PTSD treatment guideline recommendations that favor the first choice use of trauma focused interventions to target PTSD. Treatment specific factors appear to contribute to better treatment outcomes for PTSD patients in accordance with the medical model.

Prior PTSD treatment experiences

The present results also found indications that may support the common factors model that assume that non-specific factors present in all psychotherapies promote improvement (Wampold, Ahn, & Coleman, 2001). Prior PTSD treatment experiences had a stronger and significant detrimental effect on treatment outcome. Prior PTSD treatment experiences may represent negative learning experiences (treatment failures) that strongly influence future treatment expectancies (Benedetti, 2008; Colloca & Benedetti, 2006). Previous studies reported a modest significant relationship between treatment outcome expectancies and subsequent treatment improvement for a range of disorders—including PTSD among veterans (Benedetti, 2008;

Delsignore & Schnyder, 2007; Price et al., 2015). Patients with prior treatment failures may envisage treatment success as more difficult to obtain, have less faith in their own efficacy, are more likely to avoid and less likely to engage in and persist with treatment-related tasks, diminishing their chances of recovery (Bandura, 1977; Delsignore & Schnyder, 2007).

Patients with prior PTSD treatment experiences were more likely to fulfill the DSM-IV-TR diagnosis of dependent substance disorder, experienced on average one additional comorbid disorder, and were more likely to receive inpatient treatment. These factors might also explain poor outcome results for treatment-experienced patients. Though there are also meta-analytic findings that demonstrate that comorbidities, such as substance use disorders, do not impede PTSD treatment outcome (Leeman et al., 2017). Patients in inpatient settings showed less therapeutic recovery despite a much higher psychotherapy session frequency. More intense treatment may not necessarily translate to additional benefits in terms of treatment outcome.

Strengths and limitations

The virtue of the present study is realism. The focus was on the extent to which interventions produce outcomes under ordinary day-to-day circumstances and not on the extent to which interventions produce beneficial results under ideal conditions. This is difficult if not impossible to achieve in controlled studies (Hollon, 1996; Seligman, 1996). The study reflected patient and treatment conditions in real-world practice to allow for the detection of potential treatment outcome covariates that have not been screened out by patient or study restrictions and may offer more generalizable findings (Wise, 2011). To our knowledge, this is the first study to examine prior PTSD treatment experiences as a predictor of PTSD treatment outcome. We also used ANOVAs to strengthen the regression outcome results.

The current study has a number of limitations. The lack of significance may be the result of an underpowered design, we addressed this issue by providing detailed information regarding effect sizes and recovery rates. The present cohort study design emphasized external validity over internal validity. Cohort designs are less suited to eliminate unmeasured factors that could influence the results, such as medication use. Inpatient and day patient treatment programs provided weekly group sociotherapy and creative therapy, besides psychotherapy. These approaches target PTSD (related-problems) in alternative ways but were not studied in the present study because psychotherapy was considered the recommended and most effective

method for treating PTSD (Watts et al., 2013). The six months treatment time frame may be considered short, however veteran PTSD treatment studies examine, on average, three months of therapy between pre- and posttreatment (unpublished data Haagen et al., 2015). The present study doubles that timeframe. The use of only two measurement moments limited our understanding of changes over time. We did not measure whether previous prior PTSD treatment experiences were positive or negative experiences; it was assumed to indicate a negative experiences as a result of treatment failure or relapse. The common-factors assumption that interventions within each approach are equivalent in terms of their effectiveness could not be tested due to sample size limitations. Finally, our results describe predominately male veterans with PTSD and may not be generalizable to female veterans.

Implications

Whether treatment works under tightly controlled conditions is a different question than whether it works in general practice. For that reason, Seligman (1995) made the important distinction between effectiveness and efficacy studies. If researchers hope to convince clinicians to use recommended treatments, they need to demonstrate their superiority to what clinicians are already doing in practice (Bradley et al., 2005).

The present practice-based results support the preferential status of trauma focused psychotherapies for veterans with PTSD. Trauma focused and non-trauma focused approaches were equally successful in promoting reliable improvement. Trauma focused approaches may, however, be preferred because they prevent clinical worsening of PTSD symptomatology, rather than increasing the odds of recovery. These findings are supported by previous meta-analytic findings that prolonged exposure therapies did not cause symptom exacerbation among female assault survivors with PTSD (Jayawickreme et al., 2014). Whereas one-fifth of the patients in the present study that participated in non-trauma focused approaches displayed reliable symptom worsening. These findings seem counterintuitive to fears of clinicians that exposure-based therapies may promote symptom exacerbation (Van Minnen, Hendriks, & Olff, 2010). Withholding exposure-based interventions in favor of non-exposure-based interventions out of fear for symptom exacerbation may actually conflict with the abiding ethical principle of *primum non nocere* (first, do no harm). Nevertheless, these findings should not encourage a stringent predisposition among clinicians for trauma focused therapy. They underline a shared decision

process regarding the choice of each treatment approach to enable patients to balance out their expectancies and preferences against the pros and cons of each approach in an informed manner.

Prior PTSD treatment experiences was a practical indicator of treatment nonresponse, which may be explained by negative patient treatment expectancies. According to the common factors model, treatment expectancies are considered crucial in promoting therapeutic improvement (Kirsch, Wampold, & Kelley, 2015). Clinicians are encouraged to investigate whether prior PTSD treatment experiences reflect negative patient treatment expectancies. If prior PTSD treatment experiences prove to be an accurate reflection of treatment negative expectancies, clinicians may want to address the effects of negative expectancies by delivering a credible treatment rationale and instilling realistic hope-inspiring expectancies (Budge & Wampold, 2015; Constantino, Arnkoff, Glass, Ametrano, & Smith, 2011). This might require clinicians to reflect on their own verbal suggestions and their beliefs in and ability to effectively deliver a specific treatment. To improve treatment outcome, clinicians may consider periodic expectancy assessments to nurture positive expectancies and realign patient and clinician expectancies with time-varying treatment goals.

Conclusion

The present study attempted to capture the natural variation in treatment response among veterans with PTSD in clinical practice. Trauma focused psychotherapies were not superior to non-trauma focused psychotherapies based on significance testing. However, effect size calculations and reliable change observations indicated that trauma focused treatment approaches were superior to non-trauma focused approaches in improving PTSD treatment outcome and avoiding reliable symptom exacerbation. Furthermore, veterans with prior PTSD treatment experiences appeared especially at risk of nonresponse. This may be attributable to negative learning experiences that hamper patient treatment outcome expectancies. The overall findings suggest that it may be beneficial to direct attention to both *specific factors* (trauma focused approaches) and *common factors* (e.g., treatment expectancies), to guide the choice of treatment and improve the effectiveness of existing interventions.

Acknowledgements

We thank Foundation Centre ’45 [Stichting Centrum ‘45], The Military Mental Health Care [Militaire Geestelijke Gezondheidszorg], and Psychotrauma Centre South-Netherlands [Psychotrauma Centrum Zuid-Nederland, onderdeel van Reinier van Arkel Groep] for their participation. We are grateful to the Dutch National Health System for Veterans [Landelijk Zorgsysteem voor Veteranen] that spearheaded the development and implementation of a comprehensive uniform diagnostic set and for providing their support to the present project. We express our gratitude to Dr. Niels van der Aa for his statistical advice.

References

Allison, P. D. (1990). Change scores as dependent variables in regression analysis. *Sociological Methodology, 20,* 93-114.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: Author.

Australian Centre for Posttraumatic Mental Health. (2013). *Australian guidelines for the treatment of adults with acute stress disorder and posttraumatic stress disorder*. Melbourne, Victoria: ACPMH.

Bandura, A. (1977). Self-efficacy: Toward a unifying theory of behavioral change. *Psychological Review, 84*(2), 191-215.

Barlow, D. H., Bullis, J. R., Comer, J. S., & Ametaj, A. A. (2013). Evidence-based psychological treatments: An update and a way forward. *Annual Review of Clinical Psychology, 9,* 1-27. doi:10.1146/annurev-clinpsy-050212-185629

Benedetti, F. (2008). Mechanism of placebo and placebo-related effects across diseases and treatments. *Annual Review of Pharmacology and Toxicology, 48*, 33-60. doi:10.1146/annurev.pharmtox.48.113006.094711

Benish, S., Imel, Z., & Wampold, B. (2008). The relative efficacy of bona fide psychotherapies for treating post-traumatic stress disorder: A meta-analysis of direct comparisons. *Clinical Psychology Review, 28*, 746-758 doi:10.1016/j.cpr.2007.10.005

Bisson, J. I., Roberts, N. P., Andrew, M., Cooper, R., & Lewis, C. (2013). Psychological therapies for chronic post-traumatic stress disorder (PTSD) in adults. *Cochrane Database of Systematic Reviews, 12,* 1-241. doi:10.1002/14651858.CD003388.pub4.

Bradley, R., Greene, J., Russ, E., Dutra, L., & Westen, D. (2005). A multidimensional meta-analysis of psychotherapy for PTSD. *American Journal of Psychiatry, 162*(2), 214-227.

Budge, S. L., & Wampold, B. E. (2015). *The relationship: How it works.* In O. Gelo, A. Pritz, & B. Rieken (Eds.), *Psychotherapy research: Foundations, process, and outcome* (pp. 213-228). New York: Springer.

Congress of the United States (2012). *The Veterans Health Administration's treatment of PTSD and traumatic brain injury among recent combat veterans.* Congressional Budget Office.

Colloca, L. & Benedetti, F. (2006). How prior experience shapes placebo analgesia. Pain, 124, 126-133. doi:10.1016/j.pain.2006.04.005

Constantino, M. J., Arnkoff, D. B., Glass, C. R., Ametrano, R. M., & Smith, J. Z. (2011). Expectations. *Journal of Clinical Psychology, 67,* 184-192. doi:10.1002/jclp.20754

Corrigan F. M., & Hull, A. M. (2015). Neglect of the complex: Why psychotherapy for post-traumatic clinical presentations is often ineffective. *The British Journal of Psychiatry, 39,* 86-89. doi:10.1192/pb.bp.114.046995

Dalecki, M., & Willits, F. K. (1991). Examining change using regression analysis: Three approaches compared. *Sociological Spectrum: Mid-South Sociological Association, 11,* 127-145. doi:10.1080/02732173.1991.9981960

Delsignore, A., & Schnyder, U. (2007). Control expectancies as predictors of psychotherapy outcome: A systematic review. *British Journal of Clinical Psychology, 46,* 467-483. doi:10.1348/014466507X226953

Edwards, J. R. (2001). Ten difference score myths. *Organizational Research Methods, 4*(3), 265-287.

Ehlers, A., Bisson, J., Clark, D., Creamer, M., Pilling, S., Richards, D., … Yule, W. (2010). Do all psychological treatments really work the same in posttraumatic stress disorder? *Clinical Psychology Review, 30*, 269-276. doi:10.1016/j.cpr.2009.12.001

Ferguson, C. J. (2009). An effect size primer: A guide for clinicians and researchers. *Professional Psychology: Research and Practice, 40*, 532-538. doi:10.1037/a0015808

Field, A. (2009). *Discovering statistics using SPSS* (3rd ed.). London: Sage Publications.

Gerger, H., Munder, T., & Barth, J. (2014). Specific and nonspecific psychological interventions for PTSD symptoms: A meta-analysis with problem complexity as moderator. *Journal of Clinical Psychology, 70*, 601-615. doi:10.1002/jclp.22059

Gerger, H., Munder, T., Gemperli, A., Nüesch, E., Trelle, S., Jüni, P., & Barth, J. (2014). Integrating fragmented evidence by network meta-analysis: Relative effectiveness of psychological interventions for adults with post-traumatic stress disorder. *Psychological Medicine, 44*, 3151-3164. doi:10.1017/S0033291714000853.

Gersons, B. P. R., & Schnyder, U. (2013). Learning from traumatic experiences with brief eclectic psychotherapy for PTSD. *European Journal of Psychotraumatology, 4*, 10.3402/ejpt.v4i0.21369. http://doi.org/10.3402/ejpt.v4i0.21369

Goodson, J., Helstrom, A., Halpern, J. M., Ferenschak, M. P., Gillihan, S. J., & Powers, M. B. (2011). Treatment of posttraumatic stress disorder in U.S. combat veterans: A meta-analytic review. *Psychological Reports, 2,* 573-599. doi:10.2466/02.09.15.16.PR0.109.5.573-599

Haagen, J. F. G., Smid, G. E., Knipscheer, J. W., & Kleber, R. J. (2015). The efficacy of recommended treatments for veterans with PTSD: A metaregression analysis. *Clinical Psychology Review, 40,* 184-194. doi:10.1016/j.cpr.2015.06.008

Hollon, S. D. (1996). The efficacy and effectiveness of psychotherapy relative to medications. *American Psychologist, 51*(10), 1025-1030.

Imel, Z. E., Laska, K., Jakupcak, M., & Simpson, T. L. (2013). Meta-analysis of dropout in treatments for posttraumatic stress disorder. *Journal of Consulting and Clinical Psychology, 81*, 394-404. doi:10.1037/a0031474

Institute of Medicine. (2008). *Treatment of posttraumatic stress disorder: An assessment of the evidence.* Washington, DC: The National Academies Press.

International Society for Traumatic Stress Studies. (2009). *Effective treatments for PTSD: Practice guidelines from the International Society for Traumatic Stress Studies.* New York: Guilford Press.

Jacobson, N. S., & Truax, P. (1991). Clinical significance: A statistical approach to defining meaningful change in psychotherapy research. *Journal of Consulting and Clinical Psychology, 59*(1), 12-19. http://dx.doi.org/10.1037/0022-006X.59.1.12

Jayawickreme, N., Cahill, S. P., Riggs, D. S., Rauch, S. A., Resick, P. A., Rothbaum, B. O., & Foa, E. B. (2014). Primum non nocere (first do no harm): Symptom worsening and improvement in female assault victims after prolonged exposure for PTSD. *Depression and Anxiety, 31,* 412-419. doi:10.1002/da.22225

Kirsch, I., Wampold, B., Kelley, J. M. (2015). Controlling for the placebo effect in psychotherapy: Noble quest or tilting at windmills? *Psychology of Consciousness: Theory, Research, and Practice,* no pagination specified. doi:10.1037/cns0000065

Kleber, R. J., & De Jong, E. (1998). D*utch version of the Impact of Event Scale-Revised. Internal report.* Utrecht: Department of Clinical Psychology, Utrecht University.

Lakens, D. (2013). Calculating and reporting effect sizes to facilitate cumulative science: A practical primer for t-tests and ANOVAs. *Frontiers in Psychology, 4*, 863. doi:10.3389/fpsyg.2013.00863.

Leeman, R. F., Hefner, K., Frohe, T., Murray, A., Rosenheck, R. A., Watts, B. V., & Sofuoglu, M. (2017). Exclusion of participants based on substance use status: Findings from randomized controlled trials of treatments for PTSD. *Behaviour Research and Therapy, 89*, 33-40. http://dx.doi.org/10.1016/j.brat.2016.10.006

National Institute for Health and Clinical Excellence (NICE). (2009). *The guidelines manual.* London: NICE.

Price, M., Maples, J. L., Jovanovic, T., Norrholm, S.D., Heekin, M., & Rothbaum, B. O. (2015). An investigation of outcome expectancies as a predictor of treatment response for combat veterans with PTSD: Comparison of clinician, self-report, and biological measures. *Depression and Anxiety, 32*, 392-399. doi:10.1002/da.22354

Robjant, K., & Fazel, M. (2010). The emerging evidence for Narrative Exposure Therapy: A review. *Clinical Psychology Review, 30,* 1030-1039. doi:10.1016/j.cpr.2010.07.004.

Seligman, M. E. P. (1995). The effectiveness of psychotherapy. *American Psychologist, 50*(12), 965-974.

Seligman, M. E. P. (1996). Science as an ally of practice. *American Psychologist, 51*(10), 1072-1079.

Smith, M. L., & Glass, G. V. (1977). Meta-analysis of psychotherapy outcome studies. *American Psychologist, 32*(9), 752.

Starcevic, V. (2003). Psychotherapy in the era of evidence-based medicine. *Australasian Psychiatry, 11*(3),278-281.

Steenkamp, M. M., Litz, B. T., Hoge, C. W., & Marmar, C. R. (2015). Psychotherapy for military-related PTSD: A review of randomized clinical trials. *JAMA, 314*, 489-500. doi:10.1001/jama.2015.8370

The management of post-traumatic stress Working Group, (2010). *VA/DoD clinical practice guideline for management of post-traumatic stress. Update of 2004 guideline.* Department of Veterans Affairs, Department of Defense.

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*, 312-320. doi:10.1016/j.brat.2009.12.003.

Viera, A. J., & Bangdiwala, S. I. (2007). Eliminating bias in randomized controlled trials: Importance of allocation concealment and masking. *Family Medicine, 39*(2), 132-137.

Wampold, B. E., Ahn, H-n., & Coleman, H. L. K. (2001). Medical model as metaphor: Old habits die hard. *Journal of Counseling Psychology, 48*(3), 268-273.

Wampold, B. E., Imel, Z. E., Laska, K. M., Benish, S., Miller, S. D., Flückiger, C., … Budge, S. (2010). Determining what works in the treatment of PTSD. *Clinical Psychology Review, 30*, 923-933. doi:10.1002/jclp.20683

Wampold, B. E., Frost, N. D., & Yulish, N. E. (2016). Placebo Effects in Psychotherapy: A flawed concept and a contorted history. *Psychology of Consciousness: Theory, Research, and Practice, 3*, 108-120. doi:10.1037/cns0000045

Watts, B. V., Schnurr, P. P., Mayo, L., Young-Xu, Y., Weeks, W. B., & Friedman, M. J. (2013). Meta-analysis of the efficacy of treatments for posttraumatic stress disorder. *Journal of Clinical Psychiatry, 74*, 541-550. doi:10.4088/JCP.12r08225.

Weiss, D. S., & Marmar, C. R. (1996). The Impact of Event Scale-Revised. In J. Wilson & T. M. Keane (Eds.), *Assessing psychological trauma and PTSD* (pp. 399-411). New York, NY: Guilford Press.

Wise, E. A. (2011). Statistical significance testing and clinical effectiveness studies. *Psychotherapy, 48*, 225-228. doi:10.1037/a0022701

Chapter 5

The dissociative PTSD subtype:

A treatment outcome cohort study in veterans with PTSD

Submitted as:

Haagen, J. F., van Rijn, A., Knipscheer, J. W., van der Aa, N., & Kleber, R. J. (2017). The dissociative PTSD subtype: A treatment outcome cohort study in veterans with PTSD.

Abstract

Dissociation is a prevalent and problematic occurrence among veterans with PTSD that may interfere with the effectiveness of treatment. The present study aimed to replicate findings of a dissociative PTSD subtype, to identify corresponding unique avoidant coping and symptom and severity patterns, and its impact on posttraumatic symptom improvement. Latent Profile Analysis (LPA) was applied to baseline data from 330 predominantly (97%) male treatment-seeking veterans (mean age 39.5 years) with a probable PTSD. Multinomial logistic models were used to identify predictors of dissociative PTSD. Eighty veterans with PTSD that commenced with psychotherapy were invited for a follow-up measure after six months. The majority (n = 64, 80% response rate) completed the follow-up measure. Changes in posttraumatic stress reactions severity scores between baseline and follow-up were explored as a continuous distal outcome. LPA revealed four distinct patient profiles: 'low' (12.9%), 'moderate' (33.2%), 'severe' (45.1%), and 'dissociative' (8.8%) PTSD. The dissociative PTSD profile was characterised by more severe pathology levels, though not posttraumatic reactions symptom severity. Veterans in the dissociative PTSD subtype showed the same degree of benefit from PTSD treatment as non-dissociative veterans with similar severity levels. Within a sample of veterans with PTSD, a subsample of severely dissociative veterans was identified, characterized by elevated severity levels on pathology dimensions. Dissociative PTSD does not appear to negatively impact PTSD treatment.

Acknowledgment contribution authors

Designed research: Haagen, van Rijn, Knipscheer, van der Aa, Kleber

Performed research: Haagen, van Rijn

Analysed data: Haagen, van der Aa

Wrote the paper: Haagen, van Rijn, Knipscheer, van der Aa, Kleber

Introduction

Posttraumatic stress disorder (PTSD) is a psychological disorder that may occur after experiencing a traumatic event (American Psychiatric Association [APA], 2013). Its core features are involuntary re-experiencing and persistent avoidance of traumatic content, negative alterations in cognitions, and symptoms of arousal and reactivity. The disorder evokes severe distress and functional impairment. With the recent inclusion of a dissociative PTSD subtype in the DSM-5 (APA, 2013), the empirical indications of a subsample of patients with PTSD that suffer from severe dissociation (Armour, Elklit, Lauterbach, & Elhai, 2014a; Armour, Karstoft, & Richardson, 2014b; Blevins, Weathers, & Witte, 2014; Frewen, Brown, Steuwe, & Lanius, 2015; Stein et al., 2013; Steuwe, Lanius, Frewen, 2012; Tsai, Armour, Southwick, & Pietrzak, 2015; Waelde, Silvern, & Fairbank, 2005; Wolf, Lunney et al., 2012; Wolf, Miller et al., 2012) were acknowledged as well as the existence of a subsample of patients at conceivable risk of treatment stagnation (Spiegel et al., 2013). Researchers and clinicians consider dissociation a potential indicator of poor PTSD treatment outcome (Becker, Zayfert, & Anderson, 2004; Hansen, Ross, & Armour, 2017), and current treatment manuals contemplate its possible adverse treatment effects (Briere & Scott, 2015). The present study presents empirical evidence of these claims in a sample of veterans with PTSD.

Conceptualization of dissociation

The concept of dissociation lacks a precise and generally accepted definition, with different conceptualizations highlighting different phenomena and processes (Giesbrecht, Lynn, Lilienfeld & Merckelbach, 2008). Dissociation has been defined as "a disruption in the usually integrated function of consciousness, memory, identity, or perception of the environment." (DSM–IV–TR; APA, 2000, p. 519). These disruptions are divided into psychoform and somatoform types that can be either pathological or non-pathological. Psychoform dissociation involves disruptions in the integration and perception of cognition, affect, memory, identity, and behaviour. Somatoform dissociation involves disruptions in the integration and perception of bodily functions, sensations, and movement (Pullin, Webster, & Hanstock, 2014).

Non-pathological dissociation is common in the general population (Ross, Joshi, & Currie, 1990). It relates to tendencies to become immersed in an activity and losing focus on

one's surroundings (Waller, Putman, & Carlson, 1996). Pathological dissociation is primarily split between two distinct phenomena, amnesia and depersonalization/derealization (Stockdale, Gridley, Balogh, & Holtgraves, 2002; Waller et al., 1996). *Amnesia* refers to the inability to recall and direct normally conscious and accessible memories (Van der Hart, Nijenhuis, & Steele, 2005). *Derealization/depersonalization* represent a state of consciousness detached from one's everyday experience of one's self or the world (Holmes et al., 2005). It includes out-of-body experiences, feeling unreal, and in a dreamlike state.

PTSD and dissociation

Dissociative and posttraumatic stress symptoms appear highly correlated (Murhpy, Elklit, Murphy, Hyland, & Sevlin, 2017). Dalenberg and Carlson (2012) provided a detailed synopsis of models that explain the relationship between PTSD and dissociation. The component model and subtype model garnered the most empirical support. Both view dissociation as a component of the traumatic response and part of re-experiencing and avoidance symptoms. The subtype model differs with respect that it assumes that dissociative PTSD would display markedly different patterns of PTSD symptom severity, clinical characteristics, or comorbid symptom presentations.

Another prominent model that describes the relationship between dissociation and PTSD is the trauma/avoidance model (Duta & Wolf, 2017). It is mostly associated with symptoms of derealization/depersonalization, corresponding with the DSM-5 conceptualization of the dissociative PTSD subtype. The model considers dissociation an avoidant coping strategy that shifts attention from traumatic memories to safeguard against overwhelming traumatic emotions. This view is supported by cognitive experimental research, demonstrating that dissociative persons consciously avoid traumatic memories using improved attention redirection strategies compared to non-dissociative patients (Chiu, Yei-Yu, Yang-Ming, Yin-Chang, & Yi-Chieh, 2009; Chiu et al., 2016; DePrince & Freyd, 1999; De Ruiter, Phaf, Veltman, Kok, & Van Dyck, 2003).

Dissociation and PTSD treatment

Dissociation has been identified as a problematic occurrence among veterans with PTSD (Kulkarni, Porter, & Rauch, 2012). A naturalistic UK veteran treatment study found baseline dissociation severity to predict negative PTSD treatment outcome (Murphy & Busuttil, 2015).

These predictive effects, however, dissipated after controlling for baseline PTSD symptom severity. Wolf, Lunney and Schnurr (2016) reported a small negative treatment effect for female veterans. The limited number of studies that examined treatment outcome for veterans with dissociative PTSD, paired with reports that dissociation may interfere with PTSD treatment outcome (Hansen et al., 2017), warrants a further investigation regarding its potential negative treatment effect (e.g., Bae, Kim, & Park, 2016).

The present study aimed to replicate DSM-5 dissociative PTSD subtype profile, identify factors that predicted membership to the subtype, and evaluate its impact on PTSD treatment in a Dutch veteran sample. We hypothesized that a dissociative PTSD profile would be characterized by distinguishable clinical features in accordance with the subtype model (Dalenberg & Carlson, 2012), and an increased use of avoidant coping strategies in accordance with the trauma/avoidance model (Duta & Wolf, 2017). Age was examined as a predictor of profile membership because older age was significantly associated with the dissociative PTSD subtype for veterans (Wolf et al., 2015). Finally, it was hypothesized that veterans with a dissociative PTSD profile would report less improvement compared to non-dissociative profiles.

Methods

Design

The present study consisted of a prospective multisite longitudinal cohort design with a pre-treatment diagnostic assessment and a routine outcome assessment after six months of PTSD psychotherapy. Four Dutch specialized psychotrauma centres participated in the study: Foundation Centre ’45, the Military Mental Healthcare Centre, the Psychotrauma Centre Zuid-Nederland Reinier van Arkel Groep, and top-reference trauma centre GGZ-Drenthe.

Procedure and participants

Treatment-seeking veterans with suspected deployment-related pathology were diagnosed by a qualified psychologist or psychiatrist regarding Axis I and II disorders (APA, 2000), and completed a baseline (pre-treatment) assessment. Between January 2013 and June 2015, 330 treatment-seeking veterans received the baseline assessment. Veterans with PTSD that

commenced psychotherapy were invited for a follow-up assessment to reassess posttraumatic reactions symptom severity levels. The sample consisted almost exclusively of male veterans (97.0%), mean aged 39.5 years, and most (80.6%) formally diagnosed with DSM-IV-TR PTSD (APA, 2000). Eighty veterans commenced psychotherapy with 64 participating in the follow-up measure, indicating an 80.0% response rate. The majority served in Afghanistan (37%), Bosnia-Hercegovina (27%), or Lebanon (19%). Their traumatic experiences were categorized during intake. Almost every veteran that commenced treatment (96.3%) experienced combat-related traumatic events, such as having killed, being shot at, sustaining injuries, losing colleagues, or witnessing extreme suffering. Table 1 provides an overview of all baseline and follow-up sample characteristics, and Figure 1 a study flowchart.

Treatment was provided according to standard clinical care and took place in outpatient, day treatment, and inpatient settings. Patients received either trauma focused interventions (e.g., eye movement desensitization reprocessing, narrative exposure therapy), or non-trauma focused PTSD interventions. The medical-ethical committee of the Utrecht University Medical Centre granted the study exemption of ethical approval (case number 12-535/C) because the assessments were part of standard procedures and did not influence treatment procedures.

Table 1

Demographic and clinical data of the baseline (n = 330-208) and follow-up (n = 64) samples

Characteristics		*Baseline Measures* *n*	Baseline Sample *n* (%)	Follow-up Sample *n* (%)	χ^2	*df*	*p*
Demographics							
Age, Mean (SD)	in Years	325	39.5(9.2)	39.8(10.1)			
Gender	Male	330	320(97.0)	62(96.9)			
Educational Level	Lower Education	276	118(42.7)	29(45.4)			
	Higher Education	276	126(45.7)	26(40.6)			
	Higher Vocational/Academic	276	32(9.7)	8(12.5)			
Marital Status	Married/Cohabitating	301	204(67.8)	47(73.5)			
	Single	301	50(16.6)	13(20.3)			
	Divorced/Widow	301	42(20.0)	3(4.7)			
Employment Status	Employed	265	126(47.5)	31(48.5)			
	Disabled	265	93(35.1)	25(39.1)			
	Unemployed	265	33(12.5)	8(12.5)			
	Other	265	13(5.0)	0(0.0)			
Treatment Centre	Centre 1	330	82(24.8)	42(65.6)			
	Centre 2	330	68(20.6)	14(21.9)			
	Centre 3	330	58(17.6)	8(12.5)			
	Centre 4	330	122(37.0)	0(0.0)			
Diagnosis	PTSD	325	262(80.6)	64(100.0)	14.8	1	.00
	Major Depressive Disorder	208	79(38.0%)	26(40.6)			
	Substance use Disorder	208	54(26.0%)	15(23.4)			
Questionnaires	*Instrument*	*n*	*M(SD)*	*M(SD)*	*t*	*df*	*p*
PTSD	IES-R	275	52.8(17.3)	58.8(12.7)	3.2	337	.002
Psychoform Dissociation	DES-II	329	24.5(15.0)	27.9(17.6)			
Somatoform Dissociation	SDQ-20	327	28.9(7.6)	29.6(8.8)			
Avoidant Coping	UCL	327	18.0(3.9)	18.56(3.8)			
Agoraphobia	SCL-90-R	328	17.6(7.2)	19.0(7.2)			
Anxiety	SCL-90-R	328	27.8(8.6)	29.5(8.1)			
Depression	SCL-90-R	327	45.6(12.5)	49.9(12.0)	2.5	389	.02
Somatisation	SCL-90-R	327	28.9(9.7)	31.1(9.6)			
Cognitive performance deficits	SCL-90-R	328	26.6(7.2)	29.1(7.7)	2.4	390	.02
Interpersonal sensitivity	SCL-90-R	327	44.0(13.8)	45.7(13.5)			
Hostility	SCL-90-R	328	16.0(5.8)	17.8(5.9)	2.2	390	.03
Sleep difficulties	SCL-90-R	327	10.9(3.3)	11.4(2.8)			
Total Pathology score	SCL-90-R	327	236.7(60.1)	254.9(59.5)	2.2	389	.03

Measures

Indicators of latent subtype membership. The Dutch Impact of Event Scale-Revised (IES-R; Kleber & De Jong, 1998; Weiss & Marmar, 1996) measures the psychological impact of traumatic events. Respondents reported how often they experienced symptoms of intrusions, avoidance, and hyperarousal in the past seven days. The 22 items correspond directly with 14 of the 17 PTSD DSM-IV-TR criteria, each rated on a 5-point Likert scale ranging from 0 (*not at all*) to 4 (*extremely*). A posttraumatic symptom severity score was computed by summing the responses on the 22 items (range 0-88). Higher scores reflected more severe symptoms. The IES-R is considered a psychometrically sound and widely used PTSD measure for clinical and research purposes (Beck et al., 2008). The IES-R reliability in the present study was excellent (Cronbach's $\alpha = .93$).

The Dutch version of the Dissociative Experiences Scale-II (DES-II; Bernstein & Putnam, 1986; Boon & Draijer, 1995) assessed the level of psychoform dissociation. Respondents reported the frequency of experienced dissociative symptoms. Four DES-II items 7, 12, 13 and 27 (watching yourself", "people/objects are unreal", "your body is not yours", "hearing voices"), were used. These items corresponded with the DSM-5 definition of the dissociative PTSD subtype as indicators of pathological depersonalization/derealisation (Waller et al., 1996; Stockdale et al., 2002). Each item was rated on a 10-point scale ranging from 0% (*never*) to 100% (*always*). The questionnaire is considered reliable and valid (Van IJzendoorn & Schuengel, 1996).

Predictors (covariates) of latent subtype membership. Age, somatoform dissociation, a comorbid substance or depression diagnosis, the three PTSD DSM-IV-TR dimensions (intrusions, avoidance, hyperarousal), and eight psychopathology severity dimensions were used to predict profile membership.

The Symptom Checklist-90-Revised (SCL-90-R; Arrindell & Ettema, 2003) self-report questionnaire was used to measure eight psychopathology dimensions (i.e., agoraphobia, anxiety, depression, somatisation, cognitive performance deficits, interpersonal sensitivity-mistrust, hostility and sleep difficulties), and provides a measure of overall psychological distress. Patients are asked to rate the severity of 90 symptoms over the past week on a 5-point scale ranging from 0 (*not at all*) to 4 (*extremely*). Sum scores were used, with higher scores indicating more distress.

The SCL-90-R is well established as a reliable and valid instrument (Arrindell & Ettema, 2003). The reliability ranged from good to excellent in the present study (Cronbach's α = .75.-97).

The Dutch version of the Somatoform Dissociation Questionnaire-20 (SDQ-20; Nijenhuis, Spinhoven, van Dyck, Van der Hart, & Vanderlinden, 1996) assessed the level of somatoform dissociation in the past year on a 20-item list. Bodily dissociative symptoms included: anaesthesia, difficulty swallowing, and temporary paralysis. Each item was rated on a 5-point Likert scale ranging from 1 (*not at all*) to 5 (*extremely*). The sum score was used in the analysis (range 20-100). Higher scores indicated more severe symptoms. The SDQ-20 has good psychometric qualities (Nijenhuis et al., 1996), and the reliability was considered good in the present study (Cronbach's α = .82).

The Utrecht Coping List (UCL; Schreurs, Van de Willige, Brosschot, Tellegen, & Graus, 1993) is a frequently used Dutch self-report questionnaire to measure different cognitive, emotional and behavioural coping styles when confronted with stressful or unpleasant situations. The scale consists of 47-items rated on a 4-point Likert scale ranging from 1 (*rarely or never*) to 5 (*very often*). The instrument has good psychometric qualities (Schreurs et al., 1993). The avoidance subscale (8 items) sum score (range 8-32) was used. The avoidant coping subscale measures the extent in which one uses avoidance to deal with stressful situations. Higher scores reflect an increased use of avoidant coping strategies. The reliability was considered acceptable for the present study (Cronbach's α = .65).

Analyses

Demographic and Completer Analyses. Cross tabs (chi-square) and t-tests were performed in SPSS Version 20 to examine differences between the total sample and psychotherapy baseline sample, and between treatment completers and treatment dropouts.

Latent Profile Analysis. Latent Profile Analysis (LPA) (Muthén & Muthén, 1998-2012) was used to assess the presence of distinct patient profiles in MPlus 7.3 based on posttraumatic stress and dissociative symptoms. LPA allows for the classification of individuals into homogenous subgroups or profiles (Geiser, 2013). The technique is considered ideal for investigating dissociative PTSD because it can account for the heterogeneity in symptom presentations that can manifest in specific symptom constellations and severities (Hansen et al.,

2017). The IES-R and DES score ranges were transformed into a single z-scale to simplify the LPA interpretation.

Based on the number of previously identified dissociative PTSD profiles, a series of five models with two- to six-profile solutions were estimated using the robust maximum likelihood estimator (MLR) with full information maximum likelihood estimation to include participants with missing data (Muthén & Muthén, 1998-2012). To avoid local likelihood maximum 500 random sets of starting values in the first and 50 in the second step of optimization were requested and 50 initial stage iterations were used. To compare models with different profile solutions Bayesian Information Criterion (BIC), sample-size adjusted Bayesian Information Criterion (aBIC), and the bootstrapped likelihood ratio test (BLRT) were used. BIC and aBIC make a trade-off between model fit and model complexity with lower values of BIC and aBIC indicating a better fit of the model to the data (Van de Schoot, Lugtig, & Hox, 2012). BLRT compares the fit of a model with the fit of a model with one profile less. A significant BLRT demonstrates that the model fits the data better then the model with one profile less (Nylund et al., 2007). The entropy index was used to evaluate the quality of patient classifications to the profiles. Values range between 0 and 1 and values above .80 indicate adequate classification quality (Celeux & Soromenho, 1996). The optimal model was chosen based on the above-mentioned statistics, clarity of interpretation and model parsimony (Geiser, 2013).

Next, profile membership was predicted by regressing the latent profiles of the most optimal latent profile solution on the observed predictor variables. Multinomial logistic regression in a three-step procedure was used in Mplus (Asparouhov & Muthén, 2014). The resulting odds ratios were compared between profiles with one of the profiles acting as reference.

To test whether profile membership is associated with different treatment outcomes, posttraumatic stress symptom improvement was explored as a continuous distal outcome of the latent profiles of the most optimal latent profile solution. Change scores were computed by subtracting the follow-up scores from the baseline severity scores. Change scores deliver acceptable and corresponding results to alternative regression methods in naturalistic study settings (Williams & Zimmerman, 1996). For the distal outcome analysis, again, a three-step procedure in Mplus was performed (Asparouhov & Muthén, 2014). A Wald chi-squared test for every pair of identified profiles tested whether their profile-specific probabilities differed significantly in symptom change.

Results

Baseline and completer analyses

Veterans that received psychotherapy reported somewhat elevated levels compared to the total baseline sample regarding posttraumatic stress severity, depression, cognitive performance deficits, hostility, and overall SCL-90-R pathology. Table 1 provides the cross tabs and t-test information for each significant variable.

Veterans that started psychotherapy and completed the follow-up measure were considered study completers. Veterans that started psychotherapy but withdrew before the follow-up without achieving therapeutic recovery according to their clinician, were considered premature dropouts. Veterans that successfully completed treatment before follow-up with their diagnosis or symptoms in remission according to their clinician, were considered successful treatment completers. Study completers reported comparable posttraumatic stress severity rates than dropouts (M = 58.8, SD = 12.7 vs. M = 70.2, SD = 7.4; $t(67) = -2.00$, $p = .052$), and higher severity rates than successful treatment completers (M = 58.8, SD = 12.7 vs. M = 42.0, SD = 19.3; $t(67) = 2.7$, $p < .01$). There were no significant differences in pre-treatment posttraumatic reactions severity between study completers and patients unwilling or unavailable to participate and patients who did not receive a follow-up measurement due to the end of data collection ($p > .05$).

Latent profile analysis

The 22 IES-R and 4 DES-II items were used as indicators of the latent subtype membership to estimate the profile solutions. Table 2 provides the fit indices for each profile solution. The fit indices favoured different profile solutions. The two-, three- and four-profile solutions yielded significant BLRT tests, indicating that each profile solution was superior to the profile solution with one profile less. The five-profile solution did not provide a better BLRT fit compared to the four-profile, hence the four-profile solution was most favoured. The BIC was lowest in the five-profile solution, indicating the superiority of this model. In contrast, the aBIC was lowest and most favourable for a six-profile solution. The BIC and BLRT are considered superior to aBIC (Nylund et al., 2007), favouring the four- or five-profile solution. The five-profile closely mirrored the four-profile solution. However, the five-profile model yielded smaller prevalence

rates for the dissociative profiles, the smallest being 6.7%, limiting their clinical relevance. The four-profile model was consequently selected as the optimal model based on the fit statistics, profile prevalence rates, and clarity of interpretation. The entropy index four-profile solution was satisfactory (.86). The average profile assignment probabilities supported a high entropy precision: .98 for the first, .96 for the second, .85 for the third, and 1.0 for the fourth profile.

Figure 2 provides a graphic overview of the standardized profile mean scores on the indicators of the latent subtype membership. The mean z-scores reveal that participants in the first profile demonstrated the lowest posttraumatic stress severity scores (*M* z-score = -1.26) compared to the participants in the other profiles. Participants in the second profile demonstrated moderate posttraumatic severity stress scores (*M* z-score = -.35) positioned above the first profile and below the third (*M* z-score = .46) and fourth profiles (*M* z-score = .59). The third and fourth profile endorsed the highest and most severe posttraumatic stress severity scores. Both profiles were indistinguishable regarding the severity of posttraumatic reactions, but differentiated in dissociative symptom, with the third profile endorsing low dissociative symptom levels (*M* z-score = .-.13), and the fourth (*M* z-score = 1.82) endorsing severe symptom levels. None of the other profiles scored high on dissociative symptom severity (*M* z-score = .-.35 first profile, -.17 second profile). Consequently, the four profiles can be characterized as 'low' (*n* = 42, 12.9%), 'moderate' (*n* = 110, 33.2%), 'severe' (*n* = 149, 45.1%), and 'dissociative' (*n* = 29, 8.8%) PTSD. The unstandardized mean scores for each item are displayed in Table 3.

Predictors of profile membership

Separate multinomial regression analyses examined whether age, PTSD dimensions, pathology dimensions, and comorbid substance use or depression predicted latent profile membership (Table 4). The severe and dissociative PTSD profile reported equal posttraumatic severity levels, and the severe PTSD profile was subsequently selected as reference to facilitate the interpretation between dissociative and non-dissociative PTSD differences.

Participants with low and moderate PTSD profiles reported significantly lower log odds (B coefficients) on all PTSD and pathology dimensions, somatoform dissociation scores, and having a formal PTSD diagnosis. This indicated a decreased likelihood of belonging to the low and moderate profile with every unit increase in these predictor variables. The low and moderate profiles only distinguished themselves from each other in respect to the reference profile on the

Table 2

Model fit comparisons for the one-, two-, three-, and four-, five-, six-profile solution

Profiles	Entropy	BIC	aBIC	Log-likelihood	BLRT	
					-2LL difference	p-value
2	.83	19528.7	19278.1	-9535.3	1849.3	<.001
3	.83	19084.1	18747.8	-9234.7	601.3	<.001
4	**.86**	**18723.2**	**18301.4**	**-8976.0**	**514.1**	**.02**
5	.89	18687.5	18179.9	-8976.0	191.1	.80
6	.90	18686.7	18093.6	-8801.1	156.3	.37

Note. Most optimal model is printed in bold. BIC = Bayesian information criterion; aBIC = sample-size adjusted Bayesian information criterion; BLRT = bootstrapped likelihood ratio test;-2LL difference = -2 times log-likelihood difference between a N profile solution and N – 1 profile solution.

* = $p < .001$.

Table 3

Differences between PTSD profiles on LPA indicators

Profile	Low PTSD	Moderate PTSD	Severe PTSD	Dissociative PTSD
Indicators	*n* = 42 (12.9%)	*n* = 110 (33.2%)	*n* = 149 (45.1%)	*n* = 29 (8.8%)
IES-R items (M, SE)				
1 Brought back feelings	.85(.17)	2.2(.10)	3.0(.07)	3.3(.15)
2 Difficulty staying asleep	.52(.17)	1.9(.13)	3.2(.08)	3.3(.20)
3 Thinking of the trauma	.77(.20)	2.0(.09)	2.9(.07)	3.0(.22)
4 Irritability and anger	1.6(.20)	2.3(.10)	3.0(.09)	3.1(.21)
5 Avoid getting upset	.52(.16)	2.2(.11)	2.4(.08)	2.9(.27)
6 Strong feelings	.87(.17)	1.9(.09)	2.9(.08)	3.2(.15)
7 Intrusive thoughts	.93(.16)	2.2(.11)	3.3(.06)	3.5(.14)
8 Remove from memory	.64(.18)	2.2(.16)	3.1(.08)	3.3(.22)
9 Surrealistic feeling	.39(.14)	.85(.12)	1.5(.13)	2.0(.31)
10 Easily startled	1.3(.21)	2.1(.11)	3.0(.09)	3.4(.17)
11 Avoid reminders	.36(.12)	1.9(.15)	2.9(.09)	3.1(.28)
12 Physical reactions	.61(.18)	2.1(.12)	3.2(.09)	3.2(.21)
13 Pictures in mind	1.0(.19)	2.2(.11)	3.2(.07)	3.3(.19)
14 Dreams	.70(.21)	1.7(.13)	3.1(.10)	2.7(.30)
15 Trouble concentrating	1.7(.20)	2.5(.13)	3.3(.08)	3.7(.10)
16 Watchful and on-guard	2.1(.18)	3.0(.11)	3.6(.06)	3.5(.15)
17 Avoid thinking about it	.66(.15)	2.3(.12)	3.0(.07)	2.9(.17)
18 Avoid dealing with it	.61(.17)	1.8(.13)	2.5(.10)	2.6(.18)
19 Avoid talking about it	.88(.16)	2.2(.17)	3.1(.09)	3.5(.20)
20 Numb feeling	.70(.19)	1.6(.15)	2.4(.12)	2.5.30)
21 Back at that time	.33(.10)	1.3(.13)	2.7(.09)	2.8(.28)
22 Trouble sleeping	1.4(.24)	2.6(.14)	3.7(.06)	3.5(.21)
DES-II items (M, SE)				
7 Watching yourself	.60(.26)	1.2(.22)	1.4(.18)	5.7(.53)
12 People/objects are unreal	.27(.16)	.91(.20)	.90(.18)	4.9(.49)
13 Your body is not yours	.32(.18)	.42(.09)	.27(.07)	6.1(.35)
27 Hearing voices	.44(.19)	.73(.17)	1.1(.19)	3.8(.66)

Note. IES-R = Impact of Events-Revised; DES-II = Dissociative Experiences Scale-II.

use of avoidant coping strategies. Participants in the low PTSD profile less often used avoidant coping strategies then participants in reference profile. The odds of belonging to the low PTSD profile decreased by 13% for each unit of increase in avoidant coping. In contrast, there were no differences in the use of avoidant coping strategies between the moderate PTSD and reference profile.

Compared to participants from the reference profile, participants in the dissociative PTSD profile reported significantly higher log odds on all SCL-90-R pathology dimensions with the exception of sleep difficulties. This indicated that with each unit of increase on the pathology dimensions agoraphobia, anxiety, depression, somatisation, cognitive performance deficits, interpersonal sensitivity, hostility, and the total pathology score, the likelihood of belonging to the dissociative PTSD profile increased. The odds ratio's ranged between 1.02 and 1.13. The dissociative PTSD profile also distinguished itself from the reference group with significant higher somatoform dissociation log odds. Indicating that with each increase in somatoform dissociation, the likelihood of belonging to the dissociative PTSD profile instead of the reference profile increased with 10%. There were no differences in the odds of belonging to the dissociative PTSD profile or reference profile regarding the severity of PTSD dimension scores and avoidant coping strategies. Age, comorbid depression and substance disorder, did not differentiate for any profile compared to the reference profile.

Posttraumatic reactions symptom severity change scores as distal outcome

We performed an exploratory distal outcome analysis based on the LPA four-profile model. The LPA profile membership distribution for the total sample and the psychotherapy sample demonstrated comparable proportions for the moderate PTSD profile (33.2% vs. 34.8%), and the severe PTSD profile (45.1% vs. 46.6%). The low PTSD profile was somewhat underrepresented (12.9% vs. 8.0%), and the dissociative PTSD profile slightly overrepresented (8.8% vs. 10.6%).

Between baseline (M = 58.8, SD = 12.7) and follow-up (M = 52.7, SD = 20.2), posttraumatic stress reactions severity (IES-R) scores decreased on average 6.1 points, corresponding to a small to medium treatment effect (d = .36). The moderate (n = 26), severe (n = 35) and dissociative PTSD (n = 8) profiles each experienced IES-R symptom improvement. The moderate PTSD profile reported a small positive treatment effect (d = .10) and mean IES-R symptom reduction of 2.9 (SD = 30.5) points. The severe PTSD profile reported a mean symptom reduction of 8.6 (SD = 26.0) points, corresponding with a small to medium positive treatment effect (d = .33). The dissociative PTSD profile demonstrated a

mean symptom reduction of 8.2 (*SD* = 11.9) points, corresponding to a medium to strong positive treatment effect (*d* = .69). The low PTSD treatment profile experienced an increase in symptom severity of 19.7 points (*SD* = 18.9) and a large negative treatment effect of *d* = - 1.0. The low PTSD profile performed worse compared to the moderate PTSD profile (χ^2 = 5.3, *p* = .02), the severe PTSD profile (χ^2 =10.8, *p* = .001), and the dissociative PTSD profile (χ^2 = 10.2, *p* = .001). The other profiles did not significantly differentiated from each in posttraumatic stress symptom improvement.

Table 4

Multinomial regression analyses of IES-R and DES profiles on age, PTSD symptom dimensions, clinical characteristics and avoidant coping

		low PTSD *n* = 42 (12.9%)				moderate PTSD *n* = 110 (33.2%)				dissociative PTSD *n* = 29 (8.8%)			
		B	SE	CI(*B*)	OR	*B*	SE	CI(*B*)	OR	B	SE	CI(*B*)	OR
Demographics	Age	.00	.02	[-.04 to .04]	1.00	-.01	.02	[-.04 to .03]	.99	-.01	.02	[-.05 to .03]	.99
PTSD Dimensions	Intrusions	**-1.60*** **	.28	[-2.14 to -1.05]	.20	**-.82*** **	.18	[-1.16 to -.47]	.44	.07	.09	[-.10 to .24]	1.07
	Avoidance	**-.86*** **	.12	[-1.09 to -.63]	.42	**-.36*** **	.07	[-.49 to -.23]	.70	.08	.07	[-.06 to .22]	1.08
	Arousal	**-1.33*** **	.17	[-1.67 to -.99]	.26	**-.83*** **	.15	[-1.11 to -.54]	.44	.02	.12	[-.22 to .25]	1.02
Clinical Characteristics													
Agoraphobia	SCL-90-R	**-.45*** **	.08	[-.61 to -.29]	.64	**-.14*** **	.03	[-.20 to -.08]	.87	**.07***	.03	[.01 to .13]	1.07
Anxiety	SCL-90-R	**-.32*** **	.05	[-.42 to -.23]	.72	**-.18*** **	.03	[-.24 to -.11]	.83	**.07***	.03	[.02 to .12]	1.07
Depression	SCL-90-R	**-.17*** **	.03	[-.22 to -.11]	.84	**-.07*** **	.02	[-.10 to -.04]	.93	**.06****	.02	[.02 to .10]	1.06
Somatisation	SCL-90-R	**-.20*** **	.04	[-.28 to -.12]	.82	**-.07*** **	.02	[-.10 to -.03]	.94	**.07****	.02	[.02 to .11]	1.07
Cognitive perf. deficits	SCL-90-R	**-.26*** **	.05	[-.36 to -.16]	.77	**-.14*** **	.03	[-.19 to -.08]	.87	**.12****	.04	[.05 to .20]	1.13
Interpersonal sensitivity	SCL-90-R	**-.13*** **	.03	[-.18 to -.09]	.87	**-.06*** **	.02	[-.09 to -.03]	.94	**.07*****	.02	[.03 to .10]	1.07
Hostility	SCL-90-R	**-.25*** **	.07	[-.38 to -.12]	.78	**-.13*** **	.03	[-.19 to -.07]	.87	**.08***	.04	[.008 to .16]	1.09
Sleep difficulties	SCL-90-R	**-.64*** **	.11	[-.85 to -.43]	.53	**-.38*** **	.07	[-.52 to -.23]	.69	-.08	.10	[-1.61 to 1.45]	.92
Total Pathology score	SCL-90-R	**-.06*** **	.01	[-.07 to -.04]	.94	**-.02*** **	.01	[-.03 to -.01]	.98	**.02*****	.004	[.01 to .03]	1.02
Somatoform Dissociation	SDQ-20	**-.30*** **	.08	[-.46 to -.14]	.74	**-.10*** **	.03	[-.15 to -.04]	.91	**.10*****	.02	[.05 to .14]	1.10
Avoidant Coping	UCL	**-.12***	.05	[-.06 to -.18]	.87	-.03	.04	[-.11 to .05]	.97	.10	.06	[-.02 to .21]	1.10
Diagnoses	PTSD	**-2.20*** **	.63	[-3.42 to -.97]	.11	**-1.84****	.58	[-2.98 to -.71]	.16	-.56	.78	[-2.1 to .96]	.57
	Substance	-1.35	.88	[-3.06 to .37]	.26	.39	.43	[-.46 to 1.24]	1.48	.06	.59	[-1.10 to 1.22]	1.06
	Depression	-.17	.53	[-1.21 to .88]	.85	-.05	.40	[-.83 to .74]	.96	.15	.53	[-.89 to 1.18]	1.17

Note. Severe PTSD acted as the reference group (*n* = 145). * = $p < .05$; ** = $p < .01$; *** $p < .001$.

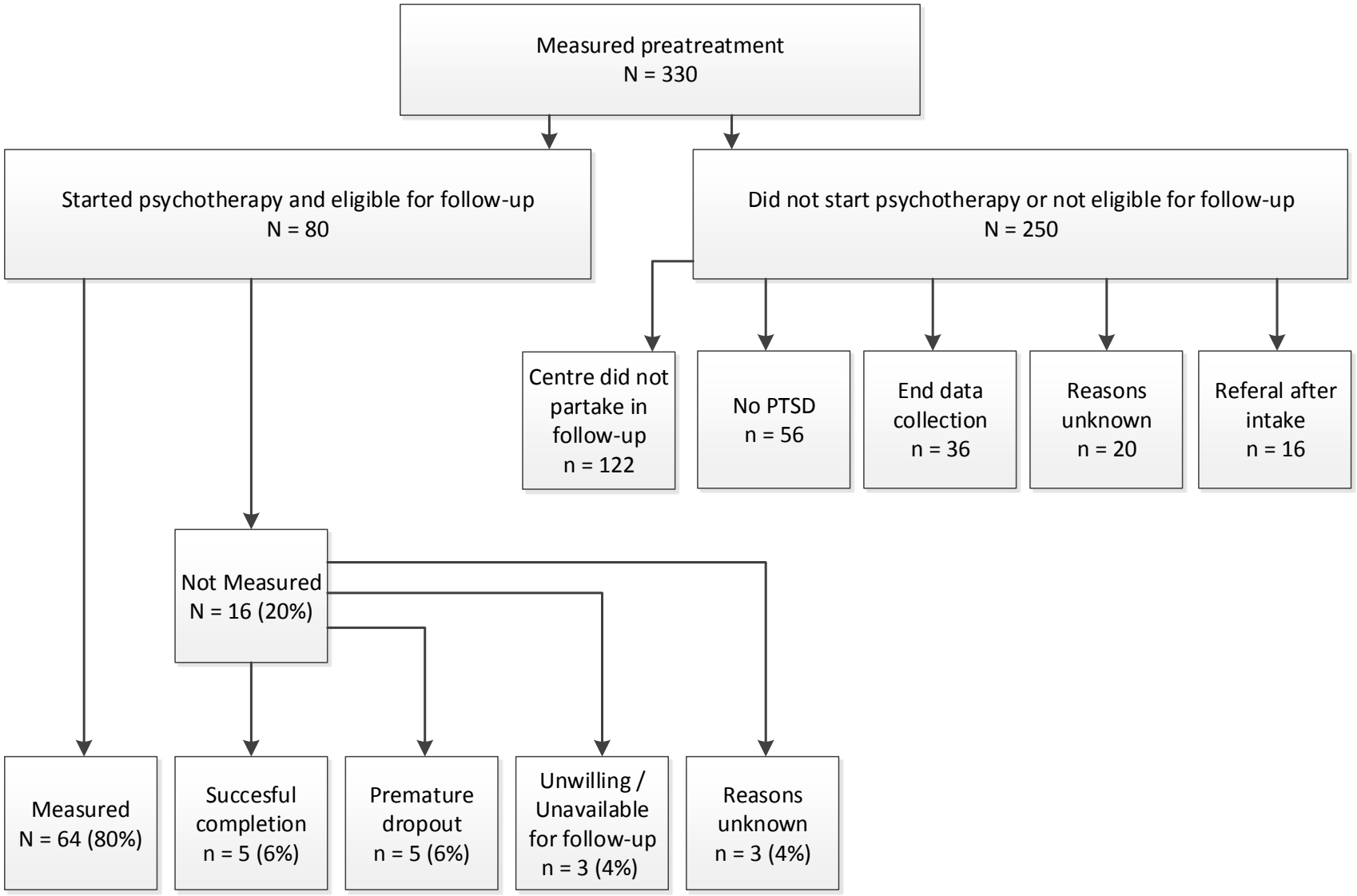

Figure 1. *Flowchart*

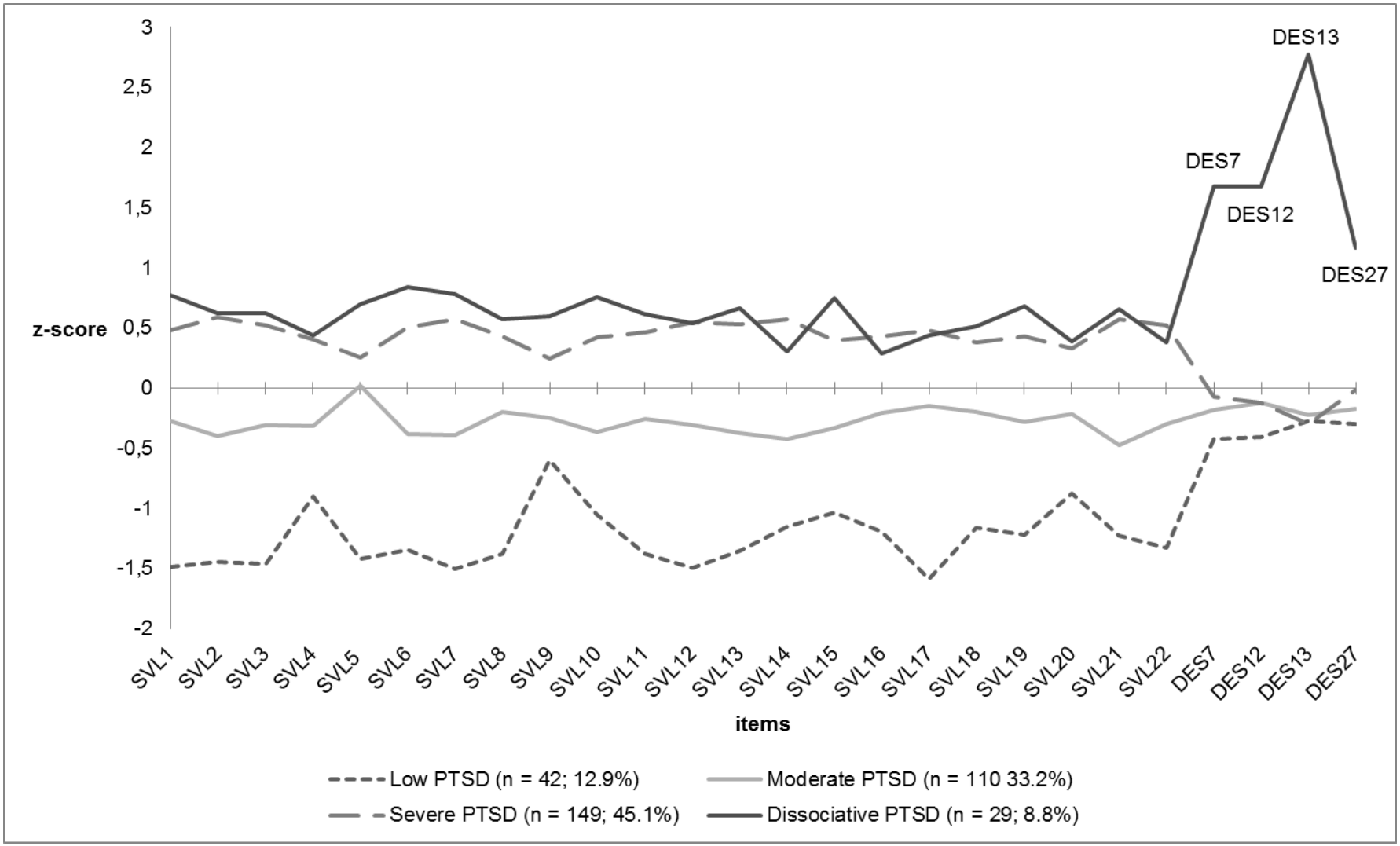

Figure 2. *Standardized profile means on PTSD (IES-R) and dissociation (DES) indicators*

Discussion

The present study identified a subsample of predominately male veterans that corresponded robustly with the criteria of the dissociative PTSD subtype. Patients in the dissociative PTSD profile displayed severe levels of dissociative and posttraumatic symptoms. Compared to patients with non-dissociative PTSD, patients belonging to the dissociative PTSD profile reported significantly more agoraphobia, anxiety, depression, somatisation, cognitive performance deficits, interpersonal sensitivity, hostility, and somatoform dissociation. Patients in the dissociative PTSD profile did not differentiate from non-dissociative patients with comparable posttraumatic stress severities in terms of age, the use of avoidant coping strategies, presence of a comorbid depression, substance disorder, and sleep difficulties. Patients with dissociative PTSD demonstrated the largest psychotherapy treatment effect size, though the effect was not statistically different from the moderate and severe PTSD profiles.

The present study replicated earlier findings of a dissociative PTSD subgroup in veterans with PTSD (Armour et al., 2014b; Waelde et al., 2005; Wolf, Lunney, et al., 2012; Wolf, Miller at al., 2012; Tsai et al., 2015). We identified four distinct PTSD patient profiles, specifically: 'low', 'moderate', 'severe', and 'dissociative' PTSD. The dissociative PTSD profile was characterized by severe PTSD symptoms and—unlike the other profiles—severe dissociation symptoms.

The dissociative PTSD profile prevalence rate (8.8%) was comparable to that of trauma-exposed veterans from a national U.S. survey sample (Wolf et al., 2015), but lower compared to the rates in prior veteran studies (12-16%) (Armour et al., 2014b; Wolf, Miller et al., 2012; Tsai et al., 2015), in particular compared with female veterans exposed to sexual assault that had a 30% dissociative PTSD prevalence rate (Wolf et al., 2016). The lower rate is likely attributable to the inclusion of veterans with subthreshold PTSD symptomatology in the LPA.

The present findings support the subtype model for dissociative PTSD as elevated psychopathology levels for veterans in the dissociative PTSD profile compared to the non-dissociative profiles were found (Dalenberg & Carlson, 2012). Our results support prior findings of elevated depression and/or anxiety scores as regular predictors of dissociative PTSD (see Hansen et al., 2017). The elevations on almost all pathology dimensions, except sleep disturbances, suggest that dissociative symptoms produce additional distress and pathology over a broad pathology spectrum.

A comorbid depression or substance use disorder was not related to a higher probability of belonging to any of the PTSD profiles, regardless of dissociation. This contrasts with the depression pathology dimension that predicted the increased likelihood of belonging to the dissociative PTSD profile. Continuous scales may be more sensitive then categorical scales because they capture the extent of the severity of these disorders, and their use preferred to better understand the heterogeneity in symptom manifestations of the dissociative PTSD subtype.

We found no differences in avoidant coping strategies between patients in the dissociative PTSD profile and patients with non-dissociative PTSD with comparable posttraumatic stress severity. These findings implicate that conscious avoidant strategies are not specifically associated with the dissociative PTSD subtype and do not support the trauma/avoidance model of dissociation (Duta & Wolf ,2017; Holmes et al., 2005). It may be possible however that the present questionnaires (UCL and PTSD avoidance dimension) were insufficiently specific for veterans to associate them with cognitive swift attention switching and dual tasking avoidant coping strategies.

Armour and colleagues (2014a) reported sleep disturbances as a predictor of membership to the dissociative PTSD subtype in female sexual-assault survivors. In our predominantly male sample we did not find indications that sleep disturbances increase the likelihood of belonging to a dissociative PTSD profile. These discrepancies may be the result of neurobiological sex differences (Steiger, Dresler, Kluge, & Schüssler, 2013). Adverse changes in sleep quality, for example rapid-eye-movement (REM) fragmentation, appear more pronounced in women than men, and the role of sex hormones and the menstrual cycle on PTSD-related sleep disturbances remains unknown (Kobayashi, Cowdin, & Mellman, 2012).

Our findings demonstrated that patients belonging to the dissociative PTSD profile benefitted alike from psychotherapy as patients without the dissociative PTSD subtype with comparable PTSD severity levels. It would also appear that patients with the most severe posttraumatic stress have greater room to improve or their baseline scores may reflected an element of over-reporting when seeking help (Forbes, Creamer, Hawthorne, Allen, & McHugh, 2003).These findings imply that dissociation does not interfere with PTSD treatment (see also Halvorsen, Stenmark, Neuner, & Nordahl, 2014; Murphy & Busuttil, 2015), or that clinicians are able to successfully mitigate its adverse effects.

Only the low-PTSD profile did not profit from psychotherapy. This may be the result of regression to the mean, indicating that patients with lower scores are more likely to worsen than improve. Alternatively, despite their relatively low symptom scores, these patients were identified by clinicians to be in need of PTSD treatment. It may that they underreported the severity of their symptoms due to social desirability (Dobie et al., 2002), or fears of displaying weakness (Greene-Shortridge, Britt, & Castro, 2007).

Strengths and limitations

The scientific identification of clinical factors associated with dissociative PTSD subtype has just begun. Only a dozen of studies investigated the dissociative PTSD subtype over a range of populations using diverse and sometimes questionable analytic methods (Hansen et al., 2017). Such varied approaches may cloud the identification of potential membership predictors. The present findings are to our knowledge the first to investigate the dissociative PTSD subtype for veterans using the advanced statistical three-step approach to examine both profile membership predictors and distal outcomes (Asparouhov & Muthén, 2014). Furthermore, there were no in- and exclusion criteria for patient participation increasing the generalizability of current findings to clinical practice. Cohort studies reflect real-world clinical practice.

There are also limitations. It is possible that the sample used for the exploratory distal outcome analysis differed from the total sample in respects that may have influenced treatment outcome, though we found few differences (see Table 1). Also, the exploratory distal treatment outcome data does not allow for strong inferences due to sample size limitations, unbalanced profiles and because the treatment circumstances for each profile are unknown. The profiles may lack sufficient power to detect all profile differences. The current findings are considered relevant because of the practical difficulties to identify and study sufficient treatment-seeking veterans with dissociative PTSD in psychotherapy considering that only between one in ten and one in six veterans fit the profile (Armour et al., 2014; Wolf, Miller et al., 2012; Tsai et al., 2015). Our study assessed only two measurement moments, therefore the assumption of sphericity could not be tested. The present study examined the first six months of treatment, not the full scope of psychotherapy. The day and inpatient treatment settings provided weekly sociotherapy and creative therapy sessions that were not examined in this study because of a focus on psychotherapy treatment as the most effective method for treating PTSD (Watts et al., 2013). The

current observational design is limited in establishing inferences regarding causal relationships (internal validity). The dissociative PTSD subtype is meant to be associated with the DSM-5 PTSD and result are likely more precise in relation to the DSM-5, though the DSM-IV PTSD criteria are considered suitable to identify the subtype (Hansen et al., 2017). The IES-R questionnaire not assess all PTSD DSM-IV criteria, though is considered a valid measure for an indication of PTSD (Beck et al., 2008).

Implications

The present findings confirmed the existence of a distinct subgroup of Dutch veterans with PTSD and highly dissociative symptoms that fit the description of the dissociative PTSD subtype. The identification of elevated pathology dimensions beyond non-dissociative PTSD profiles may indicate that a sole focus on PTSD may be too narrow and warrant additional clinical attention. PTSD treatment proved beneficial for veterans belonging to the dissociative PTSD profile. They demonstrated similar—if not stronger—posttraumatic stress improvement compared to non-dissociative veterans with similar and lower severity levels. These findings implicate that severe dissociation, though distinguishable in various pathology severity dimensions from non-dissociative PTSD, does not have a negative impact on veteran PTSD treatment. Or, that clinicians in specialist settings are well versed to circumvent potential adverse effects resulting from severe dissociation during PTSD treatment. This is a significant finding because researchers and clinicians (Becker et al., 2004; Hansen et al., 2017) tend to consider dissociation an indicator of poor PTSD treatment outcome, and treatment manuals continue to contemplate its possible adverse treatment effects (e.g., Briere & Scott, 2015). It also questions the clinical utility of the DSM-5 Dissociative PTSD subtype.

Conclusion

The present study presents empirical evidence of the existence of a subgroup of patients PTSD patients with severe symptoms of depersonalization/derealisation. Patients with dissociative PTSD profiles reported uniquely elevated pathology levels compared to patients with non-dissociative PTSD and similar posttraumatic severity levels. PTSD patients with dissociative symptoms also reported a large treatment effect size, comparable to the treatment effect size of

patients with non-dissociative PTSD with similar posttraumatic severity levels. Further investigations are required to determine whether the subtype and its associated elevated pathology dimensions are a major tenant in treatment recovery or rather a chord that befuddles the symphony of complexity.

Practitioner Points

- The present findings confirmed the existence of a distinct subgroup veterans that fit the description of dissociative PTSD
- Patients with dissociative PTSD subtype symptoms uniquely differed from patients with non-dissociative PTSD in the severity of several psychopathology dimensions
- Dissociative and non-dissociative PTSD patients with similar posttraumatic severity levels showed similar levels of improvement after PTSD treatment
- The observational design and small sample size caution interpretation of the treatment outcome data
- The IES-R questionnaire does not assess all PTSD DSM-IV diagnostic criteria (14 of 17), though is considered a valid measure for an indication of PTSD

Acknowledgements

We thank Foundation Centre ’45 [Stichting Centrum ‘45], The Military Mental Health Care [Militaire Geestelijke Gezondheidszorg], Psychotrauma Centre South-Netherlands [Psychotrauma Centrum Zuid-Nederland, onderdeel van Reinier van Arkel Groep] for their participation, and top-reference trauma centre GGZ-Drenthe [topreferent traumacentrum van GGZ-Drenthe]. We are grateful to the Dutch National Health System for Veterans [Landelijk Zorgsysteem voor Veteranen] that spearheaded the development and implementation of a comprehensive uniform diagnostic set and for providing their support to the present project.

References

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: Author.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: Author.

Arrindell, W. A., & Ettema, J. H. M. (2003). S*ymptom checklist SCL-90: Handleiding bij een multidimensionele psychopathologie-indicator.* Swets test publishers.

Armour, C., Elklit, A., Lauterbach, D., & Elhai, J. D. (2014a). The DSM-5 dissociative-PTSD subtype: Can levels of depression, anxiety, hostility, and sleeping difficulties differentiate between dissociative-PTSD and PTSD in rape and sexual assault victims? *Journal of Anxiety Disorders*, *28*, 418-426. doi:10.1016/j.janxdis.2013.12.008

Armour, C., Karstoft, K. I., & Richardson, J. D. (2014b). The co-occurrence of PTSD and dissociation: Differentiating severe PTSD from dissociative-PTSD. *Social Psychiatry and Psychiatric Epidemiology*, *49*, 1297-1306. doi:10.1007/s00127-014-0819-y

Asparouhov, T., & Muthén, B. (2014). Auxiliary variables in mixture modeling: Three-step approaches using M plus. *Structural Equation Modeling: A Multidisciplinary Journal, 21*, 329-341. http://dx.doi.org/10.1080/10705511.2014.915181

Bae, H., Kim, D., & Park, Y. C. (2016). Dissociation predicts treatment response in eye-movement desensitization and reprocessing for posttraumatic stress disorder. *Journal of Trauma & Dissociation, 17*, 112-130. doi:10.1080/15299732.2015.1037039

Beck, J. G., Grant, D. M., Read, J. P., Clapp, J. D., Coffey, S. F., Miller, L. M., & Palyo, S. A. (2008). The Impact of Event Scale-Revised: Psychometric properties in a sample of motor vehicle accident survivors. *Journal of anxiety disorders*, *22*, 187-198. doi:10.1016/j.janxdis.2007.02.007

Becker, C., Zayfert, C., & Anderson, E. (2004). A survey of psychologists' attitudes towards and utilization of exposure therapy for PTSD. *Behaviour Research and Therapy*, *42*(3), 277-292.

Bernstein, E. M., & Putnam, F. W. (1986). Development, reliability, and validity of a dissociation scale. *The Journal of Nervous and Mental Disease*, *174*(12), 727-735.

Blevins, C. A., Weathers, F. W., & Witte, T. K. (2014). Dissociation and posttraumatic stress disorder: A latent profile analysis. *Journal of Traumatic Stress, 27,* 388-396. doi:10.1002/jts.21933

Boon, S., & Draijer, N. (1995). *Screening en diagnostiek van dissociatieve stoornissen*. Lisse: Swets & Zeitlinger.

Briere, J., & Scott, C. (2015). *Principles of trauma therapy: A guide to symptoms, evaluation, and treatment* (2nd ed.). London: SAGE Publications.

Celeux, G., & Soromenho, G. (1996). An entropy criterion for assessing the number of clusters in a mixture model. *Journal of Classification, 13*(2), 195-212.

Chiu, C-D., Tseng, M-C. M., Chien, Y-L., Liao, S. C., Liu, C-M., Yeh, Y-Y., & Hwu, H-G. (2016) Switch function and pathological dissociation in acute psychiatric inpatients. *PLoS ONE 11*: e0154667. doi:0.1371/journal.pone.0154667

Chiu, C-D., Yeh, Y-Y., Huang, Y-M., Wu, Y- C., & Chiu, Y-C.(2009). The set switching function of nonclinical dissociators under negative emotion. *Journal of Abnormal Psychology, 118*, 214–222. doi:10.1037/a0014654

Dalenberg, C. J., Brand, B. L., Gleaves, D. H., Dorahy, M. J., Loewenstein, R. J., Cardena, E., ... Spiegel, D. (2012). Evaluation of the evidence for the trauma and fantasy models of dissociation. *Psychological Bulletin, 138*, 550. doi:10.1037/a0027447

Dalenberg, C., & Carlson, E.B. (2012). Dissociation in posttraumatic stress disorder part II: How theoretical models fit the empirical evidence and recommendations for modifying the diagnostic criteria for PTSD. *Psychological Trauma: Theory, Research, Practice, and Policy, 4, 5*51-559. http://dx.doi.org/10.1037/a0027900

DePrince, A. P., & Freyd, J. J. (1999). Dissociative tendencies, attention, and memory. *Psychological Science, 10*(5), 449-452.

De Ruiter, M. B., Phaf, R. H., Veltman, D. J., Kok, A., & Van Dyck, R. (2003). Attention as a characteristic of nonclinical dissociation: An event-related potential study. *Neuroimage, 19*, 376-390. doi:10.1016/S1053-8119(03)00099-5

Dobie, D. J., Kivlahan, D. R., Maynard, C., Bush, K. R., McFall, M., Epler, A. J., & Bradley, K. A. (2002). Screening for post-traumatic stress disorder in female Veteran's Affairs patients: Validation of the PTSD checklist. *General Hospital Psychiatry, 24*(6), 367-374.

Forbes, D., Creamer, M., Hawthorne, G., Allen, N., & McHugh, T. (2003). Comorbidity as a predictor of symptom change after treatment in combat-related posttraumatic stress disorder. *The Journal of Nervous and Mental Disease, 191*(2), 93-99.

Frewen, P. A., Brown, M. F., Steuwe, C., & Lanius, R. A. (2015). Latent profile analysis and principal axis factoring of the DSM-5 dissociative subtype. *European journal of psychotraumatology, 6*: 26406. http://dx.doi.org/10.3402/ejpt.v6.26406

Geiser, C. (2013). *Data Analysis with Mplus*. New York, NY: The Guilford Press.

Giesbrecht, T., Lynn, S. J., Lilienfeld, S. O., & Merckelbach, H. (2008). Cognitive processes in dissociation: An analysis of core theoretical assumptions. *Psychological Bulletin, 134,* 617–647. doi:10.1037/0033-2909.134.5.617

Greene-Shortridge, T. M., Britt, T. W., & Castro, C. A. (2007). The stigma of mental health problems in the military. *Military medicine, 172*(2), 157-161.

Halvorsen, J. Ø., Stenmark, H., Neuner, F., & Nordahl, H. M. (2014). Does dissociation moderate treatment outcomes of narrative exposure therapy for PTSD? A secondary analysis from a randomized controlled clinical trial. *Behaviour Research and Therapy, 57,* 21-28. doi:10.1016/j.brat.2014.03.010

Holmes, E. A., Brown, R. J., Mansell, W., Fearon, R. P., Hunter, E. C., Frasquilho, F., & Oakley, D. A. (2005). Are there two qualitatively distinct forms of dissociation? A review and some clinical implications. *Clinical Psychology Review, 25,* 1-23. doi:10.1016/j.cpr.2004.08.006

Kleber, R. J., & De Jong, E. (1998). D*utch version of the Impact of Event Scale-Revised.* Internal report. Utrecht: Department of Clinical Psychology, Utrecht University.

Kobayashi, I., Boarts J. M., Delahanty, D. (2007). Polysomnographically measured sleep abnormalities in PTSD: A meta-analytic review. *Psychophysiology 2007, 44,* 660–669. doi:10.1111/j.1469-8986.2007.537.x

Kulkarni, M., Porter, K. E., & Rauch, S. A. (2012). Anger, dissociation, and PTSD among male veterans entering into PTSD treatment. *Journal of Anxiety Disorders, 26,* 271-278. doi:10.1016/j.janxdis.2011.12.005

Murphy, D., & Busuttil, W. (2015). Exploring outcome predictors in UK veterans treated for PTSD. *Psychology Research, 5,* 441-451. doi:10.17265/2159-5542/2015.08.001

Murphy, S., Elklit, A., Murphy, J., Hyland, P., & Shevlin, M. (2017). A cross-lagged panel study of dissociation and posttraumatic stress in a treatment-seeking sample of survivors of childhood sexual abuse. *Journal of Clinical Psychology, 0,* 1-12. doi:10.1002/jclp.22439

Muthén, L. K., & Muthén, B. O. (1998-2012). *Mplus user's guide* (7th ed.). Los Angeles, CA: Muthén & Muthén.

Nijenhuis, E. R., Spinhoven, P., Van Dyck, R., Van Der Hart, O., & Vanderlinden, J. (1996). The development and psychometric characteristics of the Somatoform Dissociation Questionnaire (SDQ-20). *The Journal of Nervous and Mental Disease, 184*(11), 688-694.

Nylund, K. L., Asparouhov, T., & Muthén, B. O. (2007). Deciding on the number of classes in latent class analysis and growth mixture modeling: A Monte Carlo simulation study. *Structural Equation Modeling, 14*(4), 535-569.

Pullin, M. A., Webster, R. A., & Hanstock, T. L. (2014). Psychoform and somatoform dissociation in a clinical sample of Australian adolescents. *Journal of Trauma & Dissociation, 15*, 66-78. doi:10.1080/15299732.2013.828149

Ross, C. A., Joshi, S., & Currie, R. (1990). Dissociative experiences in the general population. *American Journal of Psychiatry, 147*, 1547-1552. doi:10.1176/ajp.147.11.1547

Schreurs, P. J. G., Van de Willige, G., Brosschot, J. F., Tellegen, B., & Graus, G. M. H. (1993). *Handleiding Utrechtse Coping Lijst UCL (herziene versie)* [Manual Dutch Coping List (revised edition)]. Lisse: Swets & Zeitlinger.

Spiegel, D., Lewis-Fernandez, R., Lanius, R., Vermetten, E., Simeon, D., & Friedman, M. (2013). Dissociative disorders in DSM-5. *Annual Review of Clinical Psychology, 9*, 299-326. doi:10.1146/annurev-clinpsy-050212-185531

Steiger, A., Dresler, M., Kluge, M., & Schüssler, P. (2013). Pathology of sleep, hormones and depression. *Pharmacopsychiatry, 46*, S30-S35. doi:10.1055/s-0033-1337921

Stein, D. J., Koenen, K. C., Friedman, M. J., Hill, E., McLaughlin, K. A., Petukhova, M., …Kessler, R. C. (2013). Dissociation in posttraumatic stress disorder: Evidence from the World Mental Health Surveys. *Biological Psychiatry, 73*, 302-312. doi:10.1016/j.biopsych.2012.08.022

Steuwe, C., Lanius, R. A., & Frewen, P. A. (2012). Evidence for a dissociative subtype of PTSD by latent profile and confirmatory factor analyses in a civilian sample. *Depression and Anxiety, 29,* 689-700. doi:10.1002/da.21944

Stockdale, G. D., Gridley, B. E., Balogh, D. W., & Holtgraves, T. (2002). CFA of models of the DES confirmatory factor analysis of single- and multiple-factor competing models of the Dissociative Experiences Scale in a nonclinical sample. *Assessment, 9*(1), 94-106.

Tsai, J., Armour, C., Southwick, S. M., & Pietrzak, R. H. (2015). Dissociative subtype of DSM-5 posttraumatic stress disorder in U.S. veterans. *Journal of Psychiatric Research, 66,* 67-74. doi:10.1016/j.jpsychires.2015.04.017

Van de Schoot, R., Lugtig, P., & Hox. J. (2012). A checklist for testing measurement invariance. *European Journal of Developmental Psychology, 9*, 486-492. doi:10.1080/17405629.2012.686740

Van der Hart, O., Nijenhuis, E. R,, & Steele, K. (2005). Dissociation: An insufficiently recognized major feature of complex posttraumatic stress disorder. *Journal of Traumatic Stress, 18*, 413-23. doi:10.1002/jts.20049

Van IJzendoorn, M. H., & Schuengel, C. (1996). The measurement of dissociation in normal and clinical populations: Meta-analytic validation of the Dissociative Experiences Scale (DES). *Clinical Psychology Review, 16*, 365-382. doi:10.1016/0272-7358(96)00006-2

Waelde, L. C., Silvern, L., & Fairbank, J. A. (2005). A taxometric investigation of dissociation in Vietnam veterans. Journal *of Traumatic Stress, 18*(4), 359-369.

Waller, N. G., Putman, F. W., & Carlson, E. B. (1996). Types of dissociation and dissociative types: A taxometric analysis of dissociative experiences. *Psychological Methods, 1*(3), 300-321.

Watts, B. V., Schnurr, P. P., Mayo, L., Young-Xu, Y., Weeks, W. B., & Friedman, M. J. (2013). Meta-analysis of the efficacy of treatments for posttraumatic stress disorder. *Journal of Clinical Psychiatry, 74*, 541-550. doi:10.4088/JCP.12r08225

Weiss, D. S., & Marmar, C. R. (1996). The Impact of Event Scale-Revised. In J. Wilson & T.M. Keane (Eds.), *Assessing psychological trauma and PTSD* (pp. 399-411). New York, NY: Guilford Press.

Williams, R. H., & Zimmerman, D. W. (1996). Are Simple Gain Scores Obsolete? *Applied Psychological Measurement, 20*(1), 59-69.

Wolf, E. J., Lunney, C. A., Miller, M. W., Resick, P. A., Friedman, M. J., & Schnurr, P. P. (2012). The dissociative subtype of PTSD: A replication and extension. *Depression and Anxiety, 29,* 679-688. doi:10.1002/da.21946

Wolf, E. J., Lunney, C. A., & Schnurr, P. P. (2016). The influence of the dissociative subtype of posttraumatic stress disorder on treatment efficacy in female veterans and active duty service members. *Journal of Consulting and Clinical Psychology, 84*, 95-100. http://dx.doi.org/10.1037/ccp0000036

Wolf, E. J., Mitchell, K. S., Sadeh, N., Hein, C., Fuhrman, I., Pietrzak, R. H., & Miller, M. W. (2015). The Dissociative Subtype of PTSD Scale: Initial evaluation in a national sample of trauma-exposed veterans. *Assessment*, doi:10.1177/1073191115615212.

Wolf, E.J., Miller, M.W., Reardon, A.F., Ryabchenko, K.A., Castillo, D., & Freund, R. (2012). A latent class analysis of dissociation and posttraumatic stress disorder: Evidence for a dissociative subtype. *Archives of General Psychiatry, 69,* 698-705. doi:10.1001/archgenpsychiatry.2011.157

Chapter 6

Adverse consequences of disturbed sleep in veteran PTSD treatment

A ruffled mind makes a restless pillow

Charlotte Brontë

Submitted as:

Haagen, J. F. G., van der Aa, N., Knipscheer, J. W., & Kleber, R. J. (2017). Adverse consequences of disturbed sleep in veteran PTSD treatment.

Abstract

Sleep disturbances may unfavourable impact PTSD treatment symptom reduction for veterans with PTSD. The present study used a prospective cohort design to measure the severity of sleep disturbances (SCL90-R Sleep Disturbances Scale) and posttraumatic reactions (IES-R) at pre-treatment. After six months of PTSD psychotherapy, the severity of posttraumatic reactions was re-measured. Eighty veterans with PTSD enrolled in the study and completed the pre-treatment measurement, 64 veterans (80.0%) completed the follow-up measurement and were included in the analysis. Multiple regression analyses were preformed with IES-R pre-post change scores as the dependent variable and sleep disturbances, IES-R pre-treatment severity scores, treatment location, and the number of psychotherapy sessions as independent variables. Sleep disturbances negatively predicted posttraumatic stress reactions symptom improvement after six months of PTSD psychotherapy (β = -.35, p = .007), and added an additional 8.8% of explained variance to the total model. Sleep disturbances frustrate PTSD treatment improvement. It is recommended to target sleep disturbances before or parallel to PTSD treatment using evidence-based sleep interventions. Replication studies that examine how sleep disturbances impair treatment symptom reduction are recommended.

Acknowledgment contribution authors

Designed research: Haagen, Knipscheer, Kleber

Performed research: Haagen

Analysed data: Haagen, van der Aa

Wrote the paper: Haagen, Knipscheer, Van der Aa, Kleber

Introduction

After combat deployment, 3-9% of the combat veterans develop posttraumatic stress disorder (PTSD) (Dohrenwend et al., 2006; Engelhard et al., 2007; Marmar et al., 2015; Reijnen, Rademaker, Vermetten, & Geuze, 2014; Wisco et al., 2014). PTSD is the most prominent stressor-related psychological disorder (American Psychiatric Association, 2013). The disorder causes significant symptom-related distress and functional impairment. Its core dimensions are intrusive traumatic memories, persistent avoidance of trauma reminders, negative alterations in mood and cognitions, and alterations in arousal and reactivity.

According to conditioning theories and emotional processing theory (Rauch & Foa, 2006), traumatic memories are the result of 'fear condition'. Individuals learned to associate the traumatic event with neutral stimuli present during the traumatic event. These stimuli elicit a conditioned fear response similar to the original fear response. To overcome conditioned fear responses to traumatic memories, new non-threatening neutral associations need to be encoded (learned) and consolidated in the memory. The non-threatening associations coupled to the traumatic memories are meant to suppress, weaken, inhibit, compete, or otherwise counteract the original conditioned fear response when confronted with trauma reminders, which enables emotional processing of traumatic memories and recovery (Pace-Schott, Germain, & Milad, 2014). This process is coined 'fear extinction'.

Sleep has been implicated in the development and maintenance of PTSD (McHugh et al., 2014; Pace-Schott et al., 2014; Van Liempt, Van Zuiden, Westenberg, Super, & Vermetten, 2013). Sleep promotes extinction learning by prioritization and integration of newly acquired memories within existing stores (Pace-Schott et al., 2014), and by facilitating (new) memory retrieval (Steiger, Dresler, Kluge, & Schüssler, 2013). In contrast, sleep disturbances disrupt reconsolidation memory processes that are necessary for fear extinction learning (Germain, 2013; Germain, Buysse, & Nofzinger, 2008; Pace-Schott et al., 2014; Rauchs & Peigneux, 2012). The inability to *learn* as a result of sleep disturbances (Blissit, 2001; Pace-Schott et al., 2014), may leave patients unable to fully consolidate new non-threatening fear extinction associations acquired during psychotherapy. Sleep disturbances include difficulties with falling asleep, waking up often in the night or waking up too early, insomnia, and experiencing nightmares

There is indirect evidence that sleep disturbances decrease PTSD treatment effectiveness. Sleep-specific interventions are known to increase memory consolidation and retrieval performance (Rauchs & Peigneux, 2012). Nijdam, De Vries, Gersons and Olff (2015) demonstrated that improved memory encoding and retrieval processes were associated with improved PTSD treatment symptom reduction, and poor memory performance resulted in an inferior PTSD treatment response. This may explain why sleep interventions also alleviate PTSD symptom severity (Gerhart, Hall, Russ, Canetti, & Hobfoll, 2014; Krystal et al., 2016; Spoormaker & Montgomery, 2008; Zayfert & DeViva, 2004). Untreated sleep disturbances however tend to persist after PTSD treatment with significant residual psychopathology (Gerhart et al., 2014; Krystal et al., 2016; Spoormaker & Montgomery, 2008; Zayfert & DeViva, 2004).

Despite the potential significance of sleep disturbances in the emergence of psychopathology and possible effects on PTSD treatment improvement, it has rarely been examined directly. Lommen and colleagues (2016) examined sleep disturbances in a randomized controlled trial. They delivered 10 sessions of cognitive trauma focused therapy in a heterogeneous PTSD sample with a variety of traumatic experiences. No relationship between sleep disturbances and PTSD treatment symptom reduction was found. The authors state that sleep is not predictive of treatment symptom reduction, but merely a symptom of a disorder that improves concurrently with PTSD improvement (Lommen et al., 2016). A large-scale Veteran Affairs outpatient PTSD treatment study however associated sleep disorders with membership to a PTSD treatment trajectory characterized by severe symptoms and little improvement over time (Sripada et al., 2017). Combat veterans may be more susceptible to the impact of sleep disturbances because of long-term deployment related disrupted sleep patterns (Lewis, Creamer, & Failla, 2009). Sleep disturbances are a widespread concern among veterans; nine out of every ten treatment-seeking combat veteran with PTSD reported sleep disturbances (Krystal et al., 2016).

The aim of the current study was to examine the impact of sleep disturbances on PTSD treatment symptom reduction for treatment-seeking veterans with PTSD. It was hypothesized that more severe sleep disturbances interfere with PTSD treatment symptom reduction. The clinical importance of sleep disturbances during PTSD treatment may be considerable, although treatment experts may be unaware of its potential impact (Spoormaker & Montgomery, 2008).

Sleep disturbances serve as a transdiagnostic phenomenon and targeting sleep may transcend the single disorder treatment approach that ignores important comorbid disorders (Ginzburg, Ein-Dor, & Solomon, 2010; Skodol et al., 1996). It may also influence recovery on a much broader scale considering its general impact on mental and physical wellbeing (Alvarez & Ayas, 2004; Gerhart et al., 2014).

Method

Study design

A prospective multisite longitudinal cohort design was used. Three specialized psychotrauma treatment centres participated in the current study (Centre ’45, Military Mental Health Care Centre, and Reinier van Arkel Groep). The questionnaires used in the present study were part of a pre-treatment and follow-up assessment used for diagnostic purposes and treatment evaluation. The study was granted exemption of ethical approval by the medical ethical committee of the Utrecht University (case number 12-535/C) because the assessments were part of standard diagnostic procedures, routine outcome monitoring, and because the study did not influence treatment procedures.

Participants and procedure

The study participants were treatment-seeking veterans with a DSM-IV-TR PTSD diagnosis who started PTSD psychotherapy. Eighty veterans filled out a pre-treatment assessment. Six months after the first psychotherapy session, 66 (82.5%) veterans completed a short follow-up measurement. The remaining 14 (17.5%) veterans did not fill out the follow-up because they successfully completed PTSD treatment prematurely (before the six months follow-up measurement) (n = 5, 6.3%), dropped out of treatment prematurely (n = 5, 6.3%), were unwilling or unavailable for follow-up (n = 3, 3.8%), and one (1.3%) veteran was not measured for reasons unknown. After the data collection, two (2.5%) veterans were excluded from the analysis on suspicion of item response biases. As such, 64 (80.0%) veterans of the original 80 veterans were included in the analyses. A Flowchart is provided in Figure 1. All data were collected between January 2013 and June 2015.

Table 1 provides an overview of demographic data. Most of the 64 participants were males (96.9%), with a mean age of 40 years. The veterans tended to be in a relationship (73.5%), almost half of the participants were employed on a full-time basis (46.9%), and a large portion (40.6%) were diagnosed with a comorbid major depression.

Treatment

There are two major perspectives that shape the field of psychotherapy. According to the *medical model*, specific diseases or disorders are best treated with specific intervention, whereas the *common factors model* states that treatment effectiveness is primarily dependent on common factors present in all psychotherapies (Wampold, Ahn, & Coleman, 2001). Key common factors are considered therapeutic alliance, (treatment) expectations, treatment credibility, instillation of hope, and a therapeutic set of actions that are believed helpful (Wampold, Frost, & Yulish, 2016). There is evidence to support the credibility of both models in the field of psychotrauma (Benish, Imel, & Wampold, 2008; Ehlers et al., 2010; Wampold et al., 2010).

The current study used a middle ground approach; in accordance with the medical model, it was assumed that interventions that target PTSD offer the best results for recovery compared to interventions not intended to target PTSD. This study consequently only examined the impact of interventions intended to alleviate PTSD. In accordance with the common factors model, psychotherapy data of veterans with PTSD were pooled, irrespective of the type of PTSD intervention. This may offer a practical approach to examine common psychotherapy change mechanisms.

Psychotherapy was provided according to standard clinical care. Patients received a range of interventions at the three participating centres, namely: eye movement desensitization reprocessing [EMDR], brief eclectic psychotherapy [BEP], narrative exposure therapy [NET], cognitive behavioral therapy [CBT], and patient-centered therapy. These interventions were delivered in outpatient, day treatment, or inpatient settings. Sleep education (sleep hygiene, nightmares) was regularly discussed with the patients, though not standardized.

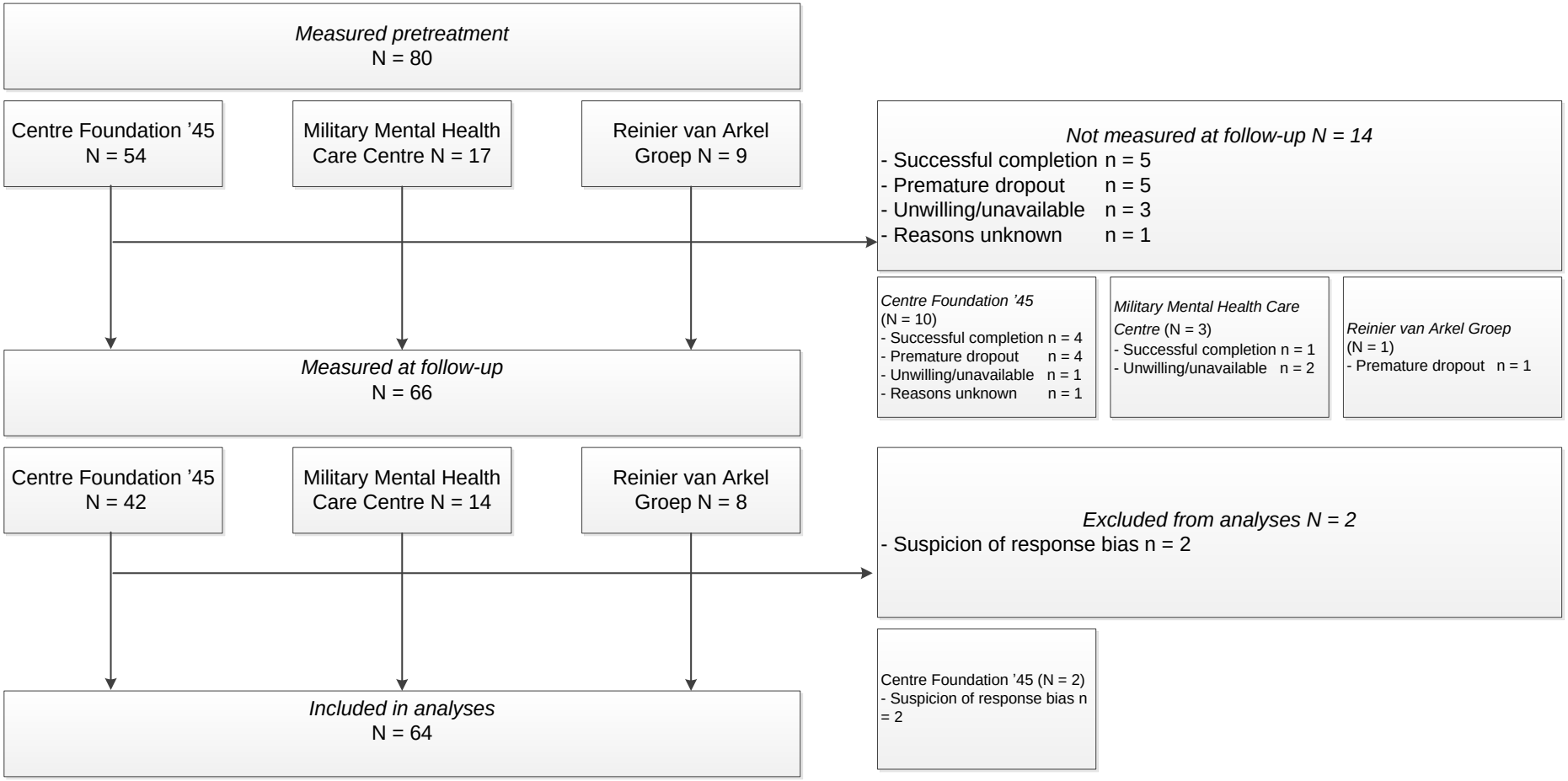

Figure 1. *Flowchart*

Table 1

Demographic data

Characteristics		Sample			
Demographics		*n*	*%*	*M*	*SD*
Age					
	Years			39.8	10.1
Sex					
	Male	62	96.9		
Educational Level					
	High school	4	6.3		
	Lower Secondary Education	25	39.1		
	Higher Secondary Education	26	40.6		
	Higher Vocational/Academic	8	12.5		
Marital Status					
	Married	27	42.2		
	Cohabitating	20	31.3		
	Single	13	20.3		
	Divorced	3	4.7		
Employment Status					
	Full-time Employed	30	46.9		
	Part-time Employed	1	1.6		
	Disabled	25	39.1		
	Unemployed	8	12.5		
Comorbid Diagnosis					
	Major Depressive Disorder	26	40.6		
	Substance Dependence	7	10.9		
	Substance Abuse	15	23.4		

Note: $n = 64$

Measures

The Dutch Impact of Event Scale-Revised (Kleber & De Jong, 1998; Weiss & Marmar, 1997). The Dutch Impact of Event Scale-Revised (IES-R) measures the psychological impact of traumatic events. Respondents reported how often they experienced symptoms of intrusions, avoidance, and hyperarousal in the past seven days. The 22 items are closely linked to the PTSD symptoms as described in the DSM-IV-TR and rated on a 5-point Likert scale ranging from 0 = *not at all* to 4 = *extremely*. The sum score range from 0-88. The IES-R is considered a psychometrically sound measure for clinical and research purposes with a 6-month test-retest reliability of .94 (Weiss & Marmar, 1997). The IES-R reliability in the present study was considered excellent (Cronbach's α = .93)

The Symptom Checklist-90-Revised (Arrindell & Ettema, 2003; Derogatis, 1994). The Symptom Checklist (SCL-90-R) is a self-report questionnaire that measures eight psychopathology severity dimensions (agoraphobia, anxiety, depression, somatization, cognitive performance deficits, interpersonal sensitivity-mistrust, acting-out hostility and sleep difficulties), and provides a measure of overall psychological distress. Patients are asked to rate the severity of their experiences with 90 symptoms over the past week on a 5-point scale ranging from 0 = *not at all* to 4 = *extremely*. Higher scores indicate more severe distress. The SCL-90-R is well established as a reliable and valid instrument (Arrindell & Ettema, 2003).

The Dutch SCL-90-R scale 'Sleep Difficulties ' was used to assess sleep disturbances. The scale is based on three items: 'trouble falling asleep', 'waking up early in the morning', and 'sleep that is restless or disturbed'. The sum score range from 0-12, and were used to observe the distribution of patient score based on Dutch norm categories besides regression analyses. The Sleep Difficulties scale is a psychometrically sound subscale that reflects its specific primary symptoms well, differentiates from general psychological distress, with reliability ratings ranging from high to acceptable (Cronbach's α = .88-.73) (Arrindell & Ettema, 2003; Kloens, Barelds, Luteijn, & Schaap, 2005; Smits, Timmerman, Barelds, & Meijer, 2015). The present study scale reliability was acceptable (Cronbach's α = .72).

Data analysis

All analyses were performed with SPSS version 23. Independent *t*-tests comparisons were performed to examine clinical variables between study completers and dropouts. ANOVA and

correlational analyses were performed to examine the relationships between study variables. A reliable change index (RCI) score was calculated to assess the percentage of participants that improved, remained stable, or worsened during treatment, based on IES-R severity change scores. The RCI was based on the mean pre- and posttreatment IES-R severity scores and standard deviations, the questionnaire test-retest reliability scores (α = .94; Weiss & Marmar, 1996), and a 95% confidence interval (Jacobson and Truax, 1991).

The main analyses consisted of multiple regression analyses that examined the effects of sleep disturbances on PTSD treatment symptom reduction. IES-R change scores (T1-T2) were used as the dependent variable. Change scores deliver acceptable and corresponding results to alternative regression methods in naturalistic study settings (Dalecki & Willits, 1991; Williams & Zimmerman, 1996), and are recommend over ANCOVA analysis methods in naturalistic designs under the assumption of a single treatment group in which the different psychotherapies are considered on an equal basis (Van Breukelen, 2013). Change scores reguraly used in veteran prognostic treatment studies (e.g., Boden, Bonn-Miller, Vujanovic, & Drescher, 2012; Bonn-Miller, Vujanovic, & Drescher, 2011; Forbes, Creamer, Hawthorne, Allen, & McHugh, 2003).

Pre-treatment PTSD symptom severity was included as a covariate in the multiple regression analysis, a recommended strategy to adjust for possible effects due to the association between pre-post scores and pre-treatment scores (Dalecki & Willits, 1991). Besides pretreatment IES-R posttraumatic stress reactions severity, treatment location and the number of received psychotherapy sessions were included as covariates due to the multisite nature of the study and the assumption that the number of sessions influences treatment symptom reduction. The data for 'number of sessions' was missing for two participants (2.5%). A mean imputation was performed to impute this missing data and enable both participants to be included in the analysis.

Results

Completer vs. dropout analysis

The five veterans that dropped out of psychotherapy before the follow-up reported higher - though not significant - levels of pre-treatment posttraumatic stress reactions severity scores (M = 70.2, SD = 7.4 vs. M = 58.8, SD = 12.7, $t(67) = -2.0$, p = .052), and comparable levels of

pre-treatment sleep disturbances (M = 13.2, SD = 2.5 vs. M = 11.4, SD = 2.8, $t(67) = -1.4$, p = .42), compared to participants that completed the pre-treatment and follow-up measurements.

In contrast, the five participants that successfully concluded psychotherapy before the follow-up measurement reported significantly lower levels of pre-treatment posttraumatic stress reactions severity scores (M = 42.0, SD = 19.3 vs. M = 58.8, SD = 12.7, $t(67) = 2.7$, $p < .01$), and pre-treatment sleep disturbances (M = 7.6, SD = 3.5 vs. M = 11.4, SD = 2.8, $t(67) = 2.9$, $p < .01$).

There were no differences in IES-R pre-treatment posttraumatic stress reactions (M = 59.7, SD = 15.4 vs. M = 58.8, SD = 12.7, p = .67), and sleep disturbances scores (M = 9.7, SD = 2.3 vs. M = 11.4, SD = 2.8, p = .54), between the three participants that were unable or unwilling to complete the follow-up measure, and those that completed both measurements.

Treatment response

Participants that completed the pre-treatment and follow-up measurement demonstrated a significant average decrease of 6.1 points in posttraumatic stress reactions severity between pre-treatment and follow-up severity (M = 58.8, SD = 12.7) and follow-up (M = 52.7, SD = 20.2) t (63) = 37.0, $p < .001$, corresponding to a small to medium treatment effect (d = .36). The RCI calculation indicated that a 9 point improvement or worsening in posttraumatic stress reactions severity scores demonstrated statistical reliable change. One third (31.3%, n = 20) of the sample demonstrated statistical reliable improvement, 18.8% (n = 12) worsened, and 50.0% (n = 32) of the participants remained stable (i.e. no statistical reliable change).

Sleep disturbances score distributions

The sleep disturbances mean item scores (range 0-4) were M = 2.9, SD = 1.3 (trouble falling asleep), M = 2.5, SD = 1.3 (waking up early in the morning), M = 3.2, SD = 1.0 (sleep that is restless or disturbed). None of the veterans reported an absence of sleep disturbances at the start of treatment. The severity of sleep disturbances varied across the sample (Figure 2). Compared to a Dutch norm group of 5611 psychiatric outpatients, one-fifth (18.8%) reported ‘extreme’ levels, 43.8% reported ‘high’ levels, 10.9% reported ‘above average’ levels, and one-quarter (26.6%) reported ‘average’ to ‘below average’ sleep disturbances scores.

Relationships between study variables

Table 2 provides a correlation matrix regarding the continuous study variables of interest. Pre-treatment sleep disturbances were moderately correlated to the pre-treatment (r = .47, $p <$

.001) and posttreatment (r = .38, p = .002) posttraumatic stress reactions severity scores. There was no significant association between pre-treatment sleep disturbances and the pre-post posttraumatic stress reactions severity change score (r = -.09, p = .51). There was a strong correlation between the post-treatment posttraumatic stress reactions severity score and the pre-post posttraumatic stress reactions change scores score (r = .81, p < .001), indicating a shared variance of 66.6% between both scores. There were significant relationships between pre-treatment sleep disturbances, and the covariates number of received psychotherapy sessions (r = .28, p = .03). An ANOVA analysis detected no differences in pre-treatment sleep disturbances severity between the treatment locations (p = .22).

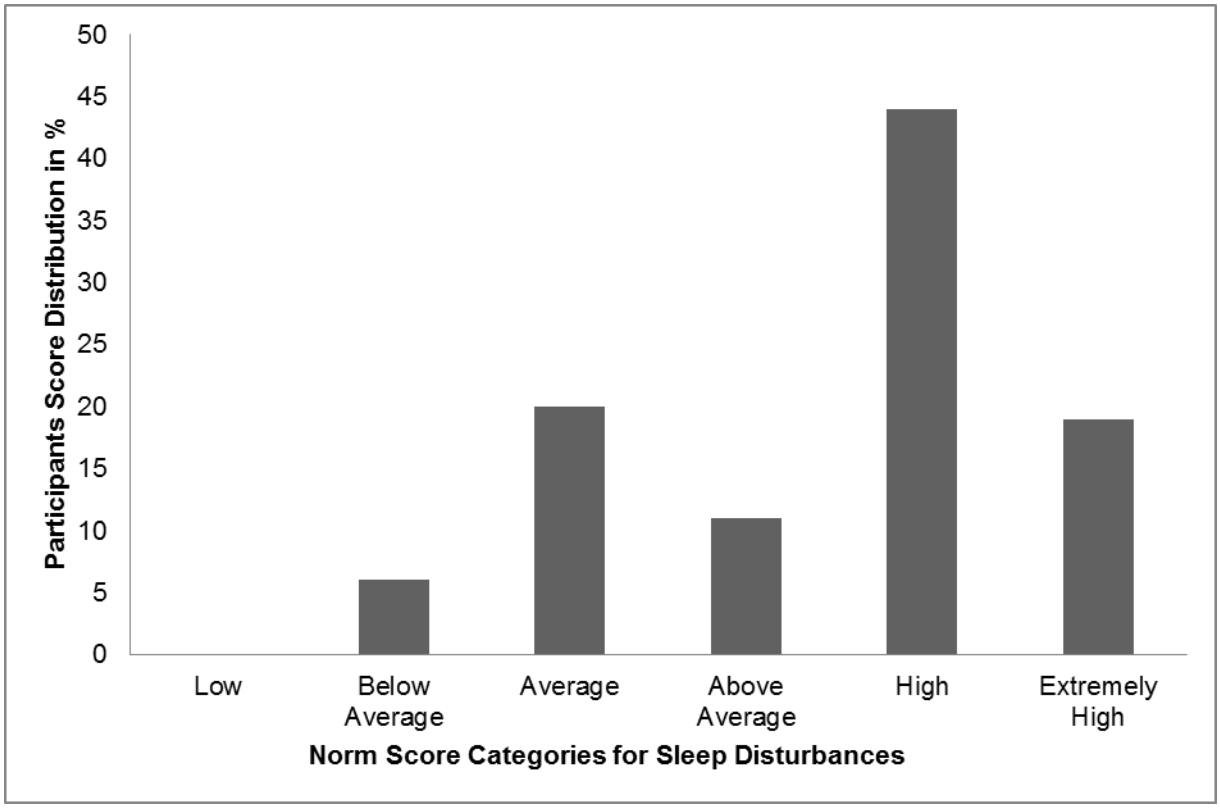

Figure 2. *Participants allocated to norm score category*

Note: Norm scores for comparison originated from Dutch policlinic psychiatric patients (n = 5611) on the SCL-90 sleep difficulties scale. See Dutch SCL-90-R manual (Arrindell & Ettema, 2003).

Table 2

Correlation matrix

		PTSD *Pre*	PTSD *Post*	PTSD *PrePost*	Sleep *Pre*	No. of Sessions
PTSD severity pre	IES-22	—	26*	35**	.47**	.26*
PTSD severity post	IES-22		—	-.81**	.38**	.34**
PTSD severity symptom pre-post	IES-22			—	-.08	-.17
Sleep Disturbances Severity pre	SCL90				—	.28*
No. of sessions						—
M		58.8	52.7	6.1	8.4	24.5
SD		12.7	20.2	20.8	2.8	19.0

Note. Pre = pre-treatment; Post = posttreatment; PrePost = difference between pre and posttreatment PTSD severity. No. of sessions = Number of received psychotherapy sessions. Sleep Disturbances were measured with the SCL-90 Sleep Difficulties scale (sum score range 0-12).

*$p < .05$. ** $p < .01$

Sleep disturbances as PTSD treatment symptom change predictor

The assumptions (no multicollinearity, predictor variance, normality of the standardized residuals, homoscedasticity, independent errors, normally distributed errors, independent outcome variables, linearity; Field, 2009) for performing multiple hierarchical regression analyses were met, except for the assumption of normality for the standardized residuals. A visual inspection of the standardized residuals showed a normal distribution with a slight positive skew. A Kolmogorov–Smirnov (K-S) test was performed for a formal assessment of normality. The results signified non-normality $D(64) = .13$, $p = .01$. A log transformation of the dependent variable and removal of one extreme outlier did ensure a normal distribution of the standardized residuals scores $D(63) = .07$, $p = .20$). The data transformation however did

not alter the hierarchical regression model results compared to the untransformed model results; the changes were minor and considered redundant. It was decided to abandon the log transformation for the sake of simplicity and ease in interpreting the results. The log transformation information is available and can be requested from the first author (Haagen).

A hierarchical multiple regression analysis was conducted (Table 3). In the first step, the three covariates were entered to the model. Together, the covariates contributed significantly to the posttraumatic stress reactions change score (F (4, 59) = 5.3, $p < .001$) and accounted for 26.4% of the observed differences in the posttraumatic stress reactions change score. Pre-treatment posttraumatic stress reactions severity was significantly and positive related to the posttraumatic stress reactions change score, indicating that veterans with more severe posttraumatic stress reactions symptoms experienced more posttraumatic stress reactions symptom alleviation (improvement).The number of psychotherapy sessions, and one of the treatment locations were significantly and negative related to the posttraumatic stress reactions change score, meaning that one treatment location and the number of sessions were associated with a diminished posttraumatic stress reactions treatment effect.

In the second and final step, sleep disturbances was added to the model (Table 3). Adding sleep disturbances to the model led to a significant increase of 8.8% in the amount of observed differences in the posttraumatic stress reactions change score accounted for by the model (F (5, 58) = 6.3, $p < .001$). The overall model with covariates and sleep disturbances accounted for 35.2% of the observed differences in the posttraumatic stress reactions change score. Sleep disturbances severity was significantly negative related to the posttraumatic stress reactions change score, indicating that higher sleep disturbances severity was associated with a diminished posttraumatic stress reactions treatment effect.

Table 3

Sleep disturbances as a predictor of PTSD treatment symptom reduction

					95% CI*(B)*	
Variables	ΔR^2	*B*	*SE(B)*	β	Lower	Upper
Step 1 (Control Variables)	26.4%**					
Pre-treatment PTSD symptom severity		1.0***	.20	.62***	.60	1.4
Number of psychotherapy sessions		-.35*	.13	-.32*	-.61	-.08
Treatment Centre 1		-1.5	5.7	-.03	-12.9	9.8
Treatment Centre 2		-21.3**	7.2	-.34**	-35.8	-6.8
Step 2	8.8%**					
Sleep Disturbances Severity		-2.6**	.93	-.35**	-4.5	-.75
Total R^2	35.2%***					

Note: CI = Confidence Interval. SE = Standard Error. Pre-treatment PTSD symptom severity was measured with the IES-22 (sum score range 0-88). Sleep Disturbances were measured with the SCL-90 Sleep Difficulties scale (sum score range 0-12). The participating centers were dummy coded in Centre 1 and Centre 2. The dependent variable was pre-post posttraumatic reactions severity score change. A positive score reflected posttraumatic reactions severity decrease.

* $p < .05$. ** $p < .01$. *** $p < .001$

Discussion

The current study examined the impact of sleep disturbances on treatment symptom reduction for veterans with PTSD. PTSD psychotherapy was effective in reducing posttraumatic stress reactions severity. In keeping with the hypothesis, pre-treatment sleep disturbances had a negative significant impact on psychotherapy effectiveness, after controlling for pre-treatment posttraumatic stress reactions severity, the number of received psychotherapy sessions and the treatment location. In other words, veterans with more severe sleep disturbances were less

likely to reduce posttraumatic stress reactions severity after six months of psychotherapy. These findings demonstrated the negative impact of sleep disturbances on PTSD treatment.

The determination of the working mechanism for sleep disturbances on treatment symptom reduction is beyond the scope of this article. A number of promising explanations can be forwarded. Sleep plays a significant part in the assimilation and consolidating of new memories, making them more resistant to change or suppression, and may unwarrantedly entrench traumatic experiences overnight within our memory (Liu et al., 2016). The same mechanism can also be used to explain why PTSD psychotherapy is less effective for those with severe sleep disturbances. Psychotherapy delivers new information that fosters non-threatening memory associations above the conditioned traumatic memory associations (i.e., fear extinction) that elicit a conditioned fear response. Psychotherapeutic experiences are encoded into new memories that are susceptible to change until sleep promotes their consolidation and change-resistance (Liu et al., 2016). Severe sleep disturbances obstruct the consolidation efforts of the new memories (Germain, 2013; Germain et al., 2008; Pace-Schott et al., 2014; Rauchs & Peigneux, 2012), meaning that the new memories are less effective in suppressing or otherwise counteracting traumatic memories.

Alternatively, sleep disturbances may be the results of clinical depression or depressive symptoms. Nightmares are strongly associated with depressive mood states (Köthe, Lahl, & Pietrowsky, 2006), and there is a ten times higher likelihood of clinical depression among patients that reported insomnia-induced sleep disturbances (Taylor, Lichstein, Durrence, Reidel, & Bush, 2005). The presence of a clinical depression and depressive symptoms predicted poor PTSD treatment symptom reduction in refugees with PTSD, a population also affected by traumatic war-experiences (Haagen, Ter Heide, Mooren, Knipscheer, & Kleber, 2016), and may be indicative of veteran PTSD nonresponse (Sripada et al., 2017). However, another study found depression to moderate the relationship between PTSD and sleep disturbances, reducing the speed of PTSD recovery for depressed persons with PTSD, though it did not lead to poorer PTSD treatment symptom reduction in the long-term (on average 8 months) (Lommen et al., 2016).

The present findings contrasted with findings by Lommen and colleagues (2016), who reported no evidence of sleep as a negative predictor of PTSD treatment symptom reduction. There are a number of differences between both studies that may explain the findings. Lommen examined predominantly female patients (60%), whereas the present study focused almost exclusively on men (3% female). There are neurobiological sex differences that may impact sleep quality and sleep processes differently (e.g., Steiger et al., 2013).

Electroencephalography (EEG) studies with females demonstrated longer rapid eye movement (REM) sleep duration and sleep percentage, compared to healthy female controls. Males with PTSD demonstrated no differences compared to their healthy counterparts (Richards et al., 2013). REM is considered an important sleep phase in promoting memory consolidation (Pace-Schott et al., 2014). These findings indicate that sleep disturbances may be especially associated with memory consolidation disturbances in men with PTSD, possibly disrupting their processing of traumatic experiences. sex-specific differences may also be related to cyclic menstrual hormonal changes that impact fear extinction processes (Kobayashi, Cowdin, & Mellman, 2012). Furthermore, the present study examined veterans with warzone-related PTSD, as opposed to National Health Service (NHS) outpatient patients with PTSD that reported a variety of traumatic experiences (Lommen et al., 2016). Sleep disturbances were measured with the SCL90-R 3-item subscale (trouble falling asleep', 'waking up early in the morning', and 'sleep that is restless or disturbed'). These items correspond well with the specific nature of sleep disturbances (Smits et al., 2015). They may be more distinct from general distress compared to the single-item in the study of Lommen and colleagues: 'how well did you sleep?'. The contrasting findings may also be explained by the chronic nature of deployment. Perhaps the extent of sleep disturbances is more pronounced in veterans due to sleep deprivation as a result of constant vigilance required to operate in theatres of war and civil unrest (Lewis et al., 2009).

Implications

Sleep disturbances are commonplace among veterans with PTSD, but the extent of the disturbances tends to vary between veterans. Compared to a general psychiatric population, roughly one in every two veterans reported 'severe' to 'extreme' levels of sleep disturbances in the current study. In contrast, one in every four veterans with PTSD reported 'average' or 'below average' sleep disturbances levels. Sleep disturbances exacerbate general discomfort and symptom severities (Cox & Olatunji, 2015), suppresses the quality of live and functioning, and cause premature mortality (Alvarez & Ayas, 2004). These issues warrant addressing sleep disturbances, irrespective of PTSD treatment symptom reduction.

Progressively severe sleep disturbances appear to compromise the effectiveness of PTSD psychotherapies for veterans and support recent veteran treatment findings (Sripada et al., 2017), though a similar finding was not reported in a general outpatient population (Lommen et al., 2015). It is recommended to screen and assess the extent of the sleep disturbances before starting treatment. Insomnia is primarily diagnosed by clinical evaluation,

and can include a sleep history, medical, substance and psychiatric history, self-report questionnaires, sleep logs, and a partner interview (Schutte-Rodin, Broch, Buysse, Dorsey, & Sateia, 2008). Early assessment offers opportunities to address sleep disturbances before - or parallel with - PTSD treatment, to enhance the effectiveness of PTSD psychotherapy. PTSD treatment alone does not necessarily provide sufficient attention to addressing sleep disturbances. Sleep education may not be sufficient without sleep intervention. As significant residual sleep disturbances often remain after PTSD treatment (Spoormaker & Montgomery, 2008), it is recommended to target sleep disturbances with interventions that are specifically targeting disrupted sleep. Sleep disturbances are modifiable in treatment (Germain, 2013), and evidence-based interventions for different types of sleep disturbances exist (Aurora et al., 2010).

Strengths and limitations

The use of a prospective longitudinal cohort design with no in- or exclusion criteria, should increase the generalizability of the results, reflecting patient and treatment conditions in real world practice. Cohort designs are however less suited to eliminate unmeasured factors that could influence the current results. One of the unmeasured factors was medication use by the participants. It is possible that medication use interacted with sleep processes and treatment symptom reduction without our knowledge. Furthermore, the study examined a male veteran PTSD sample, the current findings may not be generalizable to women. Treatment drop-out and premature successful treatment termination may also have affected the generalizability of the results. However, treatment dropouts did not differentiate in IES-R severity and sleep disturbances severity, compared to the study completer sample. Those that successfully terminated treatment before the six months follow-up measure demonstrated significantly less sleep disturbances compared to the completer sample; their lower sleep disturbances levels may actually explain why they sufficiently recovered from PTSD to end treatment.

Sleep disturbances were measured in a reliable and valid manner, unfortunately, the instrument offers only limited insight into the nature of the sleep disturbances. It does not differentiate between insomnia and nightmare related sleep disturbances, or assess sleep habits and patterns, or the use of sleep medication. It is recommended to use more comprehensive measures (e.g., the Sleep Disorders Questionnaire; Douglass et al., 1994) that differentiate between specific sleep disturbances categories.

Different interventions targeting PTSD were pooled together in accordance with the common factors model. This perspective contrasts with the medical model that attributes

different outcomes for different interventions. Unfortunately, the influence of any treatment-specific differences could not be examined as it would have resulted in a lack of power.

Furthermore, sleep disturbances were measured subjectively, using a self-report questionnaire, rather than by objective measures, such as an EEG instrument. There may be discrepancies between the perception of sleep disturbances and actual sleep disturbances (Cox & Olatunji, 2015). As such, the current promising results require further replication.

Conclusion

Sleep disturbances obstruct PTSD treatment improvement. The current results require replication. If current results are upheld, it will have practical consequences for clinicians. Severe sleep disturbances need to be addressed before - or parallel with - PTSD treatment to enhance effectiveness. Clinicians need to be aware that sleep disturbances are almost always present but vary in intensity between individuals with PTSD. PTSD interventions do not necessarily target sleep disturbances. There are effective sleep interventions for insomnia and nightmares that can be straightforwardly deployed to address sleep disturbances, to raise the odds of recovery for veterans with PTSD in psychotherapy treatment.

Acknowledgements

We thank Foundation Centre ’45 [Stichting Centrum ‘45], The Military Mental Health Care [Militaire Geestelijke Gezondheidszorg], and Psychotrauma Centre South-Netherlands [Psychotrauma Centrum Zuid-Nederland, onderdeel van Reinier van Arkel Groep] for their participation. We are grateful to the Dutch National Health System for Veterans [Landelijk Zorgsysteem voor Veteranen] that spearheaded the development and implementation of a comprehensive uniform diagnostic set and for providing their support to the present project.

References

Alvarez, G. G., & Ayas, N. T. (2004). The impact of daily sleep duration on health: A review of the literature. *Progress in Cardiovascular Nursing, 19,* 56–59. doi:10.1111/j.0889-7204.2004.02422.x

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders,* (5th ed.). Washington, DC: Author.

Arrindell, W. A., & Ettema, J. H. (2003). *SCL 90 Symptom checklist: Handleiding bij een multidimensionele psychopathologie indicator.* Lisse: Swets Test Publishers.

Aurora, R. N., Zak, R. S., Auerbach, S. H., Casey, K. R., Chowduri, S., Krippot, A. …, Morgenthaler, T.I. (2010). Best practice guide for the treatment of nightmare disorder in adults. *Journal of Clinical Sleep Medicine, 6*(4), 389-401.

Benish, S., Imel, Z., & Wampold, B. (2008). The relative efficacy of bona fide psychotherapies for treating post-traumatic stress disorder: A meta-analysis of direct comparisons. *Clinical Psychology Review, 28,* 746-758. doi:10.1016/j.cpr.2007.10.005

Blissit, P. A. (2001). Sleep, memory, and learning. *Journal of Neuroscience Nurses, 33*(4), 208-215.

Boden, M. T., Bonn-Miller, M. O., Vujanovic, A. A., & Drescher, K. D. (2012). A prospective investigation of changes in avoidant and active coping and posttraumatic stress disorder symptoms among military veteran. *Journal of Psychopathology and Behavioral Assessment, 34,* 433-439. doi:10.1007/s10862-012-9293-6

Bonn-Miller, M. O., Vujanovic, A. A., & Drescher, K. D. (2011). Cannabis use among military veterans after residential treatment for posttraumatic stress disorder. *Psychology of Addictive Behaviors, 25,* 485-491. doi:10.1037/a0021945

Cox, R. C., & Olatunji, B. O. (2015). A systematic review of sleep disturbance in anxiety and related disorders. *Journal of Anxiety Disorders 37,* 104-129. doi:10.1016/j.janxdis.2015.12.001

Dalecki, M., & Willits, F. K. (1991). Examining change using regression analysis: Three approaches compared. *Sociological Spectrum: Mid-South Sociological Association, 11,* 127-145. doi:10.1080/02732173.1991.9981960

Derogatis, L. (1994). *SCL-90-R: Administration, scoring and procedure manual.* Minneapolis, MN: National Computer Systems.

Dohrenwend, B. P., Turner, J. B., Turse, N. A., Adams, B. G., Koenen, K. C., & Marshall, R. (2006). The psychological risks of Vietnam for US veterans: A revisit with new data and methods. *Science, 313*(5789), 979-982.

Douglass, A.B., Bornstein, R., Nino-Murcia, G., Keenan, S., Miles, L., Zarcone, V. P. …, Dement, W. C. (1994). The Sleep Disorders Questionnaire-I: Creation and multivariate structure of SDQ. *Sleep, 17*(2), 160-167.

Ehlers, A., Bisson, J., Clark, D., Creamer, M., Pilling, S., Richards, D., … Yule, W. (2010). Do all psychological treatments really work the same in posttraumatic stress disorder? *Clinical Psychology Review, 30*, 269-276. doi:10.1016/j.cpr.2009.12.001

Engelhard, I. M., Van den Hout, M. A.,Weerts, J., Arntz, A., Hox, J. J. C. M., & McNally, R. (2007). Deployment-related stress and trauma in Dutch soldiers returning from Iraq. *British Journal of Psychiatry, 191*(2), 140–145.

Field, A. (2009). *Discovering statistics using SPSS.* 3 ed. London: SAGE publications

Forbes, D., Creamer, M., Hawthorne, G., Allen, N., & McHugh, T. (2003). Comorbidity as a predictor of symptom change after treatment in combat-related posttraumatic stress disorder. *The Journal of Nervous & Mental Disease, 191*(2), 93-99.

Gerhart, J. I., Hall, B. J., Russ, E. U., Canetti, D., & Hobfoll, S. E. (2014). Sleep disturbances predict later trauma-related distress: Cross-panel investigation amidst violent turmoil. *Health Psychology, 33*, 365-372. doi:10.1037/a0032572

Germain, A. (2013). Sleep disturbances as the hallmark of PTSD: Where are we now? *The American Journal of Psychiatry, 170*, 372-382. doi:10.1176/appi.ajp.2012.12040432

Germain, A., Buysse, D. J., & Nofzinger, E. (2008). Sleep-specific mechanisms underlying posttraumatic stress disorder: Integrative review and neurobiological hypotheses. *Sleep Medicine Reviews 12*, 185–195. doi:10.1016/j.smrv.2007.09.003

Ginzburg, K., Ein-Dor, T., & Solomon, Z. (2010). Comorbidity of posttraumatic stress disorder, anxiety and depression: A 20-year longitudinal study of war veterans. *Journal of Affective Disorders, 123*, 249-257. doi:10.1016/j.jad.2009.08.006

Haagen, J. F. G., Ter Heide, F. J. J., Mooren, T. M., Knipscheer, J. W., & Kleber, R. J. (2016). Predicting post-traumatic stress disorder treatment response in refugees: Multilevel analysis. *British Journal of Clinical Psychology, 56*, 69–83. doi:10.1111/bjc.12121

Jacobson, N. S., & Truax, P. (1991). Clinical significance: A statistical approach to defining meaningful change in psychotherapy research. *Journal of Consulting and Clinical Psychology, 59*(1), 12-19. http://dx.doi.org/10.1037/0022-006X.59.1.12

Kleber, R. J., & De Jong, E. (1998). D*utch version of the Impact of Event Scale-Revised. Internal report.* Utrecht: Department of Clinical Psychology, Utrecht University.

Kloens, G. J., Barelds, D. P. H., Luteijn, F., & Schaap, C. P. D. R. (2005). *Diagnostiek met vragenlijsten in de eerste lijn.* Katwijk: Ichthusgroep.

Kobayashi, I., Cowdin, N., & Mellman, T. A. (2012). One's sex, sleep, and posttraumatic stress disorder. *Biology Sex Differences, 3*:29. doi:10.1186/2042-6410-3-29

Köthe, M., Lahl, O., & Pietrowsky, R. (2006). Trait variables of coping, mood, and, behavior after nightmares [Habituelle Stressverarbeitung, Befindlichkeit und Verhalten nach Alpträumen]. *Zeitschrift Fur Klinische Psychologie Und Psychotherapie*, *35*, 306-313. doi:10.1026/1616-3443.35.4.306

Krystal, J. H., Pietrzak, R. H., Rosenheck, R. A., Cramer, J. A., Vessicchio, J., Jones, K. M., ... Krystal, A.D. (2016). Sleep disturbance in chronic military-related PTSD: Clinical impact and response to adjunctive risperidone in the Veterans Affairs Cooperative Study# 504. *The Journal of Clinical Psychiatry, 77*, 483-491. doi:10.4088/JCP.14m09585

Lewis, V., Creamer, M., & Failla, S. (2009). Is poor sleep in veterans a function of post-traumatic stress disorder? *Military Medicine, 174*(9), 948-951.

Liu, Y. Lin, W., Liu, C., Luo, Y., Wu, J., Bayley, P. J., & Qin, S. (2016). Memory consolidation reconfigures neural pathways involved in the suppression of emotional memories. *Nature Communications, 7*:13375. doi:10.1038/ncomms13375

Lommen, M. J., Grey, N., Clark, D. M., Wild, J., Stott, R., & Ehlers, A. (2016). Sleep and treatment outcome in posttraumatic stress disorder: results from an effectiveness study. *Depression and anxiety, 33*, 575-583. doi:10.1002/da.22420

Marmar, C. R., Schlenger, W., Henn-Haase, C., Qian, M., Purchia, E., Li, M., ... Karstoft, K. I. (2015). Course of posttraumatic stress disorder 40 years after the Vietnam War: Findings from the National Vietnam Veterans Longitudinal Study. *JAMA psychiatry, 72*, 875-881. doi:10.1001/jamapsychiatry.2015.0803

McHugh, R. K., Hu, M-C., Campbell, A. N. C., Hilario, E. Y., Weiss, R. D., & Hien, D. A. (2014). Changes in sleep disruption in the treatment of co-occurring posttraumatic stress disorder and substance use disorders. *Journal of Traumatic Stress, 27,* 82-89. doi:10.1002/jts.21878

Nijdam, M. J., De Vries, G-J., Gersons, B. P., & Olff, M. (2015). Response to psychotherapy for posttraumatic stress disorder: The role of pretreatment verbal memory performance. *The Journal of Clinical Psychiatry, 76*, 1023-1028. doi:10.4088/JCP.14m09438

Pace-Schott, E. F., Germain, A., & Milad, M. R. (2014). Sleep and REM sleep disturbance in the pathophysiology of PTSD: The role of extinction memory. *Biology of Mood & Anxiety Disorders, 5*:3. doi:10.1186/s13587-015-0018-9

Rauchs, G., & Peigneux, P. (2012). Covert Reorganization / Spatial Learning. In: N. M. Seel (Ed.). *Encyclopedia of the Sciences of Learning* (pp. 828-833). New York: Springer doi:10.1007/978-1-4419-1428-6_579

Rauch, S., & Foa, E. (2006). Emotional processing theory (EPT) and exposure therapy for PTSD. *Journal of Contemporary Psychotherapy, 36*, 61–65. doi:10.1007/s10879-006-9008-y.

Reijnen, A., Rademaker, A. R., Vermetten, E., & Geuze, E. (2014). Prevalence of mental health symptoms in Dutch military personnel returning from deployment to Afghanistan: A 2-year longitudinal analysis. *European Psychiatry, 30*, 341-346. doi:10.1016/j.eurpsy.2014.05.003

Richards, A., Metzler, T. J., Ruoff, L. M., Inslicht, S. S., Rao, M., Talbot, L. S., … Neylan, T. C. (2013). Sex differences in objective measures of sleep in post-traumatic stress disorder and healthy control subjects. *Journal of Sleep Research, 22,* 679–87. doi:10.1111/jsr.12064.

Schutte-Rodin S., Broch. L., Buysse, D., Dorsey, C., & Sateia, M. (2008). Clinical guideline for the evaluation and management of chronic insomnia in adults. *Journal of Clinical Sleep Medicine, 4*(5), 487-504.

Skodol, A. E., Schwartz, S. H. A. R. O. N., Dohrenwend, B. P., Levav, I., Shrout, P. E., & Reiff, M. (1996). PTSD symptoms and comorbid mental disorders in Israeli war veterans. *The British Journal of Psychiatry, 169*(6), 717-725.

Smits, I. A. M., Timmerman, M. E., Barelds, D. P. H., & Meijer, R. R. (2015). The Dutch Symptom Checklist-90-Revised: Is the use of the subscales justified? *European Journal of Psychological Assessment, 31*, 263-271. doi:10.1027/1015-5759/a000233.

Spoormaker, V. I., & Montgomery, P. (2008). Disturbed sleep in post-traumatic stress disorder: Secondary symptom or core feature? *Sleep Medicine Reviews, 12,* 169–184. doi:10.1016/j.smrv.2007.08.008

Sripada, R. K., Pfeiffer, P. N., Rampton, J., Ganoczy, D., Rauch, S. A. M., Polusny, M. A., & Bohnert, K. M. (2017). Predictors of PTSD symptom change among outpatients in the U.S. Department of Veterans Affairs Health Care System. *Journal of Traumatic Stress, 30,* 45–53. doi:10.1002/jts.22156

Steiger, A., Dresler, M., Kluge, M., & Schüssler, P. (2013). Pathology of sleep, hormones and depression. *Pharmacopsychiatry, 46*, S30-S35. doi:10.1055/s-0033-1337921

Taylor D. J., Lichstein, K. L., Durrence, H. H., Reidel, B. W., & Bush, A. J. (2005). Epidemiology of insomnia, depression, and anxiety. *Sleep, 28*(11), 1457-64.

Van Breukelen, G. J. P. (2013) ANCOVA versus CHANGE from baseline in nonrandomized studies: The difference. *Multivariate Behavioral Research, 48*6, 895-922. doi:10.1080/00273171.2013.831743

Van Liempt, S., Van Zuiden, M., Westenberg, H., Super, A., & Vermetten, E. (2013). Impact of impaired sleep on the development of PTSD symptoms in combat veterans: A prospective longitudinal cohort study. *Depression and Anxiety, 30*, 469-474. doi:10.1002/da.22054

Wampold, B. E., Ahn, H-n., & Coleman, H. L. K. (2001). Medical model as metaphor: Old habits die hard. *Journal of Counseling Psychology, 48*(3), 268-273.

Wampold, B. E., Imel, Z. E., Laska, K. M., Benish, S., Miller, S. D., Flückiger, C., … Budge, S. (2010). Determining what works in the treatment of PTSD. *Clinical Psychology Review, 30*, 923-933. doi:10.1002/jclp.20683

Wampold, B. E., Frost, N. D., & Yulish, N. E. (2016). Placebo Effects in Psychotherapy: A Flawed Concept and a Contorted History. *Psychology of Consciousness: Theory, Research, and Practice, 3*, 108-120. doi:10.1037/cns0000045

Weiss, D. S., & Marmar, C. R. (1997). *The impact of event scale— Revised*. In J. P. Wilson, & T. M. Keane (Eds.), Assessing psychological trauma and PTSD (pp. 399-411). New York, NY: Guilford Press.

Williams, R. H., & Zimmerman, D. W. (1996). Are simple gain scores obsolete? *Applied Psychological Measurement, 20*(1), 59–69.

Wisco, B. E., Marx, B. P., Wolf, E. J., Miller, M. W., Southwick, S. M., & Pietrzak, R. H. (2014). Posttraumatic stress disorder in the US veteran population: Results from the National Health and Resilience in Veterans Study. *The Journal of clinical psychiatry, 75*, 1338-1346. doi:10.4088/JCP.14m09328

Zayfert C., & De Viva, J. C. (2004). Residual insomnia following cognitive behavioral therapy for PTSD. *Journal of Traumatic Stress, 17*(1), 69–73

Chapter 7

Using different frameworks to advance veteran PTSD psychotherapy effectiveness

Submitted as:

Haagen, J. F. G., Knipscheer, J. W., & Kleber, R. J. (2017). Using alternative frameworks to examine veteran PTSD psychotherapy effectiveness

Abstract

Does the working of psychotherapy depend on the specific ingredients of a given intervention? Or is the type of intervention rather irrelevant and does psychotherapy effectiveness depend on common factors instead? The arguments in this controversy are relevant not only to the field of psychotherapy outcome research but also to clinical practice as well as policy making with regard to psychological interventions. In this paper we focus on this controversy in relation to posttraumatic stress disorder (PTSD) and the effectiveness of treatments for veterans suffering from this disorder as PTSD guideline-recommendations do not generalize well to veterans. Also, RCT comparison studies deliver ample evidence of the superiority of certain interventions above other interventions. However, results of recent meta-analyses show that the differences between bona fide therapies are small. Consequently, the efficacy of psychotherapies cannot be solely attributed to specific effects of the various interventions. We discuss three models that explain psychotherapy effects, the dominant medical model of psychotherapy, the placebo expectancy / conditioning model, and the common factors / contextual model. The placebo and common factors models appear equally or more influential to recovery compared to the dominant model. Improving existing treatments and developing new treatments are needed. Finally, implications for research and clinical practice are discussed.

Acknowledgment contribution authors

Designed research: Not applicable

Performed research: Not applicable

Analysed data: Not Applicable

Wrote the paper: Haagen, Knipscheer, Kleber

Introduction

Eighty years ago, Saul Rosenzweig (1936) made his famous remark on the Dodo Bird based on a quote from the novel Alice in Wonderland: 'Everybody has won, and all must have prizes'. Rosenzweig argued that all psychotherapies are equally effective, operating via factors common in most psychotherapies, rather than specific factors alleged to be responsible for the effectiveness of a given therapy. A controversy erupted that has lasted till today. Does the working of psychotherapy depend on the specific ingredients of a given intervention? Or is the type of intervention rather irrelevant and does psychotherapy effectiveness depend on common factors instead? The arguments in this controversy are highly relevant not only to the field of psychotherapy outcome research but also to clinical practice as well as policy making with regard to psychological interventions. In this paper we will focus on this controversy in relation to posttraumatic stress disorder (PTSD) and the effectiveness of treatments for veterans suffering from this disorder. Rosenzweig's statement remains timely and provides opportunities to enhance insights in PTSD treatment effectiveness for veterans.

Veterans and PTSD

Due to the nature of their profession, combat veterans were exposed to life-threatening events, such as battles, ambushes and enemy fire. Such challenges make soldiery a risk occupation for the development of PTSD with a prevalence rate of 3-9% (Dohrenwend et al., 2006; Engelhard et al., 2007; Marmar et al., 2015; Wisco et al., 2014). PTSD is a disruptive psychological disorder that is characterized by intrusions of a traumatic event, avoidance behavior, negative alterations in cognitions, and symptoms of arousal and reactivity (American Psychiatric Association [APA], 2013).

There are several treatment guidelines available on how best to treat PTSD (American Psychological Association [APA], 2017; Australian Centre for Posttraumatic Mental Health [ACPMH], 2013; Institute of Medicine [IOM], 2008; International Society for Traumatic Stress Studies [ISTSS], 2009; National Institute for Health and Clinical Excellence [NICE], 2009; The management of post-traumatic stress Working Group [VA-DOD], 2010). These guidelines strongly favour cognitive behavioural therapy (CBT), cognitive processing therapy (CPT), cognitive therapy (CT), prolonged (prolonged) exposure therapy (PE), and favour to a somewhat lesser extent brief eclectic psychotherapy (BEP), eye movement desensitization and reprocessing therapy (EMDR), narrative exposure therapy (NET), and stress inoculation

therapy (SIT), albeit in varying degrees. Nearly all of these interventions are characterized by the use of exposure to characteristics of the traumatic experience as a therapy component.

Veterans with PTSD are considered a difficult-to-treat population (Haagen, Smid, Knipscheer, & Kleber, 2015). Guideline-recommended interventions are effective for veterans with PTSD (g = 1.12; Haagen et al., 2015). Despite its effect, one-third to two-thirds of the veterans with PTSD retain their diagnosis with considerable residual symptomatology after guideline-recommended treatment (Bradley et al., 2005; Goodson et al., 2011; Steenkamp, Brett, Litz, Hoge, & Marmar, 2015).

To increase the efficacy of veteran PTSD psychotherapy, the United States Department of Veterans Affairs (VA) selected two guideline-recommended exposure-based interventions (PE and CPT) to implement them nationwide (Cook et al., 2015). The vast and decade-long undertaking led to the training of thousands of mental health providers in either approach, the development of consultation programs, and the introduction of evidence-based psychotherapy coordinators in all VA centers in the USA (Cook et al., 2015). These actions follow the VA policy mandate to ensure that all veterans should have access to PE or CPT (VA/DoD Clinical Practice Guideline Working Group, 2010).

A critical moment in the treatment of veterans with PTSD

Ten years after the start of the large scale VA implementation project, it appears that the veteran PTSD health care field is caught up in an uncertain juncture as old certainties regarding the superiority of guideline-recommended interventions seem to waver. First, according to the most up-to-date PTSD treatment guideline (APA, 2017, p. 77):

> "there is insufficient evidence from the systematic review to know whether any of the psychological or pharmacological treatments have stronger or weaker effects across subgroups based on any of the following: demographic characteristics (e.g., … military veteran, …), type of trauma (e.g., … combat, …), comorbid diagnoses (e.g., substance use disorder, depression), duration of symptoms, exposure to childhood trauma, repeat victimization, and level of severity at presentation."

The APA statement implies that PTSD guideline-recommendations do not generalize well to veterans. Not only because of their occupation, but due to the nature of their traumatic experiences (combat) and common comorbid symptom manifestations of depression (37-51% prevalence) and substance disorder (21% prevalence) (Marmar et al., 2015; Petrakis,

Rosenheck, & Desai, 2011; Wisco et al., 2014). Second, PTSD guideline-recommended interventions appear to lose their superior treatment effect for PTSD patients with complex problems, including veterans, as was found in studies in the USA as well as the Netherlands (Gerger, Munder, & Barth, 2013; see also Ter Heide, Mooren, van de Schoot, De Jongh & Kleber, 2016). Guideline-recommended interventions were only marginally superior in effect size compared to control interventions (g = .11). Third, recent evidence revealed that PE and CPT, the two guideline-recommended PTSD interventions that the VA adopted, are only marginally superior in efficacy to other well-defined and trustworthy, although non-recommended interventions (e.g., present centered therapy [PCT]) for veterans with PTSD (Steenkamp et al., 2015). Similar marginal differences were found in a comprehensive meta-analytic comparison of trauma focused treatments and other professional but non-trauma focused psychotherapies of PTSD (Tran & Gregor, 2016). The latter interventions are frequently labelled as bona fide therapies (bona fide – in good faith - in the sense of sincerity, earnestness and absence of fraud or deception).

These findings do not discount PE or CPT as credible and effective interventions for veterans, but suggest that the factors responsible for their (and other PTSD interventions) efficacy, are less relevant compared to factors common in most psychotherapies to promote therapeutic recovery. To understand the workings of psychotherapy and how veterans health care can best continue forward, requires knowledge of meta-models that explain the workings of psychotherapy. We discuss three models that explain psychotherapy effects, the medical model of psychotherapy, the placebo expectancy / conditioning model, and the common factors / contextual model.

Medical model of psychotherapy outcome

Modern psychotherapy research benefitted significantly from adopting the medical model of intervention outcome (Castelnuovo, 2010). This model for psychotherapy is a meta-theory explaining how psychological or biological factors are connected to recovery. It is divided into five components (Wampold & Impel, 2015, p. 28):

1. psychological disorders occur in patients;
2. there is a biological or psychological explanation for their existence;
3. disorders operate via specific mechanisms of change that can be altered;
4. specific therapeutic procedures (ingredients) can be derived from the explanatory model to intervene in mechanisms of change;
5. these ingredients produce specific effects that are instrumental to recovery.

The medical model for psychotherapy requires that any given intervention demonstrates specificity: its unique added value beyond spontaneous remission or other interventions. Recovery is maximized with the application of specific interventions that produce the strongest treatment effects (Barlow, Bullis, Comer, & Ametaj, 2013). The model gave impetus to treatment research designs that isolate and demonstrate the specific effects (i.e., unique contributions) of psychotherapies (Walach, 2016). This approach enhanced psychotherapy's credibility as a recognized healing practice in a time when there was little evidence of its effects (Castelnuovo, 2010), and psychotherapy was even challenged as ineffective as was stated in the classical article by Eysenck (1952). The medical model became the dominant model in psychotherapy evaluation research (Elkins, 2007). It spurred the development of empirically supported interventions and treatment guidelines to assist clinicians in providing the best possible care for their patients by distinguishing between untrustworthy and credible interventions and to determine which interventions deliver superior treatment results.

Methodological designs to isolate specific effects

The randomized controlled trial (RCT) design excels in isolating and demonstrating specific effects by minimizing any threats to the internal study validity (Starcevic, 2003). The design favors diagnostic precision by generally investigating homogeneous samples of patients defined by a single disorder (Castelnuovo, 2010). RCTs use multiple treatment conditions that allow for head-to-head treatment comparisons. Participants are allocated *at random* to either treatment condition. Randomization is a methodological approach to equalize the influence of external factors (e.g., patient characteristics) on outcome between each condition to minimize selection bias (Viera & Bangdiwala, 2007). Rigorously trained clinicians and standardized treatment procedures ensure that treatment is delivered as intended with therapist idiosyncrasy minimized (Starcevic, 2003). The interventions under comparison are furthermore designed to be as similar as possible, except for those distinguishable specific therapeutic procedures under scrutiny. These therapeutic procedures represent the experimental (active) intervention. The control condition acts as a comparator and does not include the therapeutic procedures under scrutiny. The differences in final treatment outcomes between conditions demonstrate the specific effects of the superior intervention (or not, of course).

Support for the medical model of psychotherapy effects

RCT comparison studies delivered ample evidence of the superiority of certain interventions above other interventions. The results of comprehensive meta-analyses can be summarized as follows. Guideline-recommended interventions demonstrated strong pre-post treatment effects (d = 1.43 and g = 1.16), outperformed natural recovery (d = 1.11), as well as supportive psychotherapy control conditions that, according to the authors, were not intended to be therapeutic (d = .83 and g = .61) (Bradley et al., 2005; Gerger et al., 2014). Head-to-head comparisons demonstrated that TF-CBT (d = 1.27) and EMDR (d = 1.24) were more efficacious then hypnotherapy (d = .94), psychodynamic therapy (d = .90), and relaxation therapy (d = .45) (Van Etten & Taylor, 1992). In another meta-analysis it was found that CBT (exposure, CPT, and blended therapies) (g = 1.26) and EMDR (g = 1.01), outperformed psychodynamic therapy (g = .78) and hypnotherapy (g = .72) (Watts et al., 2013). A metaregression analysis showed that CPT (g = 1.33) and exposure therapy (g = 1.06) outperformed EMDR (g = .38) and stress management therapies [SM] (g = .16) (Haagen, Smid, Knipscheer, & Kleber, 2015). Furthermore, trauma focused CBT and EMDR were superior to non-trauma focused CBT at follow-up (Bisson, Roberts, Andrew, Cooper, & Lewis 2013). Also, CBT (regardless of exposure) outperformed exposure-only therapy and EMDR (Bradley et al., 2005). Finally, exposure therapy (effect size rank (EFR = 7.94), CT (EFR = 8.83), a blended approach (EFR = 8.04), were superior to EMDR (EFR = 5.89), PCT (EFR = 5.67), supportive counseling (EFR = 5.00) and treatment as usual (EFR = 5.00) (Cloitre, 2009). All these findings demonstrate varying effect sizes between interventions.

The medical model for psychotherapy: Partial confirmation of the evidence

The evidence does not, however, consistently add up in support of the medical model and the inference that specific effects are the engine behind therapeutic recovery. A considerable number of empirical studies demonstrated non-existent to negligible (small) superior effects between PTSD interventions. For example, there were no significant differences between two individual trauma focused therapies (CBT, EMDR) and one non-trauma focused therapy (SM) at post-treatment (Bisson et al., 2013). Another meta-analysis showed that PE, CPT, CT, EMDR, SIT were equally effective in reducing PTSD symptoms (Powers et al., 2010). Conceptually distinct PTSD interventions and mechanisms of change (psychodynamic, exposure, hypnotherapy) were equally effective in a head-to-head comparison in the first PTSD directed RCT (Brom, Kleber, & Defares, 1989). Non-trauma focused PCT, originally

developed to control for placebo effects, proved on par in efficacy with guideline-recommended PTSD interventions in a small meta-analysis (Frost, Laska, & Wampold, 2014). Finally, the lack of exposure to traumatic memories did not alter the size of the treatment effects for CBT (Bradley et al., 2005).

The differences in effects size between conceptually diverse PTSD interventions seem to wither and balance out when comparative non-therapeutic control conditions were restricted to those interventions that were genuine and intended to be therapeutic (Benish, Impel, & Wampold, 2008). However, this finding was contested by Ehlers and colleagues (2010), whose arguments were in turn were disputed by Wampold and colleagues (2010). Recently, researchers demonstrated that the difference between specific and non-specific psychological interventions of PTSD was reduced to a nonsignificant effect (g = .11) (Gerger et al., 2013), once analyses were restricted to complex clinical problems and structural equivalence of interventions. An extended meta-analysis using the data of an additional 48 studies revealed a markedly similar pattern. The treatment effect size differences between conceptually diverse genuine (bona fide) PTSD interventions were small (g = .27) to absent (g = .00) (Gerger et al., 2014). Likewise, Tran and Gregor (2016) found in another meta-analysis that trauma focused treatments (PE and exposure therapies) were only slightly more efficacious (g = .19) to than non-trauma bona fide therapies for PTSD. The differences were not clinically meaningful.

In this context findings of psychotherapy component studies are relevant. These studies are explicitly designed to examine specific effects by removing (dismantling) or adding key specific ingredients from or to a given intervention and compare the intervention to a control condition that mirrors the experimental condition (with or without the specific ingredient). A meta-analysis of 66 component studies demonstrated that key treatment components (e.g., exposure, cognitive therapy) increased the effect size of psychotherapy by d = .14 posttreatment and d = .28 at follow-up (Bell, Marcus, & Goodlad, 2013). Though this component meta-analysis of Bell and colleagues (2013) did not exclusively address PTSD, it included almost a dozen PTSD studies. These studies demonstrated similar outcomes as the main results.

These findings are indeed not unique for PTSD psychotherapy. Conceptually diverse interventions were also reported equally effective in a multitude of other fields, including—but not limited to— psychotherapy in general (Smith & Glass, 1977), medicine (Fulton, 2015, p. 13-16), Parkinson's disease (De La Fuente- Fernández et al., 2001), addiction (Millers & Moyers, 2015) and depression (Barth et al., 2013). This demonstrates

that superior interventions do not necessarily deliver superior results. The magnitude of the specific effects appears to be small (d = .00-.28) (Bell et al., 2013; Gerger et al., 2014; Marcus et al., 2014; Wampold et al., 1997). Giving rise to the notion that different factors influence treatment outcome besides specific therapeutic ingredients.

The medical model for psychotherapy: A limited source of information

The medical model favors the use of RCTs with homogeneous samples centered on a single disorder (e.g., PTSD), a specific treatment population (e.g., refugees, veterans, sexual assault survivors), with confounding symptom manifestations minimized (suicidality, comorbid disorders, including depression and substance disorders). RCTs are generally considered to be the most reliable form of scientific evidence because they reduce spurious causality and bias and because they are able to show whether interventions really work (separating the wheat for the chaff) (Van Everdingen et al., 2004).

Nevertheless, RCTs also have disadvantages. Any effort to isolate and demonstrate specific effects is irrevocable coupled with the loss of external validity (generalizability) (Cartwright, 2010). It was found that RCTs excluded a third of all treatment-seeking PTSD patient from participating (Bradley, Greene, Russ, Dutra, & Westen, 2005). Taking into account all stages of a RCT dropout would exclude a total of approximately 45% of the participants, therefore seriously limiting the comparability between those treated in applied clinical practice (Toerien et al., 2009). RCTs require informing patients and receiving their consent to participate, creating a dependence on the willingness and motivation of patients to participate. This introduces a volunteer or self-selecting bias of participants more willing to change and committed to any program.

Furthermore, RCT treatment deliverance itself also does not reflect clinical practice. Standardization and adherence to treatment procedures proved extremely difficult and often unattainable in applied clinical settings (Starcevic, 2003), and highlights a short segment of a longer treatment process. Most importantly, no design, including RCTs, can truly establish a cause-effect relationship regarding the specific effects or any other effects, meaning that any prove of the efficacy of an intervention does not prove that the theory behind it is responsible. A plethora of patient, therapist, and contextual factors are likely influencing the course of treatment effectiveness. The influence of these factors becomes visible in the large heterogeneity in treatment effects. There are not only significant differences in treatment effect between *different* interventions, but also between *identical* interventions and between participants within any given intervention (e.g., Haagen et al., 2016). These issues limit the

generalizability of RCTs and some authors even argue that PTSD patients in RCTs do not reflect the patients that are treated in clinical practice (Corrigan & Hull, 2015).

Alternative psychotherapy evaluation frameworks: Understanding general effects

The medical model of psychotherapy specified how unique therapeutic ingredients produce specific effects. Likewise, alternative models (also referred to as placebo or non-specific models) indicated how factors present in most psychotherapies produce general effects (Wampold & Imel, 2015, p. 41). To understand how general effects influence psychotherapy outcome, we highlight two partly overlapping general effects models.

The Placebo Expectancy / Conditioning Model. A placebo can be defined as the act of receiving any substance or therapeutic procedure within a set of sensory (e.g., a doctors coat) and social stimuli (e.g., words, rituals), that tell the patient that a beneficial treatment is being given (Benedetti, Carlino, & Pollo, 2011). Its effects are not attributable to the substance or procedure itself, but rather the result of outcome expectancies and learning (conditioning) (Stewart –Williams & Podd, 2004). These two mechanisms can occur separately and, at times, interact to produce placebo effects (Benedetti et al., 2011). The expectancy mechanism proposes that placebos elicit expectations of therapeutic benefits. Neurobiological studies demonstrated that such expectations stimulate the dopamine reward system that is associated with feelings of wellbeing and reducing anxiety (Benedetti et al., 2011; De La Fuente-Fernández et al., 2001). Any expectations of anxiety reductions may boost immune functioning, decrease self-defeating thoughts, and may be related to behaviour changes that positively impact health outcome (Stewart –Williams & Podd, 2004). Likewise, expectations of worsening are related to actual clinical worsening (e.g., amplification of anxiety or pain) (Benedetti et al., 2011).

Besides expectations, three separate learning mechanisms are proposed to exert placebo effects. First, classical conditioning states that a neutral stimulus can be paired to an unconditioned response to acquire the capacity to illicit an identical (conditioned) response (Stewart –Williams & Podd, 2004). For example, by pairing a placebo with a drug, it has been found that the placebo exercised the same response on the immune system in human and animal studies (see Benedetti et al., 2011). Second, conscious learning can take place via conditioning that reinforces the expectancy mechanism (Benedetti et al., 2011). Third, social learning allows for learning by observation and imitation, and may be as powerful as conditioning and presumably more powerful than verbal suggestions (Benedetti et al., 2011).

The Common Factors / Contextual Model. According to the common factors model, recovery can be attributed to factors present in almost all bona fide psychotherapies that produce general effects (Benish et al., 2008). As mentioned before, the term bona fide relates to the delivery of a therapy by a trained therapist, including a professional and truthful relationship between the patient and therapist, with the therapy based on accepted psychological principles tailored to the patient. In other words, it has to concern a genuine psychological treatment. The most commonly identified factors are "the relationship with the psychotherapist, expectations, instillation of hope, the provision of a reasonable and acceptable explanation for one's difficulties, a therapeutic set of actions that the patient believes will be helpful, and the therapeutic alliance." (Wampold, Frost, & Yulish, 2016, p. 116).

The contextual model of psychotherapy is an elaboration of the common factors model. It explains how common factors establish recovery via three pathways (Wampold & Imel, 2015, p. 55). The first pathway is the patient-therapist interaction. Psychotherapy is viewed as a social (supportive) healing process, intended to increase well-being by nurturing an open, trusting, empathic relationship, and providing a connection and sense of belongingness. The second pathway revolves around treatment expectations as a source of recovery and motivation for change. Treatment expectations are based on prior (learning) experiences and can be influenced by verbal suggestions regarding the disorder and the treatment rationale consistent with the cultural practices of the patient. Expectancies may assist in overcoming demoralization by instilling hope. The third pathway is the engagement in specific therapeutic actions. The contextual model does not attribute recovery to any specific effects, but states that rather the application of any credible treatment, in a goal-directed manner, promotes well-being and symptom alleviation through lifestyle activities, exercise, and social interactions.

Are general or specific effects more important?

Paula Schnurr, a leading PTSD psychotherapy researcher, hypothesized that the outcome of PTSD therapies depends for 30% on specific effects, 40% on general effects, and 30% on natural recovery (Schnurr, 2007). In several studies it has been attempted to determine the impact of specific and general effects. Meta-analyses comparing treatment with placebo PTSD control conditions demonstrated that 20% of the treatment effect could be attributed to natural recovery, 52-58% to specific effects and 22-48% to general effects (Bradley et al., 2005; Gerger, et al., 2014). However, the authors of these meta-analyses explicitly stated that

these control conditions were not bona fide; the conditions were not intended nor perceived by therapists to be therapeutic (Bradley et al., p. 226; Gerger et al., 2014, p. 2).

Based on the findings from component studies and studies that took bona fide interventions and treatment complexity into account, a small treatment effect size can be expected in favour of specific effects (ranging between *d* = .00-.28) (Bell et al., 2013; Gerger et al., 2014; Marcus et al., 2014). This would suggest that – at best - 25% of the treatment effectiveness can be attributed to the specific effects in recommended psychotherapies for veterans with PTSD (as an overall treatment effect – comparing PTSD treatments with control conditions - was found of *g* = 1.12; Haagen et al., 2015). The small effect sizes for specific effects would implicate that general effects deliver larger treatment results. This assumption is supported by several meta-analyses that are forwarded by proponents of the common-factors approach (Wampold & Imel, 2015, p. 209) and determined the treatment effect size of specific general effects, such as expectancies (*d* = .24), therapeutic alliance (*d* = .57), empathy (*d* = .63), being genuine (*d* = .49), establishing goal consensus (*d* = .72) (Benish, Quintana, & Wampold, 2011; Constantino, Arnkoff, Glass, Ametrano, & Smith, 2010; Horvath et al., 2011; Kolden et al., 2011; Tryon & Winograd, 2011).

It should be noted that specific and general effects are also interwoven and interact with each other. Separating general effects and specific effects from each other is very difficult if not impossible (Wampold et al., 2016). The boundaries between specific and general effects are also to some extent unclear, as cited by Ehlers and colleagues (2010, p.275): "some of the non-specific elements of psychological treatments may actually represent active mechanisms of change". For example, establishing a trusting relationship may convince patients to follow specific techniques, such as in exposure therapy. In short, the studies mentioned here demonstrate the importance of both specific effects and general effects on PTSD treatment recovery, and appear to favour general effects above specific effects, in agreement with the estimation made by Schnurr (2007).

Implications

The medical model for psychotherapy is and remains important to the field of psychotherapy as it is able to establish the efficacy of innovative interventions, to tailor interventions to specific disorders and populations, and to better comprehend the workings of specific therapeutic ingredients to maximize their specific effects. In isolation, however, the medical model for psychotherapy is flawed. Its emphasis on specific effects is inherently limited

because specific effects are not synonymous to the total psychotherapy treatment effect (Schnurr, 2007). Consequently, specific effects consider a sliver of the factors involved in therapeutic change. General effects models, such as common factors and placebo models, offer credible supplementing explanations regarding the workings of psychotherapy.

The RCT is the preferred treatment design to isolate the specific effects of any given therapeutic ingredient (Walach, 2016). It is a highly relevant design with many strengths to establish the efficacy of interventions and gets as close as a design can get to implying causation (Cartwright, 2010). According to Cartwright, strong theories and robust data are sufficient to justify the causal interpretation of an experiment's results in most fields. Psychotherapy unfortunately does not allow for such strong theoretical explanations with many contending and conceptually diverse theories that cannot be dismissed (Cartwright, 2010). RCTs are unable to prove whether specific effects or general effects cause therapeutic recovery (Wampold et al., 2016) and do not generalize well to clinical practice for veterans with PTSD (APA, 2017).

Common or placebo factors may actually influence RCT results via general effects. As mentioned, general effects models consider treatment expectancies to be a key factor in promoting treatment outcome (Delsignore & Schnyder, 2007). Their impact on psychotherapy outcome was demonstrated for veterans with PTSD (Price et al., 2015). RCT designs by nature influence treatment expectancies at various stages. Treatment expectancies are strongly influenced by verbal suggestions (Benedetti, 2008). In a bid to convince patients to participate, researchers may (un)consciously promote experimental interventions as state-of-the-art (raising positive treatment expectancies) and undermine participation in anything less than state of-the-art control conditions. According to the Hawthorne effect, patients that are aware that they are part of a clinical trial and under scrutiny may demonstrate improved therapeutic results attributable to the additional special attention from staff and researchers and the trust in the new intervention (McCambridge, Witton, &, Elbourne, 2014). Furthermore, psychotherapy does not allow for proper randomization because blinded randomization is impossible (Starcevic, 2003). Patients and clinicians are aware of the treatment condition they partake in and a participant's treatment outcome effects may be biased as a result of his or her preferences and expectations. Clinicians may moreover (un)wittingly convey their own treatment allegiance regarding a particular intervention to influence participants expectancies in the effects of the treatment (Vanheule, 2009), and influence treatment outcome itself (Luborsky, Diguer, Seligman, & Schweizer, 1999).

Recommendations

The dominant medical model of approaching treatment results overshadows different frameworks of psychotherapy (Wampold & Imel, 2015). As the field recognized RCTs as providing the highest 'level of evidence' (Burns, Rohrich, & Chung, 2011), PTSD treatment guidelines base their recommendations principally or exclusively on the results of RCT designs. Grant reviewers appear to disfavor non-RCT design grant proposals (ZonMw conference, 2015). Treatment centers prioritize guideline-recommended interventions (VA/DoD Clinical Practice Guideline Working Group, 2010) at the expense of alternative bona fide PTSD interventions, as was stated by Yehuda and Hoge (2016b). Guideline developers have admonished clinicians for divergence from recommended interventions for veterans with PTSD (see also Yehuda & Hoge, 2016b). Clinicians are trained and sensitized to treat specialized disorders using a few preferential methods. In other words, the medical model directs funding for research, policy, training and treatment of PTSD (Elkins et al., 2007), delivering the dominant framework on how psychotherapy is supposed to work. Alternative general effects frameworks are rarely investigated regarding their efficacy (Gerger et al., 2014). Consequently, the field has become a rather self-sustaining closed system that allows for little variation, emphasizing favored interventions without full considerations whether such interventions deliver superior results

It would make sense to expand psychotherapy evaluation research and to focus explicitly on both specific and general effects of PTSD interventions, especially because it is becoming more and more clear that there are more empirical supported interventions than the various forms of CBT as well as EMDR. Several recent meta-analyses have shown the efficacy of psychotherapies such as NET, BEP, PCT, and Mindfulness (Banks, Newman & Saleem, 2015; De Jong, Knipscheer, Ford, & Kleber, 2014). Even a rather speculative therapy as Emotional Freedom Techniques was recently found to be effective in a meta-analyses of seven studies, although there are doubts regarding the methodological rigor of the studies (Sebastian & Nelms, 2017). The small differences in effect size between PTSD interventions may be bridged by maximizing general effects that play a bigger part in recovery. Offering additional treatment options using various conceptual rationales and approaches will facilitate alignment with patient preferences. Taking such preferences into account might increase the chance of treatment improvement by 60% and decrease the risk of dropout by 50% (Swift & Callahan, 2009).

With regard to methodology, it is recommended to supplement RCTs with alternative psychotherapy treatment outcome designs to improve treatment effectiveness. While RCT

designs may be best suited to determine specific effects (Walach, 2016), alternative designs can be considered that better generalize any findings, considering the cost and time consumption associated with RCTs, and the difficulties in generalizing RCT to clinical practice for veterans with PTSD (APA, 2017). Attention should be paid to the cheaper quasi-experimental and cohort designs to focus on effectiveness rather than efficacy in understanding how therapy works. The purpose of effectiveness studies is to establish the generalizability and feasibility of an intervention (Jacobson & Christensen, 1996; Seligman, 1995). Effectiveness studies take place in the unrestricted natural habitat of psychotherapy (viz. applied clinical settings). They are based on nonrandomized systematic assessments of the nature of treatment, the natural variation in treatment outcome, and the relationship with external variables (that efficacy studies – RCTs - try to rule out), to determine their influence on treatment outcome (Hollon, 1996). The choice of intervention in these studies is more likely to depend on patient preference instead of random choice (due to randomization). There are no, or minimal, inclusion and exclusion criteria and even standardized routine outcome measurements could be used with the patient's consent. Effectiveness studies such as cohort studies are not meant to substitute RCTs (Vandenbroucke, 2009). They are more limited than RCTs in minimizing the effects of confounders and ruling out the effects of natural recovery on treatment outcome. Rather, cohort studies may supplement RCTs and assist in uncovering additional information regarding the relationship between therapy and its environment by capturing the natural variation that RCTs tries to minimize. Still another methodological alternative could be time-series methodology (Borckardt, Nash, Murphy, & O'Neil2008). For example, in a series of single case studies (conducted in low-income countries) quantitative outcome indicators (such as PTSD symptoms) and qualitative process indicators (such as treatment perceptions) were measured repeatedly before, during and after care (Jordans et al., 2012). Commonalities in treatment processes associated with change profiles within and between cases could be explored in this way. The problem of generalization of findings of single case studies was in this case compensated by replication on a case-by-case basis and by repeated measurements (often more than 10).

Conclusion

PTSD therapies are clearly found to be effective, also among veterans, but one should not overestimate their success. Even among veterans receiving an evidence-based intervention, approximately 50 percent still had PTSD after the treatment (Resick et al., 2017). Therapies have been found to be more effective than control conditions. However, the differences between bona fide therapies are rather small. Consequently, the efficacy of psychotherapies cannot be solely attributed to specific effects of the various interventions. Common factors appear equally or more influential to recovery. The current favoritism of RCT research and specific effects approaches is a costly and time-consuming affair, which does not always translate well to veterans with PTSD and may overlook highly relevant general factors. Improving existing treatments and developing new treatments are needed. The common factor and contextual model offer alternative frameworks to maximize the effectiveness of PTSD psychotherapies. Paul Rosenzweig's Dodo bird verdict can continue to be embraced and contended. No intervention is truly equal, yet, among bona fide efficacious interventions, none excels.

References

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (5th ed.).* Washington, DC: Author.

American Psychological Association, 2017. *Clinical Practice Guideline for the Treatment of Posttraumatic Stress Disorder (PTSD) in Adults.* [Adopted as APA Policy February 24 2017]. Published ahead of publication. http://www.apa.org/about/offices/directorates/guidelines/ptsd.pdf

Australian Centre for Posttraumatic Mental Health. (2013). *Australian guidelines for the treatment of adults with acute stress disorder and posttraumatic stress disorder.* Melbourne, Victoria: ACPMH.

Banks, K., Newman, E. & Saleem, J. (2015). An overview of the research on mindfulness–based interventions for treating symptoms of posttraumatic stress disorder: A systematic review. *Journal of Clinical Psychology, 71,* 935-963. doi: 10.1002/jclp.22200

Barlow, Bullis, Comer, & Ametaj, 2013; Evidence-based psychological treatments: An update and a way forward. *Annual Review of Clinical Psychology, 9,* 1-27. doi:10.1146/annurev-clinpsy-050212-185629

Barth, J., Munder, T., Gerger, H., Nüesch, E., Trelle, S., Znoj, H., ... Cuijpers, P. (2013). Comparative efficacy of seven psychotherapeutic interventions for patients with depression: A network meta-analysis. *PLOS Medicine, 10*(5), e1001454. doi:10.1371/journal.pmed.1001454

Bell, E. C., Marcus, D. K., & Goodlad, J. K. (2013). Are the parts as good as the whole? A meta-analysis of component treatment studies. *Journal of Consulting and Clinical Psychology, 81,* 722–736. doi:10.1037/a0033004

Benedetti, F. (2008). Mechanism of placebo and placebo-related effects across diseases and treatments. *Annual Review of Pharmacology and Toxicology, 48,* 33-60. doi:10.1146/annurev.pharmtox.48.113006.094711

Benedetti, F., Carlino, E., & Pollo, A. (2011). How placebos change the patient's brain. *Neuropsychopharmacology Reviews, 36,* 339–354. doi:10.1038/npp.2010.81

Benish, S., Imel, Z., & Wampold, B. (2008). The relative efficacy of bona fide psychotherapies for treating post-traumatic stress disorder: A meta-analysis of direct comparisons. *Clinical Psychology Review, 28,* 746-758. doi:10.1016/j.cpr.2007.10.005

Benish, S. G., Quintana, S., & Wampold, B. E. (2011). Culturally adapted psychotherapy and the legitimacy of myth: A direct-comparison meta-analysis. J*ournal of Counseling Psychology, 58,* 279-289. doi:10.1037/a0023626

Bisson, J.I., Roberts, N.P., Andrew, M., Cooper, R., & Lewis, C. (2013). Psychological therapies for chronic post-traumatic stress disorder (PTSD) in adults. *Cochrane Database of Systematic Reviews, 12,* 1-241. doi:10.1002/14651858.CD003388.pub4.

Borckardt, J. J., Nash, M. R., Murphy, M. D., & O'Neil, P. (2008) Clinical practice as natural laboratory for psychotherapy research: A guide to case-based time-series analysis. *American Psychologist, 63,* 77–95. doi:10.1037/0003-066X.63.2.77

Bradley, R., Greene, J., Russ, E., Dutra, L., & Westen, D. (2005). A multidimensional meta-analysis of psychotherapy for PTSD. *American Journal of Psychiatry, 162*(2), 214-227.

Brom, D., Kleber, R. J., & Defares, P. B. (1989). Brief psychotherapy for posttraumatic stress disorders. *Journal of Consulting & Clinical Psychology, 57(*5), 607-612.

Burns, P. B., Rohrich, R. J., & Chung, K. C. (2011). The levels of evidence and their role in evidence-based medicine. *Plastic and Reconstructive Surgery, 128,* 305–310. doi:10.1097/PRS.0b013e318219c171

Cartwright, N. (2010). A philosopher's view of the long road from RCTs to effectiveness. *The Lancet, 377,* 1400-1401. doi:10.1016/S0140-6736(11)60563-1

Castelnuovo, G. (2010). Empirically Supported Treatments in Psychotherapy: Towards an Evidence-Base or Evidence-Biased Psychology in Clinical Settings? *Frontiers of Psychology,* 1: 27. doi:10.3389/fpsyg.2010.00027

Elkins, D. N. (2007). The medical model in psychotherapy its limitations and failures. *Journal of Humanistic Psycholog, 49,* 66-84. doi:10.1177/0022167807307901

Cloitre, M. (2009). Effective psychotherapies for posttraumatic stress disorder: a review and critique. *CNS spectrums, 14*(1), 32-43.

Constantino, M. J., Arnkoff, D. B., Glass, C. R., Ametrano, R. M., & Smith, J. Z. (2011). Expectations. *Journal of Clinical Psychology, 67,* 184–192 doi:10.1002/jclp.20754

Cook, J. M., Dinnen, S., Coyne, J. C., Thompson, R., Simiola, V., Ruzek, J., & Schnurr, P. P. (2015). Evaluation of an implementation model: A national investigation of VA residential programs. *Administration and Policy in Mental Health and Mental Health Services Research, 42,* 147-156. doi:10.1007/s10488-014-0555-3

Corrigan F. M., & Hull, A. M. (2015). Neglect of the complex: Why psychotherapy for post-traumatic clinical presentations is often ineffective. *The British Journal of Psychiatry, 39,* 86-89. doi:10.1192/pb.bp.114.046995

De Jong, K., Knipscheer, J. W., Ford, N. & Kleber, R. J. (2014). The efficacy of psychosocial interventions for adults in contexts of ongoing man-made violence - A systematic review. *Health, 6*, 504-516. doi.org/10.4236/health.2014.66070

De la Fuente-Fernández, R., Ruth, T. J., Sossi, V., Schulzer, M., Calne, D. B., & Stoessl, A. J. (2001). Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. *Science, 293*(5532), 1164-1166.

Delsignore, A., & Schnyder, U. (2007). Control expectancies as predictors of psychotherapy outcome: A systematic review. *British Journal of Clinical Psychology, 46,* 467-483. doi:10.1348/014466507X226953

Dohrenwend, B. P., Turner, J.B., Turse, N. A., Adams, B. G., Koenen, K. C., & Marshall, R. (2006). The psychological risks of Vietnam for US veterans: A revisit with new data and methods. *Science, 313*(5789), 979-982.

Ehlers, A., Bisson, J., Clark, D., Creamer, M., Pilling, S., Richards, D., … & Yule, W. (2010). Do all psychological treatments really work the same in posttraumatic stress disorder? *Clinical Psychology Review, 30*, 269-276 doi:10.1016/j.cpr.2009.12.001

Engelhard, I. M., Van den Hout, M. A.,Weerts, J., Arntz, A., Hox, J. J. C. M., & McNally, R. (2007). Deployment-related stress and trauma in Dutch soldiers returning from Iraq. *British Journal of Psychiatry, 191*, 140–145.

Eysenck, H. J. (1952). The effects of psychotherapy: An evaluation. *Journal of Consulting Psychology, 16,* 319-324.

Frost, N. D., Laska, K. M., & Wampold, B. E. (2014). The evidence for present-centered therapy as a treatment for posttraumatic stress disorder. *Journal of Traumatic Stress, 27*, 1-8. doi:10.1002/jts.21881

Fulton, B. (2015). *The placebo effect in manual therapy. Improving clinical outcomes in your practice.* Edingburgh: Handspring Publishing

Gerger, H., Munder, T., Gemperli, A., Nüesch, E., Trelle, S., Jüni, P., & Barth, J. (2014). Integrating fragmented evidence by network meta-analysis: Relative effectiveness of psychological interventions for adults with post-traumatic stress disorder. *Psychological Medicine, 44*, 3151-3164. doi:10.1017/S0033291714000853.

Gerger, H., Munder, T., & Barth, J. (2013). Specific and nonspecific psychological interventions for PTSD symptoms: A meta-analysis with problem complexity as moderator. *Journal of Clinical Psychology, 70,* 601-615. doi:10.1002/jclp.22059

Goodson, J., Helstrom, A., Halpern, J. M., Ferenschak, M. P., Gillihan, S. J., & Powers, M. B. (2011). Treatment of posttraumatic stress disorder in U.S. combat veterans: A meta-

analytic review. *Psychological Reports, 2*, 573-599. doi:10.2466/02.09.15.16.PR0.109.5.573-599

Haagen, J. F. G., Smid, G. E., Knipscheer, J. W., & Kleber, R. J. (2015). The efficacy of recommended treatments for veterans with PTSD: A metaregression analysis. *Clinical Psychology Review, 40*, 184-194. doi:10.1016/j.cpr.2015.06.008

Heide, F.J.J ter, Mooren, T.M., Schoot, R, van de, Jongh, A. de & Kleber, R.J. (2016). Eye movement desensitisation and reprocessing therapy versus stabilisation as usual with refugees: Randomised controlled trial. *British Journal of Psychiatry, 209*, 311-318; doi:10.1192/bjp.bp.115.167775

Hollon, S. D. (1996). The efficacy and effectiveness of psychotherapy relative to medications. *American Psychologist, 51*(10), 1025-1030.

Horvath, A. O., Del Re, A. C., Flückiger, C., & Symonds, D. (2011). Alliance in individual psychotherapy. *American Psychological Association, 48*, 9-16. doi:10.1037/a0022186

Institute of Medicine. (2008). Tr*eatment of posttraumatic stress disorder: An assessment of the evidence.* Washington, DC: The National Academies Press.

International Society for Traumatic Stress Studies. (2009). *Effective treatments for PTSD: Practice guidelines from the International Society for Traumatic Stress Studies.* New York: Guilford Press.

Jacobson, N. S., & Christensen, A. (1996). Studying the effectiveness of psychotherapy: How well can clinical trials do the job? *American Psychologist, 51*(10), 1031.

Jordans, M. J. D., Komproe, I. H., Tol, W. A., Smallegange, E., Ntamatumba, P., & De Jong, J. T. V. M. (2012). Potential treatment mechanisms of counseling for children in Burundi: series of N=1 studies. *American Journal of Orthopsychiatry, 82*, 3, 338-348. doi:10.1111/j.1939-0025.2012.01171.x

Kolden, G. G., Klein, M. H., Wang, C.-., & Austin, S. A. (2011). Congruence/Genuineness. *Psychotherapy Theory Research Practice Training, 48*, 65-71. doi:10.1037/a0022064 ·

McCambridge, J., Witton, J., &, Elbourne, D. R. (2014). Systematic review of the Hawthorne effect: New concepts are needed to study research participation effects. *Journal of Clinical Epidemiology, 67*, 267–277. doi:10.1016/j.jclinepi.2013.08.015

Luborsky, L., Diguer, L., Seligman, D. A., Rosenthal, R., Krause, E. D., Johnson, S., ... Schweizer, E. (1999). The researcher's own therapy allegiances: A “wild card” in comparisons of treatment efficacy. *Clinical Psychology: Science and Practice, 6*, 95-106. doi:10.1093/clipsy.6.1.95

Marcus, D. K., O'Connell, D., Norris, A. L., & Sawaqdeh, A. (2014). Is the Dodo bird endangered in the 21st century? A meta-analysis of treatment comparison studies. *Clinical Psychology Review 34*, 519–530. doi:10.1016/j.cpr.2014.08.001

Marmar, C. R., Schlenger, W., Henn-Haase, C., Qian, M., Purchia, E., Li, M., ... Karstoft, K. I. (2015). Course of posttraumatic stress disorder 40 years after the Vietnam War: Findings from the National Vietnam Veterans Longitudinal Study. *JAMA psychiatry, 72*, 875-881. doi:10.1001/jamapsychiatry.2015.0803

Miller, W. R., & Moyers, T. B. (2015). The forest and the trees: Relational and specific factors in addiction treatment. *Addiction*, 110, 401–413. doi:10.1111/add.12693

Monson, C. M., Schnurr, P. P., Resick, P. A., Friedman, M. J., Young-Xu, Y., & Stevens, S. P. (2006). Cognitive processing therapy for veterans with military-related posttraumatic stress disorder. *Journal of Consulting and Clinical Psychology, 74*, 898. doi:10.1037/0022-006X.74.5.898

National Institute for Health and Clinical Excellence (NICE). (2009). *The guidelines manual.* London: NICE.

Petrakis, I. L., Rosenheck, R., & Desai, R. (2011). Substance use comorbidity among veterans with posttraumatic stress disorder and other psychiatric illness. *The American Journal on Addictions, 20*, 185-189. doi:10.1111/j.1521-0391.2011.00126.x

Powers, M. B., Halpern, J. M., Ferenschak, M. P., Gillihan, S. J., & Foa, E. B. (2010). A meta-analytic review of prolonged exposure for posttraumatic stress disorder. *Clinical Psychology Review, 30*, 635-641. https://doi.org/10.1016/j.cpr.2010.04.007

Price, M., Maples, J. L., Jovanovic, T., Norrholm, S. D., Heekin, M., & Rothbaum, B. O. (2015). An investigation of outcome expectancies as a predictor of treatment response for combat veterans with PTSD: Comparison of clinician, self-report, and biological measures. *Depression and Anxiety, 32*, 392-399. doi:10.1002/da.22354

Resick, P.A., et al. (2017). Effect of group versus individual cognitive processing therapy in active duty military seeking treatment for posttraumatic stress disorder: A randomized clinical trial. *JAMA psychiatry, 74*, 28-36. doi:10.1001/jamapsychiatry.2016.2729.

Rosenzweig, S. (1936). Some implicit common factors in diverse methods of psychotherapy. *American Journal of Orthopsychiatry,* 6(3), 412–15.

Schnurr, P. P. (2007). The rocks and hard places in psychotherapy outcome research. *Journal of Traumatic Stress, 20*, 779-792. doi:10.1002/jts.20292

Sebastan, B. & Nelms, J. (2017). The effectiveness of Emotional Freedom Techniques in the treatment of posttraumatic stress disorder: A meta-analysis. *Explore, 13*, 16-25. doi:10.1016/j.explore.2016.10.001

Seligman, M. E. P. (1995). The effectiveness of psychotherapy. *American Psychologist, 50*(12), 965-974.

Smith, M. L., & Glass, G. V. (1977). Meta-analysis of psychotherapy outcome studies. *American psychologist, 32*(9), 752.

Starcevic, V. (2003). Psychotherapy in the era of evidence-based medicine. *Australasian Psychiatry, 11*(3), 278-281.

Steenkamp, M. M., Litz, B. T., Hoge, C. W., & Marmar, C. R. (2015). Psychotherapy for military-related PTSD: A review of randomized clinical trials. *JAMA, 314*,489-500. doi:10.1001/jama.2015.8370

Stewart-Williams, S., & Podd, J. (2004). The placebo effect: dissolving the expectancy versus conditioning debate. *Psychological Bulletin, 130*, 324. http://dx.doi.org.proxy.library.uu.nl/10.1037/0033-2909.130.2.324

Swift, J. K., & Callahan, J. L. (2009). The impact of client treatment preferences on outcome: A meta-analysis. *Journal of Clinical Psychology, 65*, 368-381. doi:10.1002/jclp.20553

The management of post-traumatic stress Working Group, (2010). *VA/DoD clinical practice guideline for management of post-traumatic stress. Update of 2004 guideline*. Department of Veterans Affairs, Department of Defence.

Toerien, M., Brookes, S. T., Metcalfe, C., De Salis, I., Tomlin, Z., Peters, T. J., ... Donovan, J. L. (2009). A review of reporting of participant recruitment and retention in RCTs in six major journals. *Trials, 10*(1), 52.

Tran, U. S. & Gregor, B. (2016). The relative efficacy of bona fide psychotherapies for posttraumatic stress disorder: A meta-analytical evaluation of randomized controlled trials. *BMC Psychiatry, 16*:266. doi:10.1186/s12888-016-0979-2.

Tryon, G. S., & Winograd, G. (2011). Goal consensus and collaboration. *Psychotherapy, 48*, 50-57. http://dx.doi.org.proxy.library.uu.nl/10.1037/a0022061

VA/DoD Clinical Practice Guideline Working Group. (2010). *Management of post-traumatic stress.* Washington, DC: Veterans Health Administration, publication 10Q-CPG/PTSD-03.

Van Etten, M. L., & Taylor, S. (1998). Comparative efficacy of treatments for post-traumatic stress disorder: a meta-analysis. *Clinical Psychology and Psychotherapy, 5*(3), 126-144.

Van Everdingen, J. J. E., Burgers, J. S., Assendelft, W. J. J., Swinkels, J. A., Barneveld, T. A., & Van de Klundert, J. L. M. (2004). *Evidence-based richtlijnontwikkeling. Een leidraad voor de praktijk.* Houten: Bohn Stafleu van Loghem.

Vandenbroucke, J. P. (2009). The HRT controversy: observational studies and RCTs fall in line. *The Lancet, 373*(9671), 1233-1235.

Vanheule, S. (2009). Psychotherapy and research: A relation that needs to be reinvented. *British Journal of Psychotherapy, 25,* 91-109. doi:10.1111/j.1752-0118.2008.01103.x

Viera, A. J., & Bangdiwala, S. I. (2007). Eliminating bias in randomized controlled trials: Importance of allocation concealment and masking. *Family Medicine, 39*(2), 132-137.

Walach, H. (2016). The efficacy paradox and its consequences for research in psychotherapy (and elsewhere). *Psychology of Consciousness: Theory, Research, and Practice, 3*, 154. http://dx.doi.org/10.1037/cns0000083

Wampold & Impel, 2015. The *great psychotherapy debate. The evidence what makes psychotherapy work.* (2nd ed.). New York: Routledge.

Wampold, B. E., Imel, Z. E., Laska, K. M., Benish, S., Miller, S. D., Flückiger, …Budge, S. (2010). Determining what works in the treatment of PTSD. *Clinical psychology review, 30*, 923-33. doi:10.1002/jclp.20683

Wampold, B. E., Frost, N. D., & Yulish, N. E. (2016). Placebo effects in psychotherapy: A flawed concept and a contorted history. *Psychology of Consciousness: Theory, Research, and Practice, 3*, 108. http://dx.doi.org/10.1037/cns0000045

Watts, B.V., Schnurr, P.P., Mayo, L., Young-Xu, Y., Weeks, W.B., & Friedman, M.J. (2013). Meta-analysis of the efficacy of treatments for posttraumatic stress disorder. *Journal of Clinical Psychiatry, 74,* 541-550. doi:10.4088/JCP.12r08225.

Wisco, B. E., Marx, B. P., Wolf, E.J., Miller, M. W., Southwick, S. M., & Pietrzak, R. H. (2014). Posttraumatic stress disorder in the US veteran population: Results from the National Health and Resilience in Veterans Study. *The Journal of clinical psychiatry, 75*, 1338-1346. doi:10.4088/JCP.14m09328

Yehuda, R., & Hoge, C. W. (2016). Treatment options for veterans with posttraumatic stress disorder, In reply. *JAMA,* 73, 757-758. doi:10.1001/jamapsychiatry.2016.0572

ZonMw conference (2015). *Alternatieven voor RCT* [Alternatives for RCT]. Report of Invitational Conference

Chapter 8

Discussion

Introduction

Psychotherapy can be painful and taxing for patients struggling to overcome PTSD, and for professionals that bear witness of their pain. It is not a smooth linear progress, rather, a bumpy ride with critical transitions within and between sessions (Kowalik, Schiepek, Kumpf, Roberts, & Elbert, 1996), and it is fallible. But it is also a powerful healing tool for those in need of professional assistance. The present dissertation was inspired by the limitations of PTSD interventions for traumatized veterans and the dedication of health care professionals to better the lives of their patients. We wanted to explore the reasons behind the variability in treatment response to better understand who benefits under what circumstances. To address this matter, we resorted to prognostic methods. This dissertation is to be considered a stepping stone towards the building of comprehensive predictive models to assist clinicians, researchers, and policy advisors, but especially veterans, in overcoming PTSD.

General Summary

The dissertation began (Chapter 1) with a state-of-affairs overview of veteran deployment experiences and related pathology after experiencing shocking events. We focused on PTSD as the most prominent pathology and discussed guideline recommended psychotherapy interventions. Despite the efficacy of these interventions, a substantial number of veterans are unresponsive to such practices (Steenkamp Brett, Litz, Hoge, & Marmar, 2015). Their symptoms remain unabated and severe, regardless of the efforts of dedicated professionals. Improving the effectiveness of veteran PTSD psychotherapy has been considered a priority and our main question was whether we could predict and explain PTSD treatment effectiveness. We focused on a number of candidate predictors to unravel the roles of the actors [patients], play [intervention], and décor [setting], in setting the stage for recovery (Chapter 2-6). We finalized the dissertation (Chapter 7) by outlining a comprehensive perspective on the workings of psychotherapy. In the following sections, we summarize the main results and discuss their scientific implications. All predictors were measured at baseline (pre-treatment).

On the *patient level*, patients with prior PTSD treatment experiences tended not to improve after six months of PTSD treatment (Chapter 4). This finding may be explained using

different frameworks for psychotherapy that focus on the impact of patient treatment outcome expectancies on actual treatment outcome (Chapter 7). Sleep disturbances also predicted PTSD treatment improvement. Sleep disturbances (Chapter 6) are common among all veterans with PTSD and inherent to its classification. However, the extent of the severity varies substantially. Severe levels of sleep disturbances negatively predicted PTSD symptom improvement and may disrupt the memory consolidation of therapeutic experiences that counteract traumatic memories (Pace-Schott, Germain, & Milad, 2014). Furthermore, PTSD severity had a positive and negative effect on PTSD treatment improvement (Chapters 2 and 5). In the metaregression, PTSD severity predicted a negative treatment outcome for veteran patients with relatively low and severe PTSD symptoms. In the Dutch veteran patients study, PTSD severity predicted a negative treatment outcome for patients with relatively low PTSD severity scores. However, in contrast with the metaregression findings, it predicted an increased PTSD treatment symptom improvement for patient with severe PTSD. These findings make it a poor treatment outcome indicator because of its fickle nature. We also examined whether dissociative PTSD predicted treatment outcome. The concepts of dissociation and dissociative PTSD are often remarked upon as potential adverse treatment outcome predictors. Whether such attention is warranted remains to be seen. Our findings did not indicate that dissociative PTSD predicted a lower PTSD treatment effectivity (Chapter 5). We also examined whether we could identify PTSD treatment outcome predictors in a civilian sample exposed to war zones. For refugees, a negative PTSD treatment outcome was predicted by the presence and increased severity of a comorbid depression (Chapter 3). We found no evidence that depression predicted PTSD treatment outcome for veterans. These findings favour explanations regarding the role of depression in PTSD recovery more attuned to the traumatic experiences of refugees.

On the *therapy level*, there is an ongoing debate which type of therapy best serves veterans with PTSD (Chapter 7). Our metaregression findings (Chapter 2) may be interpreted as a resounding victory in favour of the superiority of trauma focused interventions. It was not, however, intended to demonstrate beforehand whether trauma focused interventions were superior to non-trauma focused interventions. Rather, the metaregression aimed to identify PTSD psychotherapy treatment efficacy predictors in guideline recommended interventions. To answer whether trauma focused interventions are superior would require including data from bona fide non-trauma focused interventions, such as present centered therapy [PCT] (Frost, Laska, & Wampold, 2014). PCT was not included in the metaregression because it did

not fulfil the guideline criteria to be a recommended psychotherapy. It is likely that at the time of the metaregression, the number of PCT studies were insufficient to warrant a formal guideline assessment. For example, the Australian Guidelines for the Treatment of Acute Stress Disorder and Posttraumatic Stress Disorder (2013), reported only one PCT study. At this time, there are results from five randomized controlled trials (Frost et al., 2014). By not including data from bona fide non-trauma focused interventions, it resulted in an unfair comparison between an overwhelming number of trauma focused interventions (n = 66), versus a few aged non-trauma focused interventions (n = 3). In retrospect, it might have been more appropriate to nuance the statement 'Exposure therapy and CPT are preferred above SMT and EMDR'. Though not incorrect, it hardly tells the full story and can easily be interpreted or propagated as evidence of the superiority of trauma focused treatment.

The outcomes of the treatment study that examined trauma focused versus non-trauma focused interventions in Dutch veterans (Chapter 4), nuanced our views regarding the superiority of trauma focused interventions in clinical practice. Veterans that received trauma focused interventions were less likely to clinically worsen, and reported larger treatment effect sizes (i.e., more symptom reduction). These findings favour the guideline preferential application of trauma focused interventions for Dutch veterans. However, the results were non-significant, in part due to the small size of our treatment sample and due to minor treatment effect differences between both approaches. Veterans treated with trauma focused interventions experienced an 11.4% drop in symptom severity compared to an 8.5% drop in symptom severity for those treated with non-trauma focused interventions. It led us to conclude in Chapter 7 that, although trauma focused interventions are effective and recommended interventions, the differences in effect with non-trauma focused interventions are small. Choosing a preferential treatment may not outweigh the positive contributions from using a flexible treatment approach based on multiple treatment options to better realign with patient's (and therapist's) preferences and expectations, or using shared decisions strategies.

The metaregression from Chapter 2 demonstrated a strong treatment effect size for guideline recommended therapies. In comparison, the clinical trial among Dutch veterans proved much less effective (Chapter 4). It is unclear why the results from the Dutch clinical trial lagged behind those of U.S. clinical trials. The differences between trauma and non-trauma focused were small (Chapter 4), and we posited that the main drive behind treatment effectiveness is not likely be related to the type of intervention (Chapter 7). The lagging results might be attributed to the study cooperation with centres that are considered specialist centres and deal with more complex cases of PTSD. Perhaps this somehow affected treatment

outcome. It is also possible that cultural differences between Dutch and U.S. counterparts are at work. There may be a more societal appreciation and commitment to support U.S. veterans compared to Dutch veterans that helps promote wellbeing and symptom improvement in alternative ways. Alternatively, consumer research in 15 countries, including the U.S, demonstrated that the Dutch are culturally most likely to use the response tendency to answer all questions regarding a product under evaluation negatively, regardless of the content (Tellis & Chandrasekaran, 2010). In this case, the product under evaluation may be their state of health. Besides cultural differences, applied clinical practice may lack the special attention brought about by participating in scientific research that could increase positive treatment expectancies to promote positive treatment outcome. Regardless of the reason, the lack of effectiveness is worrisome and requires further investigation.

We demonstrated that *the setting* (manner in which treatment is provided) matters. PTSD is best treated on an individual basis and group-only approaches should be avoided (Chapter 2). Not because they are harmful or ineffective, which they are not. They were simply not as effective as individual therapy. An individual approach may also help optimize the therapeutic relationship highlighted in Chapter 7 to promote recovery. Group therapy formats are best applied in combination with individual PTSD therapies to target symptoms other than PTSD. For example, by focusing on well-being rather than PTSD symptom reduction, delivering peer social support, psychoeducation and emotional-regulation strategies (anger management), to improve a person's quality of life.

That the setting matters, is a timely finding. First, the latest PTSD treatment guideline does not address the distinction between group and individual therapy in improving PTSD treatment outcome (American Psychological Association, 2017). Second, veteran trauma focused group interventions (e.g., group cognitive processing therapy) are still frequently operated (Sloan, Bovin, & Schnurr, 2012), despite growing evidence of their less-than-optimal effects compared to their individualized counterparts (Resick et al., 2017 regarding CPT). Third, the human drive to innovate with novel or popular PTSD interventions risks using less effective approaches. Innovations such as group EMDR (e.g., Adúriz, Bluthgen, & Knopfler, 2009) or group narrative exposure (NET) therapy (De Boer, Koops, & Smit, 2014) may be less effective then their individual counterparts. Such new developments should be critically monitored with head-on-comparisons between group and individual therapy formats.

Reflections on null results

For the Dutch veteran treatment sample, we made use of a comprehensive uniform diagnostic set of questionnaires that were implemented at each of the participating centres. This set of questionnaires was developed by clinicians and researchers from the Dutch National Health System for Veterans (Landelijk Zorgsysteem voor Veteranen [LZV]). We reported predictive findings from questionnaires that were part of this set. Some of the null findings from other questionnaires that were part of this set were not discussed in the present dissertation. A patient's baseline attachment style, hostility levels, coping strategies, or comorbid depression and substance disorder, did not predict PTSD symptom improvement, despite their potential as candidate predictors of PTSD symptom improvement (Chapter 2). Null results are unlikely to see the light of day (Mervis, 2014). Reporting these null findings adds to our knowledge about these factors and their impact, or lack of impact, on treatment outcome.

Recommendations

Considerable scientific attention revolves around the development and testing of interventions. It is recommended to tailor interventions based on characteristics that predict treatment outcome for the population in question, to test whether it improves their effectiveness. For example, incorporating strategies in PTSD treatment for refugees that reduce severe depression, or strategies that improve sleep quality for veterans, may increase their effectiveness. Specifically for veterans, it is recommended to target PTSD via individual therapy, using trauma focused interventions if they realign with patients preferences and expectations, and otherwise resort to non-trauma focused empirically supported interventions.

To better understand how any intervention exerts its effect, we recommend incorporating predictive measures in treatment studies that test both specific and general effects. This would entail measuring specific mechanisms and their effect on treatment (e.g., via component studies), and also including general effects measures (e.g., working alliance measures during the first treatment sessions and outcome expectancies measures). It requires a broader perspective on the workings of psychotherapy than exclusively the treatment-rationale (and mechanisms of change) provided by any given intervention. This may help better understand the effectiveness of these interventions and how future treatments can be optimized. Also, when developing treatment studies, be aware of the extent in which a study design reflects clinical practice. RCT designs may seek to minimize those aspects that impact therapeutic recovery, or risk influencing treatment outcomes by the nature of their design (Chapter 7). The results from these studies may be augmented using observational studies.

A roadmap for predictive research

Paul Samuelson, an economist and recipient of the Nobel Memorial Prize in Economic Sciences jokingly remarked in 1966 that "Wall Street indexes predicted nine out of the last five recessions". His statement highlights the difficulties in building predictive models and the risk of false responses. Treatment forecasting is in its infancy, few veteran treatment studies examined predictors, and findings are inconsistent and paired with uncertainties (Haagen et al., 2015). Such difficulties should not deter us from predictive research. It is a proven method that can substantially improve the quality of treatment and lives of patients (e.g., in medicine and cancer). Four stages can be discerned to ensure that important predictive findings are successfully implemented in clinical practice, they need to be detected (initial development), validated and perchance updated, their impact on practice tested, and subsequently implemented in daily practice (Moons, Royston, Vergouwe, Grobbee, & Altman, 2009; Toll, Janssen, Vergouwe, & Moons, 2008).

In accordance with the first stage, the present dissertation identified several outcome predictors that can be used in the later stages to develop a prognostic comprehensive model. The predictors on the patient level were dissociation, severity of symptoms and sleep disturbances; on the level of intervention, the predictor was the focus in therapy (systematic exposure to the traumatic experiences - or not), and on the setting level the predictor was group versus individual treatment. These findings need to be validated in a second stage by testing their performance in other veterans with PTSD (i.e., new patients from the same population). Scientific replication of any finding is an important tool to avoid false alarms. It ensures that the findings are not the result of design deficiencies, modelling methods, unknown confounders, and ungeneralizable to different settings. Once the model is considered valid, its impact on practice can be determined. Valid predictors are to be implemented in PTSD diagnostic and treatment protocols. Comparative studies can accordingly test whether the novel models increase the diagnostic accuracy and treatment effectiveness in practice, and whether such models are generalizable and adaptable to similar populations (Moons, Altman, Vergouwe, & Royston, 2009).

Opportunities

Over a thousand clinicians rated the theme ‘therapeutic relationship’ and ‘mechanisms of change’ as the two most important themes for research (Tasca et al., 2015). It demonstrates that predictive research has a strong appeal on researchers and clinicians. Predictive research can act as a focal point at which all elements converge to become a centre of activity that bridged science and practice. It can facilitate cooperation and knowledge exchange between clinicians and researchers. It will help researchers gain a greater appreciation of what clinical practice entails and what occupies clinical attention. It will also help clinicians gain a better understanding of scientific research, motivate them to support it, and become better informed of the latest results (Castonguay et al., 2013).

Several examples demonstrate how this (already) translated into practice. The pre-treatment questionnaire set used in our Dutch treatment studies was implemented in all specialist LZV centres, using standardized procedures. The set was composed by diagnosticians, clinicians and researchers in the field of PTSD treatment. Using it for predictive research enabled a feedback loop to inform clinical practice. That feedback loop helped revise the questionnaire set with researchers and clinicians discussing its results. The results were also used in a to evaluate the effectiveness and satisfaction of a PTSD day treatment program in one of the participating centres. The day treatment program was revised based on best-practice knowledge combined with recent empirical insight. In this case, the new program standardized the application of individual PTSD therapy besides group therapy approaches (as recommended in Chapter 2). There are opportunities to continue the present research and expand it within the Dutch veteran health care system.

Alternatively, a lack of corporation and coordination will foster stand-alone research. This kind of research will be less likely to generalize to the entire Dutch veteran PTSD treatment population, will need more time and efforts to reach a sufficiently large sample size for predictive research, is less likely to share knowledge between veteran treatment centres that are not invested in the project, and may actually delay the identification and implementation of defining prognostic markers in practice (Altman, 2001).

Prelude

In certain aspects, the present dissertation may function as a prelude (i.e., a preliminary action of a more important one) on how researchers, policy advisors and clinicians can work together to optimize PTSD treatment. It delivered stepping stones for more advanced predictive models. It demonstrated how science and practice can interact to improve veteran PTSD treatment. The present dissertation demonstrated that observational predictive research

is viable and relatively easily attainable because Dutch veteran specialist centres are in consensus in using an identical pre-treatment questionnaire set with standardized procedures in place. Also, it demonstrated the willingness for collaboration between multiple centres that transcends what any individual centre can achieve.

To improve the quality of predictive research it would be recommended to form a major collaboration with all centres within the veteran mental health care system (Landelijk Zorgsysteem voor Veteranen), insert multiple routine outcome measures that encompass the complete treatment period for each veteran. The additional measurement moments and a larger growing sample of Dutch veterans in treatment will assist researchers to infer treatment trajectories and help inform patients and clinicians regarding the ideal course of treatment (see for example the patient-tool 'predict' http://predict.nhs.uk/index.html).

Conclusion: Setting the Stage

The present dissertation implicates that therapeutic recovery can be predicted at three separate levels: patient, therapy, and setting. Predictors from each of these levels contribute to the effectiveness of PTSD treatment and help set the stage for recovery. Researchers should be aware that the total sum of therapeutic recovery depends on specific and general effects, as well as contextual factors that promote spontaneous remission. While specific effects theories are generally well covered, general effects theories are less known. We discussed a number of useful specific and general effects models. Also, predictive research can serve as a binding theme for science and practice. The present dissertation is a proof of principle that predictive research is feasible in the Dutch veteran mental healthcare system to optimize veterans PTSD treatment outcome. The stage is set. It depends on the directors to make sure the play becomes a success.

References

Adúriz, M. E., Bluthgen, C., & Knopfler, C. (2009). Helping child flood victims using group EMDR intervention in Argentina: Treatment outcome and gender differences. *International Journal of Stress Management, 16*, 138. doi:10.1037/a0014719

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders*. (5th ed.). Washington, DC: Author.

American Psychological Association, 2017. *Clinical Practice Guideline for the Treatment of Posttraumatic Stress Disorder (PTSD) in Adults*. [Adopted as APA Policy February 24 2017]. Published ahead of publication.

Australian Centre for Posttraumatic Mental Health. (2013). *Australian guidelines for the treatment of adults with acute stress disorder and posttraumatic stress disorder*. Melbourne, Victoria: ACPMH.

Benedetti, F. (2008). Mechanism of placebo and placebo-related effects across diseases and treatments. *Annual Review of Pharmacology and Toxicology, 48*, 33-60. doi:10.1146/annurev.pharmtox.48.113006.094711

De Boer, O., Koops, M., & Smit, M. (2014). NET in een groepssetting: De Narratieve Dagbehandeling. In R. Jongedijk (Ed.), *Levensverhalen en psychotrauma. Narratieve Exposure Therapie in theorie en praktijk* (pp. 135-144). Amsterdam: Boom.

Frost, N. D., Laska, K. M., & Wampold, B. E. (2014). The evidence for present centered therapy as a treatment for posttraumatic stress disorder. *Journal of Traumatic Stress, 27,* 1-8. doi:10.1002/jts.21881

Kersting, A., Kroker, K., Horstmann, J., Ohrmann, P., Baune, B. T., Arolt, V., & Suslow, T. (2009). Complicated grief in patients with unipolar depression. *Journal of Affective Disorders, 118*, 201-204. doi:10.1016/j.jad.2009.01.033

Kowalik , Z., Schiepek, G., Kumpf, K., Roberts, L., & Elbert, T. (1997) Psychotherapy as a chaotic process II. The application of nonlinear analysis methods on quasi time series of the client-therapist interaction: A nonstationary approach. *Psychotherapy Research, 7,* 197-218. doi:10.1080/10503309712331331973

McLay, R. N., Webb-Murphy, J. A., Fesperman, S. F., Delaney, E. M., Gerard, S. K., Roesch, S., C. … Johnston, S. L. (2016). Outcomes from Eye Movement Desensitization and Reprocessing in active-duty service members with posttraumatic stress disorder.

Psychological Trauma: Theory, Research, Practice, and Policy, No Pagination Specified. doi:10.1037/tra0000120

Mervis, J. (2014). Why null results rarely see the light of day: "File drawer" study proposes for unpublished social science data. *Science, 345,* 992. doi:10.1126/science.345.6200.9

Moons, K. G. M., Altman, D. G., Vergouwe, Y., & Royston, P. (2009). Prognosis and prognostic research: Application and impact of prognostic models in clinical practice. *Research Methods & Reporting, 338,* 1487–1490.doi:10.1136/bmj.b606

Moons, K.G.M., Royston, P., Vergouwe, Y., Grobbee, D.E., & Altman, D.G. (2009b). Prognosis and prognostic research: What, why, and how? Research Methods & *Reporting, 338,* 1317–1320. doi:10.1136/bmj.b375

Moynihan, R., Henry, D., Moons, K.G., 2014. Using evidence to combat overdiagnosis and overtreatment: Evaluating treatments, tests, and disease definitions in the time of too much. *PLoS Medicine, 11*: e1001655. doi:10.1371/journal.pmed.1001655

Pace-Schott, E. F., Germain, A., & Milad, M. R. (2014). Sleep and REM sleep disturbance in the pathophysiology of PTSD: The role of extinction memory. *Biology of Mood & Anxiety Disorders, 5:*3. doi:10.1186/s13587-015-0018-9

Resick, P. A., Wachen, J. S., Dondanville, K. A., Pruiksma, K. E., Yarvis, J. S., Peterson, A. L. … Young-McCaughan, S. (2017). Effect of group vs individual cognitive processing therapy in active-duty military seeking treatment for posttraumatic stress disorder: A randomized clinical trial. *JAMA Psychiatry, 74*, 28-36. doi:10.1001/jamapsychiatry.2016.2729.

Samuelson, P. A. (1966). Science and Stocks. *Newsweek,* 92.

Sloan, D. M., Bovin, M. J., & Schnurr, P. P. (2012). Review of group treatment for PTSD. *Journal of Rehabilitation Research & Development*, *49*, 689-702. doi:10.1682/JRRD.2011.07.0123

Tasca, G. A., Sylvestre, J., Balfour, L., Chyurlia, L., Evans, J., Fortin-Langelier, B., ... Joyce, A. S. (2015). What clinicians want: Findings from a psychotherapy practice research network survey. *Psychotherapy*, *52*: 1-11. doi:10.1037/a0038252

Tellis, G. J., & Chandrasekaran, D. (2010). Does culture matter? Assessing response biases in cross-national survey research. *International Journal of Research in Marketing, Forthcoming,*

Toll, D. J., Janssen, K. J., Vergouwe, Y., & Moons, K. G. (2008). Validation, updating and impact of clinical prediction rules: A review. *Journal of Clinical Epidemiology, 61,* 1085-1094. doi:10.1016/j.jclinepi.2008.04.008.

Summary

Deployment, PTSD, and Treatment

"The essence of war is violence" (John Arbuthnot Fisher), and violence bears the fruit of tragedy. Soldiers operate in a hostile environment that demands an almost unrelenting battle readiness to safeguard against assaults, ambushes, IEDs, mortars, snipers, etc. It can be a lonely and exhausting place, away from home and kin, with little control over future events. A deployment may at times steep a soldier in feelings of anguish and sorrow over the sight of suffering men, women and children. Or overwhelm a person with feelings of fear, guilt, disgust or anger, over the actions by and against civilians, fellow soldiers, enemy combatants, and oneself. It takes courage to operate in these harsh environments, winning the hearts and minds of the local community, and working to improve the lives of those affected in warzone circumstances.

Despite the adversities of deployment, the majority of combat veterans reflect back on their deployment with a positive outlook stemming from their contributions (Schok, Weerts & Kleber, 2008). Veterans take pride in their work and how they responded to challenges and overcame adversities. They gained valuable life experiences, developed strong bonds of camaraderie and trust, and experienced a strong sense of responsibility and meaning making during the mission. Any psychological distress resulting from mission-related experiences tended to dissipate gradually over time.

A minority of veterans, however, experience enduring mental distress. Posttraumatic stress disorder (PTSD) is a psychological disorder that may develop after exposure to life threatening events and can occur as a result of mission experiences. Specialist support helps veterans overcome PTSD with treatment guidelines recommending a number of psychotherapies. Unfortunately, present psychotherapies are limited in their effectiveness for veterans. One-third to two-thirds does not recover after PTSD treatment (Steenkamp, Litz, Hoge, & Marmar, 2015).

Treatment prognosis

Predictive research can be defined as 'the probability or risk of an individual developing a particular state of health (an outcome) over a specific time, based on his or her clinical and

non-clinical profile' (Moons et al., 2009). The present dissertation aimed to address veteran treatment (non-)response by investigating candidate predictors that may explain who might benefit from therapy or remain unresponsive (**Chapter 1**). The main question was: can we predict PTSD treatment effectiveness based on specific characteristics of PTSD patients and PTSD interventions? We reviewed the current state-of-evidence (**Chapter 2**) regarding PTSD veteran psychotherapy treatment effectiveness predictors and concluded sparseness in the available data. Only a handful of predictors were previously empirically examined and the results were often inconclusive. We continued the review with metaregression and meta-ANOVA analyses to identify potential treatment outcome predictors using data from 57 guideline recommended veteran PTSD interventions. The results demonstrated that exposure therapy and cognitive processing therapy were more effective compared to eye movement desensitization and reprocessing (EMDR) therapy and stress management therapy. It also became clear that the highest improvement rates were achieved in treatment programs that consisted of combination of individual and group therapy formats. Especially the use of individual therapies doubled the effectiveness of PTSD interventions compared to group-only PTSD interventions. Furthermore, the number of trauma focused treatment sessions predicted PTSD symptom improvement, and patients with relatively low and severe PTSD symptom severities benefitted less from treatment compared to those with more moderate severity levels. We found mixed results regarding the effectiveness of EMDR, and no evidence that demographic variables influenced treatment outcome. The identified predictors play an important role in optimizing the effectiveness of PTSD interventions.

To better understand treatment effectiveness predictors after warzone exposure, we investigated the effects of PTSD psychotherapy among civilians (refugees) with PTSD (**Chapter 3**). Refugees demonstrate the same heterogeneity in treatment outcome compared to combat veterans with PTSD and the determinants for this heterogeneity are, like veterans, largely unknown. We performed an exploratory prospective longitudinal multilevel analysis using data from 72 participants that participated in a randomized controlled trial. The participants received either EMDR or stabilization psychotherapy. The data from both treatment conditions were pooled for predictive research. Pooling was possible because both conditions were equally effective at different treatment measurement intervals over time. We examined a range of candidate predictors. Only the presence and severity of a pre-treatment depressive disorder predicted a poor treatment response. Those with severe depressive comorbid disorders did not appear to benefit from PTSD psychotherapy. The findings

demonstrate the potential of predictors in tailoring PTSD treatment to improve its effectiveness for certain patients. In this example, the effectiveness of PTSD treatment could be increased targeting major depression parallel to PTSD, or adjusting the timing of PTSD treatment, for example by alleviating severe depression before commencing PTSD treatment.

The review from Chapter 2 demonstrated that our current knowledge almost exclusively depends on data from U.S. veteran studies. We conducted a Dutch veteran prospective multisite cohort study to examine PTSD treatment effectiveness predictors to amend for the lack of Dutch treatment outcome data. We completed three studies using data from 64 veterans with PTSD. All veterans completed a pre-treatment at intake and follow-up measure after six months of psychotherapy. Psychotherapy took place in three different settings (outpatient, day treatment, and inpatient) and consisted of a variety of PTSD interventions.

First, we addressed the assumed superiority of trauma focused over non-trauma focused treatment for veterans with PTSD (**Chapter 4**). Multiple regression and ANOVA analyses, supplemented with effect sizes and reliable change calculations, demonstrated that trauma focused treatment interventions apeared only slightly superior. Other factors may be more influential, instead of over-emphasizing the type of intervention, in promoting recovery. One such factor may be treatment expectancies. Our findings demonstrated that veterans with prior PTSD treatment experiences were at risk of nonresponse, which may be the result of negative prior treatment experiences that created negative treatment expectancies that subsequently led to a less effective PTSD treatment outcome.

Second, we focused on the dissociative PTSD subtype as a candidate predictor of treatment effectiveness. The dissociative PTSD subtype recently gained a lot of scientific attention with its inclusion in the DSM-5 (**Chapter 5**). The subtype is hypothesized to interfere with the effectiveness of PTSD treatment. The intake data of 330 veterans with a suspected PTSD diagnosis were used in a latent profile analysis (LPA). Besides the usual three treatment centres, an additional centre contributed data for the LPA. The LPA demonstrated the existence of four distinct patient profiles; three non-dissociative PTSD profiles and a single profile that fitted the description of the dissociative PTSD subtype. Furthermore, multinomial logistic regression models demonstrated that the likelihood of belonging to the dissociative PTSD profile could be predicted by elevated pathology severity levels. The changes in posttraumatic severity scores between baseline and follow-up were

examined for each profile using continuous distal outcomes analyses. The treatment outcome data involved 64 veterans from three treatment centres. These exploratory analyses revealed no indications that dissociative PTSD impacted PTSD treatment outcome. These results question the clinical utility of the DSM-5 dissociative PTSD subtype and whether treatment manuals should continue to underline its potential adverse treatment effects.

Third, we examined the impact of sleep disturbances on PTSD treatment outcome (**Chapter 6**). Multiple regression analyses demonstrated that severe sleep disturbances had a modest negative impact on PTSD treatment outcome. These findings help tailor present PTSD interventions. Incorporating sleep strategies in existing PTSD interventions or addressing sleep disturbances before commencing PTSD treatment might improve the effectiveness of interventions for veterans with PTSD.

PTSD treatment guideline recommendations do not seem to generalize well to veterans, and the veteran mental health care has arrived at an uncertain juncture how to best serve veterans with PTSD. In **Chapter 7** we considered the workings of psychotherapy from a comprehensive perspective. We addressed the issue whether psychotherapy effectiveness depends on the specific ingredients of a given intervention, or factors present in most psychotherapies instead. The medical model of psychotherapy embodies the specific effects approach and assumes that the specific effects from therapeutic ingredients are responsible for much of the therapeutic recovery. For PTSD, the specific effects from trauma focused psychotherapies are considered superior above other interventions based using different (non-trauma focused) specific ingredients. In contrast, the placebo expectancy / conditioning model and the common factors / contextual model for psychotherapy state that the type of intervention is rather irrelevant. Both models embody general effects approaches that focus on different pathways of therapeutic recovery related to treatment expectancies, prior treatment learning experiences, the therapeutic relationship, and therapeutic set of actions that the patient believes will be helpful. We underline the merits of each of these specific and general effects models, but, that the current emphasis on the medical model of psychotherapy is flawed. Placebo and common factors are likely to exert a similar – if not larger – impact on therapeutic recovery. An understanding of therapeutic recovery cannot be achieved without taking these alternative frameworks for psychotherapy into account. Addressing placebo or common factors enables the modification of existing treatment strategies to maximize their potential in targeting PTSD.

Conclusion

The dissertation demonstrates how predictive research can bridge the gap between science and practice to help increase the odds of recovery for veterans with PTSD (**Chapter 8**). Therapeutic recovery can be predicted at three separate levels: patient, therapy, and setting. The predictors related to each level help set the stage for therapeutic recovery. Incorporating elements that predict treatment effectiveness outcome into our treatment strategies allows us to tailor our care strategies and improve the effectiveness of PTSD treatment interventions. Besides the identification of PTSD treatment effectiveness predictors, several alternative frameworks were forwarded that challenges the exclusivity of the medical model of psychotherapy in our research, practice and policies. These alternative frameworks, based on placebo effects and common factors, allow us to explore novel pathways to improve PTSD treatment effectiveness.

References

Moons, K. G. M., Royston, P., Vergouwe, Y., Grobbee, D. E., & Altman, D. G. (2009b). Prognosis and prognostic research: What, why, and how? *Research Methods & Reporting*, *338*, 1317–1320. http://dx.doi.org/10.1136/bmj.b375

Schok, M. L., Weerts, J. M. P. & Kleber, R. J. (2008). Betekenisgeving aan militaire uitzendervaringen. *BIJB*, *24*, 42-48. doi:10.1007/BF03076379

Steenkamp, M. M., Litz, B. T., Hoge, C. W., & Marmar, C. R. (2015). Psychotherapy for military-related PTSD: A review of randomized clinical trials. *JAMA, 314*,489-500. doi:10.1001/jama.2015.8370

Samenvatting
(Summary in Dutch)

Uitzending, PTSS en Behandeling

"De essentie van oorlog is geweld" (John Arbuthnot Fisher) en geweld draagt de vrucht van de tragedie. Soldaten opereren in een vijandige omgeving die een bijna onafgebroken gevechtsparaatheid vereist als waarborg tegen aanvallen, hinderlagen, IEDs, mortieraanvallen, scherpschutters, enz. De uitzending kan een eenzame en uitputtende plek zijn, ver van huis en haard, met weinig controle over toekomstige gebeurtenissen. Soms kan het militairen onderdompelen in gevoelens van beklemming en verdriet bij het aanzicht van oorlogsleed bij mannen, vrouwen en kinderen. Oorlogsdaden door en tegen burgers, medesoldaten, vijandige strijders en zichzelf kunnen ook een overweldigende weerslag hebben op een persoon en gepaard gaan met gevoelens van angst, schuld, afkeer of woede. Er is lef nodig om te kunnen werken onder deze zware omstandigheden, je in te zetten om de *hearts and minds* van de lokale bevolking te winnen en hun leefsituatie te verbeteren.

Ondanks de uitdagingen en omstandigheden van militaire uitzendingen, blikt de meerderheid van de veteranen positief terug op hun uitzending en bijdragen aan het succes van de missie (Schok, Weerts, & Kleber, 2008). Veteranen zijn trots op hun werk en op de wijze waarin ze in staat zijn uitdagingen en tegenslagen het hoofd te bieden. Ze hebben tijdens de missie waardevolle levenservaringen opgedaan, sterke banden van kameraadschap ontwikkeld, evenals vertrouwen en een sterk gevoel van verantwoordelijkheid en betekenisgeving. Indien uitzendgerelateerde psychologische klachten zich voordoen, verdwijnen deze dikwijls stapsgewijs in de periode na de uitzending.

Een minderheid van de veteranen gaat echter gebukt onder aanhoudend psychisch leed. Na blootstelling aan levensbedreigende uitzendgerelateerde gebeurtenissen kan de psychologische stoornis posttraumatische stressstoornis (PTSS) optreden. Specialistische hulp helpt veteranen bij het overwinnen van PTSS met behulp van psychotherapie. De huidige PTSS psychotherapieën zijn helaas slechts ten dele effectief voor veteranen. Een derde tot twee derde ervaart geen herstel na behandeling (Steenkamp, Brett, Litz, Hoge, & Marmar, 2015).

Behandelprognose

Voorspellend onderzoek kan worden gedefinieerd als 'de kans of het risico van een individu om een bepaalde (wenselijke) gezondheidstoestand te ontwikkelen over een bepaalde tijd, op basis van zijn of haar klinische en niet-klinische profiel' (Moons e.a., 2009). Het onderhavige proefschrift heeft als doel de mate van behandelvoorruitgang te vergroten voor veteranen met PTSS door kandidaat-voorspellers te onderzoeken die verklaren wie van therapie kan profiteren of geen baat heeft (**Hoofdstuk 1**). De kernvraag was: kunnen we PTSS behandeleffectiviteit voorspellen op basis van de specifieke kenmerken van PTSS patiënten en PTSS interventies. De huidige stand van kennis is in kaart gebracht middels een review naar psychotherapie voorspellers van behandeleffectiviteit bij veteranen met PTSS. We constateerden een schaarste in het aantal beschikbare studies (**Hoofdstuk 2**). Slechts een handvol voorspellers was eerder empirisch onderzocht en de resultaten waren doorgaans niet eenduidig. Om potentiële voorspellers te identificeren werd de review voortgezet met metaregressie en meta-ANOVA analysen op basis van data uit 57 richtlijn aangeraden interventies bij veteranen met PTSS. De resultaten toonden aan dat *exposure* therapie en *cognitive processing* therapie effectiever waren in vergelijking met *movement desensitization and reprocessing* (EMDR) therapie en stress management therapie. Het werd daarnaast duidelijk dat de hoogste herstelcijfers werden behaald in behandelprogramma's die bestonden uit een combinatie van 'individuele en groepstherapie'. Vooral het gebruik van een 'individuele' therapie-opzet verdubbelde de effectiviteit van PTSS interventies in vergelijking met een 'groepstherapie-opzet'. Het een toenemend aantal traumagerichte therapiesessies voorspelde bovendien PTSS symptoomverbetering. Patiënten met relatief weinig of ernstige klachten profiteerden daarnaast minder van therapie dan patiënten met middelmatige klachten. We vonden gemengde resultaten met betrekking tot de effectiviteit van EMDR. Er was ook geen bewijs dat demografische variabelen van invloed waren op de behandelingsuitkomsten. De geïdentificeerde voorspellers spelen een belangrijke rol bij het optimaliseren van de effectiviteit van PTSS-interventies.

Om een beter inzicht te krijgen in voorspellers van behandeleffectiviteit na blootstelling aan oorlogsomstandigheden, onderzochten we de effecten van PTSS psychotherapie onder burgers (vluchtelingen) met PTSS (**Hoofdstuk 3)**. Vluchtelingen vertonen dezelfde heterogeniteit in behandeluitkomst als gevechtsveteranen met PTSS. De determinanten van deze heterogeniteit zijn, net als bij veteranen, grotendeels onbekend. We voerden een exploratieve prospectieve longitudinale multilevel analyse uit met data van 72 deelnemers die deelnamen aan een gerandomiseerde gecontroleerde studie. De deelnemers

ontvingen ofwel EMDR of stabilisatietherapie. De gegevens van beide behandelcondities werden samengevoegd voor voorspellend onderzoek. Samenvoegen was mogelijk omdat beide condities even effectief waren op verschillende meetmomenten gedurende het behandelverloop. We onderzochten een reeks van kandidaat voorspellers, alleen de aanwezigheid van een depressieve stoornis en ernst van depressieve symptomen voorspelden een gebrek aan behandelvooruitgang. Vluchtelingen met een ernstige comorbide depressieve stoornis leken niet te profiteren van PTSS psychotherapie. Deze bevindingen tonen aan dat voorspellers de potentie hebben om de effectiviteit van PTSS behandeling te vergroten door therapie op maat te maken voor bepaalde patiëntengroepen. In dit voorbeeld kan de effectiviteit van PTSS vergroot worden door een depressieve stoornis simultaan met PTSS te behandelen, of door de timing van de behandeling aan te passen, bijvoorbeeld door allereerst ernstige depressie te verlichten, alvorens begonnen wordt met PTSS behandeling.

De review van Hoofdstuk 2 demonstreert dat onze huidige kennis bijna uitsluitend gebaseerd is op data van veteranenstudies uit de VS. Om het gebrek aan Nederlandse data te compenseren, voerden we een Nederlandse prospectieve multicenter cohort studie uit naar voorspellers van PTSS behandeleffectiviteit. We voerden drie studies uit met data van 64 veteranen met PTSS. Alle veteranen voltooiden een meting bij aanvang van behandeling, alsook na zes maanden psychotherapie. De therapie vond plaats in verschillende settingen (poliklinisch, dagklinisch en klinisch), en bestond uit diverse PTSS interventies. Drie centra waren betrokken: De Militaire Geestelijke Gezondheidszorg, Psychotraumacentrum Zuid Nederland en Stichting Centrum ’45.

Ten eerste adresseerde we het vraagstuk betreffende de veronderstelde superioriteit van traumagerichte behandelingen boven niet-traumagerichte behandelingen (**Hoofdstuk 4**). Multiple regressie en ANOVA analysen, aangevuld met effectgrootte maten en calculaties van betrouwbare klinische verandering, toonden aan dat traumagerichte interventies ietwat effectiever waren. In plaats van de hedendaagse nadruk op het type interventie zouden andere factoren wel eens meer invloed kunnen uitoefenen op het bevorderen van herstel. Onze bevindingen tonen aan dat veteranen met eerdere PTSS behandelervaringen een groter risico liepen niet te reageren op PTSS behandeling. Dit zou het gevolg kunnen zijn van negatieve behandelverwachtingen.

Ten tweede onderzochten we het dissociatieve PTSS subtype als potentiele voorspeller van behandeleffectiviteit. Het dissociatieve PTSS subtype heeft recentelijk veel

wetenschappelijke aandacht gekregen na toevoeging aan de DSM-5 (**Hoofdstuk 5**). De veronderstelling is dat het subtype interfereert met de effectiviteit van PTSS behandeling. We voerden een latente profiel analyse (LPA) uit met de intakedata van 330 veteranen met een vermoedelijke PTSS diagnose. Naast de drie behandelcentra leverde behandelcentrum GGZ Drenthe aanvullende data voor de LPA analysen. De LPA uitkomsten wezen op de aanwezigheid van vier verschillende patiëntprofielen; drie niet-dissociatieve PTSS profielen en een enkel profiel dat voldeed aan de beschrijving van het dissociatieve PTSD subtype. Multinomiale logistische regressie modellen toonden daarnaast aan dat de kans om te behoren tot het dissociatieve PTSS profiel werd voorspeld door verhoogde psychopathologie ernstscores. De veranderingen in posttraumatische ernstscores tussen aanvang behandeling en follow-up werden voor ieder profiel geanalyseerd met behulp van continue distale behandeluitkomstanalysen. Deze verkennende analysen onthulden geen aanwijzingen dat dissociatieve PTSS een invloed uitoefende op de mate van PTSS behandeleffectiviteit. Dergelijke uitkomsten trekken het klinische nut van een DSM-5 dissociatief PTSS subtype in twijfel. Het is de vraag of handboeken de potentiële negatieve behandeleffecten van dissociatie moeten blijven onderstrepen.

Ten derde onderzochten we de potentiële weerslag van slaapverstoringen op PTSS therapeutisch herstel (**Hoofdstuk 6**). Met multiple regressie analysen werd vastgesteld dat ernstige slaapverstoringen een bescheiden negatieve weerslag hadden op PTSS behandeleffectiviteit. Deze bevindingen dragen bij aan op maat gemaakte PTSS interventies. Door slaapverstoringen te adresseren voordat PTSS behandeling aanvangt, of een aanpak hiertegen te integreren in bestaande PTSS behandeling, wordt de effectiviteit van interventies voor veteranen met PTSS mogelijk vergroot.

Nu PTSS behandelrichtlijnen niet goed generaliseren naar veteranen staat de geestelijke gezondheidszorg op een onzeker kruispunt hoe het veteranen het beste ten dienste kan staan. In **Hoofdstuk 7** staan we stil bij de werking van psychotherapie vanuit een meer omvattend perspectief. We gaan in op de vraag of de effectiviteit van psychotherapie afhankelijk is van de specifieke ingrediënten van een gegeven interventie, of in plaats daarvan afhankelijk is van factoren die voorkomen in de meeste psychotherapieën. Het ‘medisch model van psychotherapie’ belichaamt de *specifieke effecten aanpak* en veronderstelt dat de specifieke effecten van therapeutische ingrediënten verantwoordelijk zijn voor veel van het therapeutische herstel. In het geval van PTSS veranderstelt dit dat de specifieke effecten van traumagerichte psychotherapieën superieur worden beschouwd boven andere interventies

gebasseerd op alternatieve (niet-traumagerichte) specifieke ingrediënten. In tegenstelling tot het ‘medisch model’ veronderstellen het ‘placebo verwachtingen / conditionering model’ en het ‘gemeenschappelijke factoren / contextuele model’ dat het type interventie nogal irrelevant is. Beide modellen belichamen *algemene effecten aanpakken* die uitgaan van alternatieve therapeutisch herstelpaden. Deze herstelpaden zijn gerelateerd aan behandelverwachtingen, eerdere behandel(leer)ervaringen, de therapeutische relatie, en een therapeutische reeks van handelingen waarvan de patiënt overtuigd is dat ze heilzaam zijn. We onderstrepen de verdiensten van elk van deze specifieke en gemeenschappelijke effecten modellen. Echter, de huidige nadruk op het medisch model van psychotherapie is gebrekkig. Placebo en gemeenschappelijke factoren hebben waarschijnlijk een gelijkwaardig – of groter – effect op therapeutisch herstel. Een grondig besef van therapeutisch herstel kan niet bereikt worden zonder deze alternatieve kaders voor psychotherapie in acht te nemen. Door placebo en gemeenschappelijke factoren te adresseren binnen bestaande behandelaanpakken kan de effectiviteit van deze interventies vergroot worden.

Conclusie

Het huidige proefschrift illustreert hoe voorspellend onderzoek het gat tussen wetenschap en praktijk kan overbruggen om de kansen op herstel voor veteranen met PTSS te verhogen (**Hoofdstuk 8**). Therapeutisch herstel kon worden voorspeld op drie afzonderlijke niveaus: de patiënt, de therapie, en de therapie-opzet. De voorspellers op deze niveaus richten samen het podium voor herstel in. Door elementen die behandeleffectiviteit voorspellen te incorporeren in onze behandelstrategieën zijn we in staat onze aanpakken op maat te maken en de effectiviteit van PTSS behandelinterventies te verbeteren. Naast de identificatie van voorspellers van PTSS behandeleffectiviteit zijn verschillende alternatieve modellen aangekaart die de exclusiviteit van het medisch model in PTSS psychotherapie onderzoek, praktijk en beleid betwisten. Deze alternatieve modellen, gebaseerd op placebo-effecten en gemeenschappelijke factoren, stellen ons in staat om vanuit een ander perspectief de effectiviteit van PTSS behandeling te vergroten.

Referenties

Moons, K. G. M., Royston, P., Vergouwe, Y., Grobbee, D. E., & Altman, D. G. (2009b). Prognosis and prognostic research: What, why, and how? *Research Methods & Reporting*, *338*, 1317–1320. http://dx.doi.org/10.1136/bmj.b375

Schok, M. L., Weerts, J. M. P. & Kleber, R. J. (2008). Betekenisgeving aan militaire uitzendervaringen . *BIJB*, *24*, 42-48. doi:10.1007/BF03076379

Steenkamp, M. M., Litz, B. T., Hoge, C. W., & Marmar, C. R. (2015). Psychotherapy for military-related PTSD: A review of randomized clinical trials. *JAMA*, *314*,489-500. doi:10.1001/jama.2015.8370

Dankwoord

Mijn dank gaat uit naar…

…de veteranen die bijdroegen aan de totstandkoming van dit proefschrift. Ons werk, of het nu genezing of onderzoek is, begint, draait om, en eindigt bij hen. Het is een dankbare taak een bijdrage te leveren aan hun herstel.

…alle hulpverleners die zich inzetten om veteranen de beste zorg te leveren na uitzendgerelateerde pathologie. Jullie werk is fundamenteel wanneer natuurlijk herstel niet op gang komt.

...mijn promotor Rolf Kleber. Het begon ooit als student aan de Universiteit Utrecht bij de begeleiding van mijn onderzoeksthesis en het houdt voorlopig niet op. We kunnen ons inmiddels verheugen op diverse toekomstige projecten. Geen emeritaat of lichamelijke klacht kan jou, de *bullet proof* professor, stoppen noch deren. Rolf, ik ben je bijzonder dankbaar voor je rol als supervisor en mentor. Ik heb veel van je geleerd als wijsgeer, schrijver, manager en orator. Jij combineerde al deze essentiële facetten van de hedendaagse wetenschapper op je eigen wijze: een mengeling van gemoedelijkheid doorspekt met humor, en doelgerichte expertise. Gedurende het traject ben je nooit de persoon naast het werk uit het oog verloren. Dank voor je aanhoudende bemoediging en stimulans.

...mijn copromotor Jeroen Knipscheer. Jeroen, de man met een subliem gevoel voor zelfspot en een tomeloze inzet op het gebied van de wetenschap en praktijk. Ondanks de nimmer aflatende bergen werk waarvoor de meest ervaren beklimmer zou terugdeinzen, nam je altijd de tijd om de beste koers in het onderzoek uit te stippelen. Jeroen, je incidentele zelffantasieën van een genadeloze keiharde tirannieke wetenschapper slagen er niet in je ware aard te verbergen. Je bent een zachtaardige cynicus, een inspiratie als collega, wetenschapper, professional en persoon. Dank voor je aanhoudende ondersteuning.

…de Raad van Bestuur van Stichting Arq Psychotrauma Expert Groep, Jan-Wilke Reerds en Jan Schaart, voor jullie vertrouwen in mij, jullie toegankelijkheid, en jullie vooruitziende blik om wetenschap en praktijk sterk te verankeren binnen de Stichting Arq Psychotrauma Expert Groep. Jullie hebben aangetoond dat de som der delen groter is dan ieder afzonderlijk onderdeel.

…mijn collega wetenschappers bij de Universiteit Utrecht , van wie ik veel geleerd heb en veel gedeeld heb. Mijn ontwikkeling als wetenschapper heb ik mede te danken aan de welwillende knappe koppen die er werken. Jullie hebben mij een dierbaar warm aandenken aan de Universiteit en afdeling nagelaten. In het bijzonder wil ik Henk Schut, Margaret Stroebe en Sibe Doosje bedanken voor de fijne gesprekken en de altijd openstaande deuren. Maarten Eisma, voor zijn uiterst droge doch smaakvolle humor. Ik kijk met veel plezier terug op onze overpeinzingen (niet zelden onder het genot van een biertje). Arne Leer, voor je ontoombare positieve energie als wetenschapper en sporter. De eerste twee ronden mag je steevast winnen, maar de derde ronde zet ik op mijn naam. Mijn dank ook naar de vele lotgenoten, we hebben ons aan elkaar kunnen optrekken tot een hoger wetenschappelijk en

anders wel sociaal niveau: Manik, Marloes, Marieke en Sophie, Puck, Ninke en vele anderen, mijn dank! Maar ook naar de secretaresses voor hun hulp en humor, allen, en Karima in het bijzonder, mijn dank.

…de directie van Stichting Centrum ’45 voor het steunen van dit project. Twan Driessen, Ruud Jongedijk en Eddy Sas. Samen met het bestuur hebben jullie een omgeving gecreëerd waarin deze praktijkgericht onderzoek en deze promovendus in konden floreren. Ik dank jullie voor de schappelijke contacten.

…mijn collega’s bij Stichting Arq Psychotrauma Expert Groep en bij Stichting Centrum ’45. Velen van jullie een rol gespeeld in de totstandkoming van het project en geholpen mij onder te dompelen in de therapeutische wereld. Ik wil alle medewerkers, in Oegstgeest en in Diemen, van de dagkliniek en kliniek, en diagnostiek, van de receptie en secretariaat bedanken. Het zijn teveel namen om op te noemen, maar enkelen betrokkenen noem ik bij naam: Boud van der Huls, Beijka Mensink, Arnold Oostveen, Patricia Dashorst, Jelly van Essen, Rob Bouter, Hilda van Leeuwen, Marja Beuse, Jean Paul Remans, Annemarie Smith, Mayaris Zepeda Mendez en Barbara Lieuwen.

…de keteninstellingen en betrokkenen die hebben bijgedragen aan het succes van dit onderzoek en van de uitvoer een plezier maakte. In het bijzonder gaat mijn dank uit naar Edo van Helten, Sasja Dorrestein, René Vrijens, Harry van der Meer, Pauline van Eijk-Koomen, Ria Zijlstra-Havinga Debbie Janssen, Arnold Franken en alle immer sympathieke en behulpzame dames bij het secretariaat van de Militaire Geestelijke Gezondheidszorg (MGGZ). Als oud-stagiaire bij de MGGZ heb ik me altijd thuis gevoeld. Mijn dank gaat ook uit naar Jan Rodenburg en Ivan Komproe van Psychotraumacentrum Zuid Nederland (PTC ZN) en Dorien de Groot (GGZ Drenthe, topreferent traumacentrum) voor de samenwerking en onze gesprekken gaven me telkens weer nieuwe inzichten.

…mijn coauteurs voor de kritische spiegels en gedachtewisselingen om te komen tot relevante manuscripten.

…het Landelijk Zorgsysteem voor Veteranen (LZV) Programmabureau, in het bijzonder Berend Berendsen en Miranda Meijer voor hun steun bij de aanvang van het project, en het bieden van een platform en spreekbuis voor samenwerking met de keteninstellingen. Het is een voorrecht om inmiddels deel uit te mogen maken van zulks een bevlogen en vakkundig team.

...mijn paranimfen Marieke Sleijpen en Kasper Gerritsen, voor de camaraderie. Kasper, wij gaan al heel lang terug en hopelijk nog heel lang mee. Door dik en dun kerven we samen een pad uit in het leven. Marieke, het is fijn iemand met gedeelde carrière ervaringen nabij te hebben en waar je ook nog eens goed mee kunt opschieten. Onze voeten wijzen, tot mijn blijdschap, nog steeds in dezelfde richting.

… Aida Dos Santos Dias, voor de grote en warme betrokkenheid in de afgelopen jaren. Samen met Marieke waren wij een eenheid. Geef Carlos en de andere jongens een knuffel!

…Jackie, voor alles wat ik van heb kunnen leren; je scherpe analytische geest en het verheffen van wetenschappelijk Engels schrijven tot een kunst. Je openheid en zelfreflectie, gepaard met de nodige zelfspot. Voor het simpelweg meegroeien en getuige zijn van grote gebeurtenissen in onze levens.

…Niels van der Aa, onze *powerhouse* methodoloog. Dank voor het stimuleren van kritisch denken en het niet genoegen nemen met het voor de hand liggende antwoord. Ik blijf leren van je uitvoerige kennis op het gebied van statistiek, en met jou in de buurt altijd garantie op vermaak.

…alle stagiaires die zich hebben ingezet om van het project een succes te maken. Ik vond het een eer om jullie te hebben mogen begeleiden in jullie proces tot academicus. Wat mooi hoe jullie ook allerlei nieuwe uitdagingen zijn aangegaan in jullie carrières. Dank Ania, Talitha, Heleen, Nicke, Eline, Ellen, Marte, Monica, Dianne, Hilde (reddende engel bij metingen), Riad, Sana, Elke, Rita, Simone, Allison, Hedwig, Daan en Josca

…de promotiecommissie, prof. dr. Toon Taris, prof. dr. Eric Vermetten, prof. dr. Ivan Komproe, prof. dr. Pim Cuijpers en prof. dr. Iris Engelhard, voor hun tijd en inspanningen om deze dissertatie te beoordelen en te toetsen op wetenschappelijke merites.

…Marleen van de Ven om de laatste loodjes lichter te maken en succesvol te overbruggen.

…mijn dierbare vrienden die het proces door de jaren hebben gadegeslagen en extra kleur geven aan mijn leven.

…mijn schoonouders, voor de plek die jullie me in jullie gezin en hart hebben gegeven.

…mijn broers, Zebbe, Jasper en Berend, mijn bloedverwanten, met elk jullie eigen insteek op het leven. Ik hoop dat jullie trots op mij zijn zoals ik dat op ieder van jullie ben.

…mijn ouders, voor jullie liefde, warmte en zorgzaamheid, en duwtje in de rug om de juiste koers in het leven te bepalen.

...Margriet, voor het veroveren van mijn hart.

…Simon voor het stelen van mijn hart.

…Niets belangrijker dan dat.

Curriculum Vitea & List of Publications

About the author

Joris Haagen (1981) is a psychologist, researcher and senior policy advisor at Arq Psychotrauma Expert Group where he is now involved as post-doctoral researcher in a large research project for Médicins sans Frontières. He completed his PhD at Utrecht University and also works as policy advisor and research portfolio manager for the Dutch National Health System for Veterans.

Joris Haagen graduated in 2007 at the Utrecht University with a Master's degree in Clinical and Health Psychology. After graduation, he worked as a military personnel selection and assessment psychologist for the Department of Defense (2008). From 2009-2011, Joris fulfilled a junior researcher position for Foundation Centrum '45, assisting in the completion of a randomized controlled trial examining the efficacy of eye movement desensitization and reprocessing (EMDR) therapy versus stabilization therapy for traumatized refugees. After which he began a PhD track at the Utrecht University that resulted in the present dissertation. During his PhD track he supervised students with their research bachelor and master thesis, and lectured students in *Personality Theory*, *Interculturalization of the Mental Health Care*, and *Psychotrauma and Loss* (courses). He participated in structural activities of Utrecht University Wetenschapsknooppunt providing lectures for primary schoolchildren and teachers about posttraumatic stress disorder.

Joris Haagen was assistant editor of the Dutch handbook for posttraumatic stress disorders [Handboek voor Posttraumatische Stressstoornissen] (2012), and editor (2011-2014) for Impact Magazine (formerly known as Cogiscope). A quarterly for researchers and professionals regarding the psychosocial effects and consequences of shocking and psychotraumatic experiences. He was member of the Board of Advice for Echoes Online (2010-2012), and member of the Society for Traumatic Stress Studies (ISTSS) Membership Committee (2014-2016), that is committed to strengthening and promoting diversity in ISTSS membership numbers.

Scientific Publications

Haagen, J. F. G., Heide, F. J., Mooren, T. M., Knipscheer, J. W., & Kleber, R. J. (2017). Predicting post-traumatic stress disorder treatment response in refugees: Multilevel analysis. *British Journal of Clinical Psychology, 56,* 69-83. doi:10.1111/bjc.12121

Sleijpen, M., **Haagen**, J. F. G., Mooren, T., & Kleber, R. J. (2016). Growing from experience: An exploratory study of posttraumatic growth in adolescent refugees. *European Journal of Psychotraumatology, 7*: 1, 28698. http://dx.doi.org/10.3402/ejpt.v7.28698@zept20.2016.7.issue-s1

Haagen, J. F. G., Moerbeek, M., Olde, E., Van Der Hart, O., & Kleber, R. J. (2015). PTSD after childbirth: A predictive ethological model for symptom development. *Journal of Affective Disorders, 185,* 135-143. https://doi.org/10.1016/j.jad.2015.06.049

Haagen, J. F. G., Smid, G. E., Knipscheer, J. W., & Kleber, R. J. (2015). The efficacy of recommended treatments for veterans with PTSD: A metaregression analysis. *Clinical Psychology Review, 40,* 184-194. doi:10.1016/j.cpr.2015.06.008

Manuscripts submitted for Publication

Haagen, J. F. G., Knipscheer, J. W., & Kleber, R. J. (2017). Using alternative frameworks to examine veteran PTSD psychotherapy effectiveness. Manuscript submitted for publication.

Haagen, J. F. G., van Rijn, A., Knipscheer, J. W., Van der Aa, N., & Kleber, R. J. (2017). The dissociative PTSD subtype: A treatment outcome cohort study in veterans with PTSD. Manuscript submitted for publication.

Haagen, J. F. G., Knipscheer, J. W., & Kleber, R. J. (2017). The legitimacy of trauma focused psychotherapy in clinical settings: Conveying evidence into practice and practice into evidence for veterans with PTSD. Manuscript submitted for publication.

Haagen, J. F. G., Van der Aa, N., Knipscheer, J. W., & Kleber, R. J. (2017). Adverse consequences of disturbed sleep in veteran PTSD treatment. Manuscript submitted for publication.

Professional Publications

Haagen, J. F. G. (2015). Er is geen sine qua non in psychotherapie. In: P. van der Velden, T. Mooren, & J. W. Knipscheer (Red.). *Psychotrauma wel beschouwd. Liber amicorum voor prof. dr. Rolf J. Kleber* pp. 53-60). Den Haag: Boom / Arq psychotrauma Expert Groep

Haagen, J. F. G. (2014). Onverklaarbare lichamelijke klachten en PTSS: Psychotrauma en functionele somatische syndromen onder de loep. *Cogiscope, 3*, 24-26.

Haagen, J. F. G. (2014). Genocidale samenlevingen - Ugur Üngör over het spel van vergeten. *Cogiscope, 3*, 2-7.

Haagen, J. F. G. (2014). Innovatie en inspiratie in medische psychotraumatologie - Een interview met prof. dr. Eric Vermetten. *Cogiscope, 2*, 2-5.

Haagen, J. F. G. (2014). De opkomst van de SMART revolutie - Inzet van smartphone apps voor de behandeling van PTSS. *Cogiscope, 1*, 24-25.

Haagen, J. F. G. (2014). Zorgen voor elkaar: Militair voor het leven - Een interview met zorgmanager Monica Schetters van Koninklijk Tehuis Bronbeek. *Cogiscope, 1*, 16-18.

Haagen, J. F. G. (2014). Kunnen mensen 50 jaar na dato nog last hebben van een traumatische gebeurtenis? In: *50 bites of science.* Utrecht: Libertas.

Haagen, J. F. G. (2013). Mentale gevolgen van overstromingen en optimisme als buffer na een ramp. *Cogiscope, 3*, 26-28.

Haagen, J. F. G. (2013). Het Beestmensch - Journalist Arnold Karskens over zijn jacht op oorlogsmisdadiger Klaas Faber. *Cogiscope, 2*, 7-9.

Haagen, J. F. G. (2013). Zoektocht naar de man die mijn vader was: Hoe de keuze van haar vader het leven van Leoni Jansen tekende. *Cogiscope, 1*, 6-8.

Haagen, J. F. G. (2013). Review: Trauma counselling - Theories and interventions. *Intervention: International Journal of Mental Health, Psychosocial Work and Counselling in Areas of Armed Conflict, 11*(3), 349.

Haagen, J. F. G. (2012). Hoe voorkom je daderschap in oorlog? - Stef Scagliola over militaire excessen in Nederlands-Indië. *Cogiscope, 4*, 7-11.

Haagen J, F. G., Vermetten E, & Kleber, R, J. (2012). Algemene psychologische behandelingsmethoden en procedures. In: E. Vermetten, R.J. Kleber & O. Van der Hart (Red.). *Handboek voor Posttraumatische Stressstoornissen.* Utrecht: De Tijdstroom

Haagen, J. F. G. (2011). Het nut van schaamte. *Cogiscope, 4*, 26-27.

Haagen, J. F. G. (2011). Opmerkelijke veerkracht onder overlevenden van de Holocaust. *Cogiscope, 3*, 26-27.

Haagen, J. F. G. (2011). Wegcijferen eigen klachten drempel bij het zoeken van psychische hulp. *Cogiscope, 2*, 25-26.