Injured body, injured soul? Predicting and preventing posttraumatic stress disorder after injury

Mouthaan, J.

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Traumatic injury is common and may have a major impact on the survivor's life. In the Netherlands alone, over 7 million injuries are registered yearly, caused by accidents in traffic, at home, at work, or by interpersonal violence. Besides physical recovery, survivors often deal with the psychological impact. Although most are resilient and show a natural psychological recovery within the first year, a proportion develops persistent psychological symptoms, among which posttraumatic stress disorder (PTSD). The studies in this thesis focused on how to predict and how to prevent the development of PTSD in the acute phase after traumatic injury.

Joanne Mouthaan (1979) received her Master's degree in Psychology at Utrecht University in 2001, after which she worked as a behavioural scientist at the Veterans Institute in Doorn. In 2004, she started her PhD research on the Trauma TIPS project, the results of which are described in this thesis, at the Center for Psychological Trauma, Department of Psychiatry of the Academic Medical Center, Amsterdam, under the supervision of prof. dr. Miranda Olff, prof. dr. Berthold Gersons and dr. Marit Sijbrandij. She currently works as a lecturer in Clinical Psychology at Leiden University.
Injured Body, Injured Soul?

Predicting and Preventing Posttraumatic Stress Disorder After Injury

JOANNE MOUTHAAAN

voor Jade en Liv
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Promotores: Prof. dr. M. Olff
            Prof. dr. B.P.R. Gersons

Copromotor: Dr. M. Sijbrandij

Overige leden: Prof. dr. J.K. Sluiter
               Prof. dr. M.B. Vroom
               Prof. dr. H.C.P.M. van Weert
               Prof. dr. W.J.M.J. Cuijpers
               Prof. dr. B.M. Elzinga
               Dr. E.F. van Beeck

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CHAPTER 1: Introduction

Chapter adapted from:


1.1 General introduction

**Case of Angela¹, age 18:** It is the first day of Summer and Angela and her friend Nicole are packed and ready to go to the beach. The city is buzzing with tourists, making it almost impossible to get through on their scooter. While looking over her shoulder to see the traffic, the car in front of her suddenly stops and Angela crashes into the car at about 15 km/h with no helmet on. She falls to the street and hits her head on the curb. Angela remembers feeling panic, trying to get up to check up on her friend, but being held down by bystanders. She only just notices all the blood when Nicole finally joins her and tries to calm her down. Angela is admitted to hospital for three days with a broken hand, wrist and teeth and contusions to her kidneys, liver and ribs. As Nicole was flung into the brush during the crash, she is lucky to get off with just a fright. In the days after the crash, Angela’s panicky feeling do not seem to go away, she is very emotional and worries a lot about her injuries and about her friend. Even though Nicole was unharmed and visits her often, Angela still feels guilty about the accident.

**Case of Dwayne¹, age 33:** Dwayne has worked as a garbage collector for 7 years now, mostly on the same routes, week in, week out. He knows the neighbourhoods and the people in it. One route even passes by his house. One day, while greeting a neighbour, the garbage truck backs up and his foot gets stuck in between the tire and the curb. He screams, bangs on the side of the truck, thinking he would be run over, and loses consciousness. Luckily, Dwayne is freed almost instantly and suffers no other injuries, but undergoes several surgeries for his foot. Now, after 4 weeks, he is ready to rehabilitate. He suffers from constant pain in his foot and takes as much pain medication as he is allowed. Since the accident, he sees the truck coming towards him almost every time he closes his eyes. His colleagues and friends still pay him daily visits, and sometimes manage to take his mind of the accident or the pain, but only until they leave. Then he is back in between the truck and the curb.
Case of Josine¹, age 45: Just a quick trip to the supermarket, Josine thought. It is near dinner time, snowing and already dark outside. She remembers paying for the groceries and stepping back into the car, but then she wakes up in a hospital bed, surrounded by doctors and nurses and bright lights. A nurse holds her hand and explains that her car collided with another car, flipped on its side and that she was rescued by the fire department. She was lucky, according to the nurse, to only have a concussion and some bruises; it could all have been so much worse. Josine is discharged after a one night stay. At first, not being able to remember what happened makes her feel anxious and insecure. Did she black out in the car before or due to the accident? What if it would happen again, how would she know how to handle it? After a while, with the help from her family and friends, she manages to take her first car ride again. After a few times, driving begins to feel familiar again, although Josine firmly keeps both eyes on the road, just in case.

¹ Case present accounts of participants in the Trauma TIPS study. Names or other personal or identifiable information has been altered for anonymity purposes.

Accidental injuries may have a major impact on one’s life. Suddenly, that person may be confronted with a serious threat to his or her health or life, may be rushed off to the hospital in an ambulance or trauma helicopter, may undergo extensive medical examination and -often- hospitalisation, causing the immediate and long-term future to be uncertain. In the Netherlands alone, over 7 million injuries are registered yearly, caused by accidents in traffic, at home, at work, or by interpersonal violence (VeiligheidNL, 2014). Half of these require medical treatment and cost up to 2.5 billion euro in medical costs and 3.3 billion euro in costs for labour lost (VeiligheidNL, 2014). Highly specialised level 1 trauma centers, located in eleven hospitals across the Netherlands, provide state of the art medical care for these victims with traumatic injury. Although the (neuro-)psychological and social consequences of traumatic injury have been acknowledged since 1943 (Adler, 1945; Cobb & Lindemann, 1943) and have increasingly been the topic of study in recent years (e.g., see Bryant et al., 2010; O’Donnell, Creamer, Bryant, Schnyder, & Shalev, 2003; Sareen et al., 2013), knowledge is still needed about how many people suffer from mental health problems after injury, how these problems may be predicted, reduced, or even prevented, in order to design ways to better identify
those at risk for long-lasting psychological problems, and to improve the recovery from their physical and mental injuries.

This thesis focuses on predictors of posttraumatic stress disorder (PTSD) and prevention of PTSD in the acute phase after traumatic injury. In this introductory chapter, I will first briefly describe the prevalence of trauma and PTSD (paragraph 1.2) and discuss current theories of PTSD (paragraph 1.3). Next, I will focus on biological and psychological predictors for PTSD (paragraph 1.4), strategies for the prevention of PTSD (paragraph 1.5), and the design of the Trauma TIPS study (paragraph 1.6). In the final paragraph (1.7), I present an overview of the aims and chapters in this thesis.

### 1.2 Prevalence of trauma and Posttraumatic Stress Disorder

Approximately four out of five persons experience a potentially traumatic event, such as an accident, disaster, war or assault, during their lives (Breslau, Peterson, Poisson, Schultz, & Lucia, 2004; de Vries & Olff, 2009; Frans, Rimmo, Aberg, & Fredrikson, 2005; Kawakami, Tsuchiya, Umeda, Koenen, & Kessler, 2014; Kilpatrick et al., 2013; Norris et al., 2003). In the DSM-5 (American Psychiatric Association, 2013), a traumatic event is defined as an event involving actual or threatened death, serious injury or sexual violation. This includes both direct exposure, by experiencing or witnessing the traumatic event in person, and indirect exposure, by learning that a close family member or friend experienced actual or threatened death that was violent or accidental, or by experiencing first-hand repeated or extreme exposure to aversive details of the traumatic event (but not through media, pictures, television or movies unless work-related; American Psychiatric Association, 2013; see Box 1.1).


**Criterion A:**

**stressor.** The person was exposed to: death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence, as follows: (one required) (1) direct exposure; (2) witnessing, in person; (3) indirectly, by learning that a close relative or close friend was exposed to trauma (if the event involved actual or threatened death, it must have been violent or accidental); (4) repeated or extreme indirect exposure to aversive details of the event(s), usually in the course of professional duties (e.g., first responders, collecting body parts; professionals repeatedly exposed to details of child abuse; not including indirect non-professional exposure through electronic media, television, movies, or pictures).
Criterion B: *intrusion symptoms.* The traumatic event is persistently re-experienced in the following way(s): (one required) (1) recurrent, involuntary, and intrusive memories (Note: Children older than six may express this symptom in repetitive play); (2) traumatic nightmares (Note: Children may have frightening dreams without content related to the trauma(s)); (3) dissociative reactions (e.g., flashbacks) which may occur on a continuum from brief episodes to complete loss of consciousness (Note: Children may reenact the event in play); (4) intense or prolonged distress after exposure to traumatic reminders; (5) marked physiologic reactivity after exposure to trauma-related stimuli.

Criterion C: *avoidance.* Persistent effortful avoidance of distressing trauma-related stimuli after the event: (one required) (1) trauma-related thoughts or feelings; (2) trauma-related external reminders (e.g., people, places, conversations, activities, objects, or situations).

Criterion D: *negative alterations in cognitions and mood.* Negative alterations in cognitions and mood that began or worsened after the traumatic event: (two required) (1) inability to recall key features of the traumatic event (usually dissociative amnesia; not due to head injury, alcohol, or drugs); (2) persistent (and often distorted) negative beliefs and expectations about oneself or the world (e.g., “I am bad,” “The world is completely dangerous”); (3) persistent distorted blame of self or others for causing the traumatic event or for resulting consequences; (4) persistent negative trauma-related emotions (e.g., fear, horror, anger, guilt, or shame); (5) markedly diminished interest in (pre-traumatic) significant activities; (6) feeling alienated from others (e.g., detachment or estrangement); (7) constricted affect: persistent inability to experience positive emotions.

Criterion E: *alterations in arousal and reactivity.* Trauma-related alterations in arousal and reactivity that began or worsened after the traumatic event: (two required) (1) irritable or aggressive behavior; (2) self-destructive or reckless behavior; (3) hypervigilance; (4) exaggerated startle response; (5) problems in concentration; (6) sleep disturbance.

Criterion F: *duration.* Persistence of symptoms (in Criteria B, C, D, and E) for more than one month.

Criterion G: *functional significance.* Significant symptom-related distress or functional impairment (e.g., social, occupational).

Criterion H: *exclusion.* Disturbance is not due to medication, substance use, or other illness.
It is common for trauma survivors to experience an array of acute stress reactions in the first weeks after the event (Bryant et al., 2010), but only in a minority of individuals do these symptoms persist after one month and develop into a posttraumatic stress disorder (PTSD). PTSD is characterized by intrusive recollections of the event (i.e., memories, nightmares, flashbacks), avoidance of trauma-related stimuli (i.e., trauma-related thoughts, feelings or external cues), changes in cognition or affect (i.e., dissociative amnesia, persistent negative trauma-related emotions, constricted affect) and changes in arousal and reactivity (i.e., sleep disturbance, concentration problems, hypervigilance; American Psychiatric Association, 2013; see Box 1.1). Epidemiological studies in the general population have reported lifetime prevalence rates of PTSD ranging from less than 1% (Helzer, Robins, & McEvoy, 1987; Hepp et al., 2006) to 10% (Breslau, Davis, Andreski, & Peterson, 1991; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995), with higher rates of up to 37% in post-conflict regions (de Jong et al., 2001). The overall conditional risk of PTSD after any traumatic event ranges from 1% to 14% (Breslau et al., 1998; de Vries & Offf, 2009; Kilpatrick et al., 2013; Olaya et al., 2014), but is strongly dependent on the type of traumatic exposure, as rates of PTSD following intentional trauma (i.e., acts of violence purposefully aimed towards an individual, such as assault, rape, war or terrorist attacks) are higher than following unintentional trauma (i.e., man-made or natural disasters, accidents; Santiago et al., 2013).

Traumatic injuries are one of the most common types of traumatic exposure worldwide, accounting for 9% of global mortality. In more than 20 million people every year, traumatic injuries are estimated to cause temporary or permanent disability (World Health Organization, 2008). Recently, it was estimated that the burden of disease for injuries would increase by 50% when mental health consequences, such as posttraumatic stress disorder (PTSD), are considered (Haagsma et al., 2012). A recent meta-analysis of studies of injured trauma populations showed PTSD prevalence rates of 8%-45% at 1 month post-trauma that decreased to 7% to 26% at 12 months post-trauma (Heron-Delaney, Kenardy, Charlton, & Matsuoka, 2013). However, the mental health effects of exposure to trauma are considerably more heterogeneous than PTSD. In approximately comparable rates, survivors of traumatic events have been found to suffer from depressive disorders between 6% and 60% (Holbrook, Anderson, Sieber, Browner, & Hoyt, 1999; Mellman, David, Bustamante, Fins, & Esposito, 2001; Schnyder, Moergeli, Klaghofer, & Buddeberg, 2001; Shalev et al., 1998), anxiety disorders, other than PTSD, between 2% and 11% (Brown, Fulton, Wilkeson, & Petty, 2000; O’Donnell et al., 2003; O’Donnell, Creamer, Pattison, & Atkin, 2004) and substance use disorders between 8% and 21% (O’Donnell et al., 2004; Whelan-Goodinson, Ponsford, Johnston, & Grant, 2009) during the first year post-trauma. A diagnosis of acute stress disorder (ASD) has been reported in 6% to 14% of injury populations (Bryant & Harvey, 1998: Fuglsang, Moergeli, Hepp-Beg, & Schnyder, 2002; Harvey & Bryant, 1999a; Harvey & Bryant, 1999b; Mellman et al., 2001). Comorbidity between post-injury mental disorders was found to be as high as 53% between PTSD and depression (Shalev et al., 1998).
1.3 Theories of PTSD: appraising the traumatic event

To explain why some individuals develop PTSD after traumatic exposure and others do not, several theories on PTSD have centred on the construct of cognitive appraisal, defined by Lazarus and Folkman (1984) as “the process of categorizing an encounter, and its various facets, with respect to its significance for well-being – not information processing per se, but more a continuous, evaluative process focused on meaning and significance” (p.31). From a cognitive perspective, it is the interpretation of the traumatic event, rather than the event itself, that causes disruptions in mood and behaviour. Social-cognitive theories focus on how trauma impacts existing mental structures, more specifically cognitions about the self, others and the world, and on ways to deal with the incompatibility of the trauma information with prior beliefs (Brewin & Holmes, 2003; Sherrer, 2011). Information-processing theories focus on memory structures and the encoding, storage and retrieval of trauma-specific and fear-induced information and responses. These memory structures are considered vital to the initial appraisal and subsequent reappraisal of the event (Brewin & Holmes, 2003; Sherrer, 2011). In this paragraph, I focus on three recent theoretical models that have integrated the cumulative scientific evidence about the development and course of PTSD within their theoretical models: emotional processing theory (Foa & Rothbaum, 1998), the cognitive model by Ehlers and Clark (2000), and the traumatic stress-coping model by Olff, Langeland and Gersons (2005).

1.3.1 Emotional processing theory

Building upon previous social-cognitive, conditioning and information-processing theories, emotional processing theory theorizes that PTSD emerges as a consequence of developing a fear structure associated with the traumatic event (Foa & Rothbaum, 1998). This fear structure involves representations of the traumatic event, such as stimuli, responses and their meaning, and serves as a blueprint for escaping or avoiding harm in that type of situation. Any information related to the traumatic event activates the fear structure, causing hyperarousal symptoms, intrusive memories and avoidance behaviour (Rothbaum, Meadows, Resick, & Foy, 2000). For example, in the case of a motor vehicle crash, getting into a car would heighten physiological arousal, trigger memories of the crash, and cause the urge to leave and to consequently avoid that situation. Fear structures are in itself adaptive, when a person is faced with real danger, but become pathological when the associations between stimuli, response and representation do not reflect real danger. Specific to PTSD, the fear structure involves wrongfully interpreting safe stimuli as dangerous (e.g., “Getting into a car is dangerous”), and wrongfully interpreting responses as self-incompetence (e.g., “My symptoms mean that I can’t cope with this”; Rothbaum et al., 2000). These two basic dysfunctional cognitions
about the danger of the world and the incompetence of the self are thought to underlie PTSD.

1.3.2
A cognitive model of PTSD

Another influential PTSD model is the cognitive model of Ehlers and Clark (2000). In their model, they assume that, unlike individuals who recover naturally, individuals with persistent PTSD are unable to see the trauma as a time-limited event that does not have global negative implications for their future. They experience a continuous sense of threat through excessively negative appraisals of the trauma and/or its consequences (Ehlers & Clark, 2000). These negative appraisals include interpretations of one’s initial PTSD symptoms, interpretation of other people’s reactions in the aftermath of the event, and appraisals of the consequences of the trauma on other life domains (e.g., work, physical health, financial situation). Perceiving one’s initial reactions to the trauma, such as intrusive memories, trouble concentrating, sleep difficulties, as inadequate or abnormal, will produce negative emotions (i.e., anger, depression, anxiety) and encourage dysfunctional coping behaviour that ultimately reinforce the traumatic stress symptoms. Otherwise harmless or considerate reactions to the traumatic event of family and friends, such as not confronting the loved one with the event in order to try to minimise distress, can be perceived as careless or blameful.

1.3.3
The traumatic stress-coping model

From a psychobiological perspective, the traumatic stress-coping model of Olff, Langeland and Gersons (2005) proposes that a threat appraisal of the traumatic event is followed by an acute stress response involving emotional, behavioural and biological elements.

When confronted with danger, two neuroendocrine response systems are activated to enable a fight-flight-freeze response: the sympathoadreno-medullar (SAM) axis and the hypothalamus-pituitary-adrenal (HPA) axis. Seconds after danger is assessed, within the SAM axis, the adrenal medulla is activated to release noradrenaline and adrenaline into the blood stream. This sets in motion the central nervous system, increasing heart rate and blood pressure. This enables immediate muscular action in response to the threat. After a few minutes, the HPA axis is activated to prolong the stress response when needed. During acute stress, the hypothalamus secretes corticotrophin-releasing hormone. This in turn stimulates the pituitary gland to release adrenocorticotropic hormone, which leads to the production of glucocorticoids (cortisol) and dehydroepiandrosterone (DHEA) by the adrenal cortex (Vinson, Whitehouse, & Hinson, 2007). Cortisol suppresses metabolic, immuno- and neurodefensive processes to adequately cope with the
stressor, and triggers a negative feedback loop when sufficient circulating levels are reached. When the threat is gone, the negative feedback mechanisms help to restore basal hormone levels.

According to the traumatic stress-coping model, failure to regulate the biological stress response at the time of the trauma sets in motion a cascade of psychobiological alterations that lead to intrusions of the traumatic event, avoidance of reminders of the event and hyperarousal symptoms (Olff, Langeland, & Gersons, 2005). The pathways between the acute psychological and biological responses to the trauma are influenced by background and socio-cultural characteristics (i.e., gender, age, genetic susceptibility to stress, personality, prior trauma, social support), but also by coping strategies. Defensive coping may protect an individual from being overwhelmed and may buffer against their HPA acute stress response, but may, when constituting a general defensive coping style, lead to long term sustained sympathetic arousal. Active coping may help deal with the traumatic stressor and may prevent long term psychophysiological dysregulations and psychopathology (Olff et al., 2005).

1.3.4
Appraisal in PTSD treatment

According to the models described above, altering the appraisal of the traumatic event may result in a decrease in PTSD symptoms. Cognitive-behaviour therapy (CBT) is based on the principles that cognitions influence emotions and behaviour, and behaviour impacts cognitions and emotions (Wright, Ramirez Basco, & Thase, 2006). According to Ehlers and Clark (2000), successful treatment is aimed at identifying cognitive themes or ‘hot spots’, i.e., memories that elicit extreme distress, normalizing the PTSD symptoms, explaining how their usual coping strategies contributed to symptom persistence, and fully processing the trauma, thereby reversing the maintenance factors. According to emotional processing theory, successful treatment of PTSD means correcting the pathological elements of the fear structure by first reactivating the structure and second providing new, incompatible information (Rothbaum et al., 2000). This is the basis of the technique imaginal exposure, in which repeated imaginal reliving is thought to promote habituation and reduce anxiety to trauma-related memories (Rothbaum et al., 2000). Imaginal exposure and cognitive restructuring constitute elements of CBT for PTSD treatment (Ehlers & Clark, 2000; Wright et al., 2006). Other elements of CBT are psychoeducation about the disorder and the treatment, behavioural methods, such as behavioural activation, systematic desensitisation, breathing retraining and stress management exercises (Wright et al., 2006).
1.4 Predictors for PTSD

1.4.1 Biological PTSD predictors

Cortisol
As mentioned in the previous paragraph, an inability to attain homeostasis after HPA axis activation is considered a risk factor for developing PTSD (Olff et al., 2005; Yehuda, 2002). As a result, studies have focused on the role of the acute cortisol response in the development of PTSD. So far, findings have been inconsistent. Some studies found no direct relationship between initial cortisol and subsequent PTSD (Bonne et al., 2003; Resnick, Yehuda, Pitman, & Foy, 1995; Shalev et al., 2008). Others found that acute low cortisol levels predicted PTSD (Delahanty, Raimonde, & Spoonster, 2000; McFarlane, Atchison, & Yehuda, 1997) or PTSD symptoms (Aardal-Eriksson, Eriksson, & Thorell, 2001; Ehring, Ehlers, Cleare, & Glucksman, 2008; McFarlane, Barton, Yehuda, & Wittert, 2011), although in some the association disappeared when controlling for possible confounding variables, such as injury severity and history of PTSD (Delahanty et al., 2000), and time of the accident or blood sampling (McFarlane et al., 1997). Variations in methodology, for example, when (i.e., immediately post-trauma up to several days after the event) or how (i.e., saliva, urine or plasma) cortisol was measured, might explain these differences. Lack of power due to a small sample size has been referred to by some studies as a possibility for not finding a significant association (Delahanty et al., 2000; Ehring et al., 2008). Therefore, it has been argued that the predictive effect of cortisol should be replicated in large, consecutively recruited samples, taking into account the important confounders.

DHEA(S)
During the acute stress response, DHEA is secreted alongside cortisol by the adrenal cortex (Vinson et al., 2007). Animal studies have found DHEA and its sulfate form DHEAS to possess anabolic, neuroprotective and antiglucocorticoid effects (Kaminska, Harris, Gijsbers, & Dubrovsky, 2000; Karishma & Herbert, 2002; Kimonides, Khatibi, Svendsen, Sofroniew, & Herbert, 1998; Kimonides, Spillantini, Sofroniew, Fawcett, & Herbert, 1999). These effects may lead to an upregulation of HPA-axis responses and mitigate possible adverse effects of high cortisol levels on the brain in PTSD (Rasmusson, Vythilingam, & Morgan, Ill, 2003). As such, dysregulations in the HPA-axis associated with PTSD may also be evident in an abnormal DHEA-response. DHEAS is much more abundant than DHEA, because DHEAS has longer half-life and lower clearance (Lennartsson, Kushnir, Bergquist, & Jonsdottir, 2012). Studies on long term effects of stress have often reported on DHEAS levels, as they are more stable and show no diurnal variation (Kroboth, Salek, Pittenger, Fabian, & Frye, 1999). Studies on acute stress, on the other hand, have
often focused on DHEA, since DHEAS serves as a reservoir for DHEA biosynthesis and DHEA rather than DHEAS is expected to respond to acute psychosocial stress (Izawa et al., 2008; Morgan, III et al., 2004; Oberbeck et al., 1998; Pico-Alfonso, Garcia-Linares, Celda-Navarro, Herbert, & Martinez, 2004; Shirotsuki et al., 2009). However, in a recent study, although the response of DHEA was more pronounced, both DHEA and DHEAS were found to increase in response to acute psychosocial stress (Lennartsson et al., 2012). In addition, DHEAS was found to increase in response to low, but not high, intensity military stress exposure (Morgan, III et al., 2004; Taylor et al., 2007). As of yet, DHEA or DHEAS have not been prospectively studied in the prediction of PTSD.

Cortisol-to-DHEA(S) ratio

Cortisol and DHEA(S) are often addressed as a ratio, representing the balance between anabolic and catabolic hormones (Maninger, Wolkowitz, Reus, Epel, & Mellon, 2009). A high ratio of cortisol-to-DHEA(S), or conversely a low DHEA(S)-to-cortisol ratio, represents a catabolic balance. A low cortisol-to-DHEA(S) ratio, or a high DHEA(S)-to-cortisol ratio, reflects an anabolic balance. A higher cortisol-to-DHEA ratio has been linked to a chronic stress response in depressed adolescents and adults (Goodyer, Herbert, & Altham, 1998; Young, Gallagher, & Porter, 2002), as well as more resilient functioning in both maltreated and non-maltreated children (Cicchetti & Rogosch, 2007), whereas a higher DHEAS-to-cortisol ratio was positively correlated with fewer dissociative symptoms after prolonged and extreme training stress (Morgan, III et al., 2004; Taylor et al., 2007). Thus, previous findings are inconclusive with respect to the role of the cortisol-to-DHEA(S) ratio in the onset of psychiatric disorders such as PTSD.

Heart rate

As a parameter for increased psychophysiological arousal following trauma, studies have examined the initial basal heart rate (HR) in injured trauma survivors, assessed at the emergency department, in association with PTSD symptoms (Blanchard, Hickling, Galovski, & Veazey, 2002; Bryant, 2006; Bryant, Creamer, O’Donnell, Silove, & McFarlane, 2008; Buckley et al., 2004; Coronas et al., 2011; Kassam-Adams, Garcia-Espana, Fein, & Winston, 2005; Kraemer, Moergeli, Roth, Hepp, & Schnyder, 2008; Kuhn, Blanchard, Fuse, Hickling, & Broderick, 2006; Zatzick et al., 2005). Some studies reported a positive association between initial HR and later PTSD (Bryant et al., 2008; Kassam-Adams et al., 2005; Shaikh al et al., 2012; Zatzick et al., 2005), others found no significant association between HR and PTSD (Buckley, Holohan, Greif, Bedard, & Suvak, 2004; Kuhn et al., 2006), and one study found a lower HR to be correlated with chronic PTSD (Blanchard et al., 2002). One study found that only HR measured at the scene of the traffic accident and not HR assessed at hospital admission was predictive of later PTSD (Coronas et al., 2011).
1.4.2 Psychological PTSD predictors

Appraisal

Psychological factors related to the appraisal of the traumatic event or the immediate emotional response to the event have consistently shown to predict PTSD. One of these is perceived life threat, which is often used as a measure of the subjective severity of the traumatic exposure (Ozer, Best, Lipsey, & Weiss, 2003; Sijbrandij et al., 2013). Perceived life threat during a road traffic accident was found to be one of the largest predictors for PTSD after a road traffic accident in a recent systematic review and meta-analysis (Heron-Delaney et al., 2013).

Peritraumatic reactions

Other psychological predictors for the onset of PTSD are peritraumatic dissociation and distress. Peritraumatic dissociation refers to disturbed awareness, impaired memory, or altered perceptions during and immediately after a traumatic experience (Cardena & Spiegel, 1993). These reactions may include emotional numbing, reduction in awareness of one’s surroundings, depersonalization, and amnesia. Peritraumatic distress refers to the broader emotional response during and immediately after trauma exposure, that could lead to dissociative responses (Brunet et al., 2001). Symptoms of peritraumatic distress include sadness, grief, anger, helplessness, and disgust. Meta-analytic evidence indicates both peritraumatic dissociation and distress are predictors of PTSD (Ozer et al., 2003). Recently, however, the role of peritraumatic dissociation in the prediction of PTSD has been criticized (Briere, Scott, & Weathers, 2005; Wittmann, Moergeli, & Schnyder, 2006), since it is associated with acute PTSD (i.e., PTSD diagnosed within 3 months after traumatic exposure), but is not a predictor for chronic PTSD (i.e., PTSD diagnosed at 3 months or more after traumatic exposure; cf. DSM-IV; see American Psychiatric Association, 2000), after symptoms of acute PTSD are controlled for (van der Velden & Wittmann, 2008).

1.4.3 Trauma-related characteristics

Important trauma-related characteristics in the prediction of PTSD are: type of traumatic event, physical injury, and injury-related aspects, such as type of injury, consciousness during the event and pain.
Type of event

As mentioned briefly in paragraph 1.1, the type of traumatic event greatly impacts the prevalence of PTSD. A general distinction may be made between intentional trauma (i.e., acts of violence purposefully aimed towards an individual, such as assault, abuse, war or terrorist attacks) and unintentional trauma (i.e., man-made or natural disasters, accidents). A recent systematic review showed that whereas prevalence rates decrease during the first year following unintentional trauma (1-month median=30.1, 95% CI [16.7-35.1], 12-month median=14.0, 95% CI [2.2-28.3]), the prevalence of PTSD increases in the year after intentional trauma (1-month median=11.8, 95% CI [3.1-87.5], 12-month median=23.3, 95% CI [2.6-43.8]; Santiago et al., 2013).

Physical injury

Physical injury during a traumatic event is embedded in the A-criterion of the PTSD diagnosis in DSM-5 (American Psychiatric Association, 2013; see Box 1.1). So far, the results of studies on the association between injury severity and PTSD have been inconsistent. Some showed a positive relationship between the severity of injury and symptoms of PTSD (Blanchard, Hickling, Taylor, & Loos, 1995; Frommberger et al., 1998; Hamanaka et al., 2006; Koren, Norman, Cohen, Berman, & Klein, 2005; Michaels et al., 1998). Two studies found a negative association between injury severity and PTSD (Delahanty, Raimonde, Spoonster, & Cullado, 2003; Dougall, Ursano, Posluszny, Fullerton, & Baum, 2001), and others failed to confirm either (Bryant & Harvey, 1995; Curran et al., 1990; Ehlers, Mayou, & Bryant, 1998; Feinstein & Dolan, 1991; Gabert-Quillen, Fallon, & Delahanty, 2011; Holbrook, Hoyt, Stein, & Sieber, 2001; Joy, Probert, Bisson, & Sheikh, 2000; Perry, Difede, Musngi, Frances, & Jacobsberg, 1992; Zatzick, Jurkovich, Gentilello, Wisner, & Rivara, 2002). To understand the discrepancies in findings, it is important to account for the timing of the PTSD assessment. In the immediate days and weeks following the injury, patients are likely to be occupied with their physical recovery and the psychological processing of the event probably occurs later (O’Donnell, Elliott, Lau, & Creamer, 2007). Moreover, most injury survivors, while in the hospital, may not be exposed to trauma reminders that may cause PTSD symptoms at a later stage. Furthermore, not all studies took important confounding or moderating factors into account, such as gender (Olff, Langeland, Draijer, & Gersons, 2007), threat to life (Olff et al., 2005), type of traumatic event (Breslau et al., 1998), stress hormone levels (Delahanty et al., 2003), or peritraumatic dissociation (Sijbrandij et al., 2012).
Traumatic brain injury (TBI)

TBI is defined as trauma to the head that results in an alteration or loss of consciousness or posttraumatic amnesia (American Congress of Rehabilitation Medicine, 1995). In a study of injury burden in six European countries, the incidence of skull-brain injury was on average 25 persons per 1000 inhabitants, whereas overall incidence of (any) injury ranged between 36 persons (for Ireland) and 116 persons (England) per 1,000 inhabitants (Polinder, Meerding, Mulder, Petridou, & van, 2007). A recent review indicated 14% PTSD in TBI patients, 5.8 times the relative risk of PTSD observed in the general community population (Carlson et al., 2011). The severity of TBI is often classified with the Glasgow Coma Scale (GCS), a neurological scale to record level of consciousness. In general, brain injury is classified as: Severe (GCS ≤ 8), Moderate (GCS 9-12) and Mild (GCS 13-15; Teasdale & Jennett, 1974). In civilian populations, mild TBI is the most frequent type of TBI. Most individuals with mild TBI recover fully within 90 days after the injury (Karr, Areshenkoff, & Garcia-Barrera, 2013). However, a minority of individuals continues to suffer from post-concussive somatic, cognitive, and/or behavioural symptoms that lead to long-term functional limitations. Persistent postconcussive symptoms are often non-specific and can be identical to symptoms of chronic stress or other mental health disorders, further complicating differential diagnosis (Larrabee & Rohling, 2013).

Pain

Acute pain in the context of physical injury has been linked to the development of acute stress reactions (Fuglsang et al., 2002; Saxe et al., 2005), PTSD (Asmundson, Coons, Taylor, & Katz, 2002; Kuch, Cox, & Evans, 1996; Norman et al., 2011; Norman, Stein, Dimsdale, & Hoyt, 2008) and other post-trauma psychopathology, such as depression and substance use (Cairns, Adkins, & Scott, 1996; Tate, Forchheimer, Krause, Meade, & Bombardier, 2004). A mutual maintenance model for pain and PTSD is suggested in which pain may serve as trauma reminder, triggering flashbacks (Asmundson et al., 2002). Conversely, PTSD symptoms, such as sleep deficiency, may maintain or worsen pain (Smith, Egert, Winkel, & Jacobson, 2002).
1.5 Strategies for PTSD prevention

1.5.1 Early PTSD risk screening

Early identification of trauma survivors at risk for PTSD through risk screening may facilitate adequate monitoring of symptoms, thorough follow-up diagnostics and early treatment if needed. Studies have shown that psychological treatment of acute PTSD symptoms as early as two weeks after trauma is effective in treating acute PTSD or ASD (Roberts, Kitchiner, Kenardy, & Bisson, 2009; Sijbrandij et al., 2007). To properly assess the diagnostic accuracy of a screening tool, sensitivity (i.e., the probability that someone with PTSD has a positive test result) and specificity (i.e., the probability that someone without PTSD has a negative result) are important. The higher the sensitivity, the lower the specificity, and vice versa. Based on the trade-off between sensitivity and specificity, an optimal cut-off point is usually chosen in diagnostic accuracy studies (Smits, Smit, Cuijpers, & de Graaf, 2007). Related to sensitivity and specificity, but more important for clinical practice, are the positive predictive value (PPV) and the negative predictive value (NPV) of a screening instrument. The PPV refers to the proportion of people scoring positive on the screening instrument who indeed develop PTSD, whereas the NPV refers to the proportion of people scoring negative on the screener who do not develop PTSD. PPV and NPV are both dependent on the population prevalence of a disorder. Typically, when the prevalence of a disorder in the population is low, there is a smaller chance of an individual scoring positive on the test to actually develop the disorder, causing PPV to be low and NPV to be high. Overall, screening for concurrent (existing) PTSD shows good diagnostic accuracy (Brewin, 2005; O’Donnell, Bryant, Creamer, & Carty, 2008).

As put forward by Brewin (2005), screening instruments for PTSD may be based on any measure that predicts a PTSD diagnosis. Most instruments consist of self-report scales of acute symptoms of PTSD (Brewin et al., 2002; Meltzer-Brody, Churchill, & Davidson, 1999). Brewin (2005) systematically reviewed the diagnostic accuracy of 13 screening instruments for concurrent PTSD that did not exceed 30 items, and concluded that those with fewer items, simpler response scales and simpler scoring methods showed equal diagnostic accuracy to longer and more complex scales. Screening to predict future PTSD, i.e., assessing prognostic accuracy, has generally shown less favourable results compared to screening for a concurrent PTSD diagnosis, with lower specificity values and PPVs (O’Donnell et al., 2008). Generally, prognostic screening instruments show high NPVs, making them particularly useful in filtering out individuals who will not develop PTSD. In other studies, demographic, premorbid, injury- and recovery-related factors were used in addition to acute psychological symptoms (O’Donnell et al., 2008; Ward-Begnoche et al., 2006). Overall, these instruments showed high sensitivity, but
moderate specificity, indicating a good accuracy in identifying those with possible future PTSD, but a diminished capacity for ruling out those without future PTSD. Current literature still lacks evidence on the comparability of screening instruments for future PTSD.

1.5.2 Early psychological interventions

Until recently, the most common prevention strategy in the immediate aftermath of traumatic events has been Critical Incident Stress Debriefing or, more generally named, “psychological debriefing” (Mitchell & Everly, 2001). Key elements of psychological debriefing are an emphasis on ventilating emotions, and psychoeducation about common psychological reactions and adequate coping strategies (Mitchell & Everly, 2001). Research has shown that psychological debriefing is not effective in preventing symptoms of PTSD, anxiety, or depression and may even increase the risk of PTSD (Rose, Bisson, & Wessely, 2003). It has been suggested that the emphasis on expressing emotions related to the trauma may exacerbate and sustain arousal, causing PTSD symptoms to escalate rather than diminish (Sijbrandij, Olff, Reitsma, Carlier, & Gersons, 2006). Routine use of such trauma-focused early interventions for everyone involved in the traumatic event is currently advised against (Impact, 2007; National Institute for Clinical Excellence (NICE), 2005).

Other prevention strategies have been examined, such as written psychoeducation, but no preventative effects have been found both in non-selected trauma patients and highly symptomatic trauma patients (Ehlers et al., 2003; Scholes, Turpin, & Mason, 2007; Turpin, Downs, & Mason, 2005). The authors suggested that the unguided provision of information about acute stress symptoms could have sensitized patients, thereby disrupting the natural recovery process (Scholes et al., 2007; Turpin et al., 2005).

Psychological first aid complies with the current guidelines for early interventions based on expert consensus and scientific evidence (National Child Traumatic Stress Network and National Center for PTSD, 2005), stating that stringent attempts to make victims express their emotions and relive their experiences are to be withheld. Psychological first aid consists of supportive, empathic listening, and helping victims with practical assistance, such as ensuring safety and facilitating contact with organizations and resources that may help them to meet more basic needs (National Child Traumatic Stress Network and National Center for PTSD, 2005). The efficacy of psychological first aid awaits to be studied (Pekevski, 2013).

Other research evaluating strategies to prevent PTSD focused on offering interventions to selected individuals at high risk for developing PTSD. Zatzick et al. (2004) randomized injury patients with high initial PTSD and/or depressive symptoms to a trauma support specialist, who monitored medical and psychological
symptoms and acted as case manager during 1 year following injury (collaborative care condition), or to a usual care control condition in which patients received a list of community referrals for mental health services. Collaborative care patients did not show any change in PTSD symptoms during the follow-up year, whereas symptoms worsened in usual care patients (Zatzick et al., 2004).

The Internet is increasingly used for the administration and dissemination of mental health interventions. Curative and (guided) self-help interventions for depression and anxiety, including PTSD, have been found effective, with comparable effect sizes to face-to-face treatment (Spek et al., 2007; van’t Hof, Cuijpers, & Stein, 2009). Few initiatives have yet been undertaken using the Internet as a medium for the prevention of PTSD (Cox, Kenardy, & Hendrikz, 2010; Ruggiero et al., 2006; Ruggiero et al., 2012). One web-based program for post-disaster mental health, among which PTSD, was found feasible (Ruggiero et al., 2006), but efficacy results remain to be published (Ruggiero et al., 2012). Preliminary evidence from one other study on the efficacy of a self-guided Internet-based psychoeducational program for injured children and their parents showed greater anxiety reductions in children who had completed the program compared to those who had not (Cox et al., 2010). Another internet-based intervention for injured children, an interactive game designed to provide practical information and teach children adaptive coping strategies, with the aim of preventing or reducing PTSD symptoms after acute pediatric medical events is currently being tested (Marsac et al., 2013).

1.5.3 Early CBT for PTSD

Early interventions based on CBT have consistently shown effective in preventing chronic PTSD in a selection of highly symptomatic survivors of traumatic injury, (see for a review, Roberts, Kitchiner, Kenardy, & Bisson, 2010). Several trials were conducted studying the efficacy of early CBT in a selection of highly symptomatic survivors of traumatic injury, such as patients with a diagnosis of ASD (Bryant & Harvey, 1998; Bryant, Moulds, Guthrie, & Nixon, 2005; Bryant, Moulds, & Nixon, 2003) or patients with increased acute distress or symptoms of anxiety or PTSD (Bisson, Shepherd, Joy, Probert, & Newcombe, 2004; Sijbrandij et al., 2007). All studies showed fewer cases of PTSD at post-treatment in the CBT condition versus the control conditions. Ehlers and colleagues (2003) also demonstrated the effectiveness of 12 sessions of cognitive therapy in the prevention of chronic PTSD. Although interventions based on CBT are mostly offered in the form of individual face-to-face psychotherapy of at least 4 sessions, a recent randomized controlled trial found evidence for the effectiveness of 3 sessions of prolonged (imaginal) exposure, starting within 12 hours of the traumatic event, in counteracting later symptoms of PTSD and depression (Rothbaum et al., 2008). It is yet unclear whether CBT-techniques administered as a single session early intervention are effective in preventing PTSD.
1.5.4
Early pharmacological interventions

To intervene in the early development of PTSD symptoms, a number of pharmacological substances have been tested as a secondary prevention strategy for PTSD, such as beta-adrenergic antagonists, hydrocortisone, and benzodiazepines.

Beta-adrenergic antagonists, such as propranolol, interfere with the binding to the receptor of epinephrine and other stress hormones. A pilot RCT showed that propranolol decreased psychophysiological responding to personalize trauma scripts relative to placebo at 3 months post-trauma in trauma survivors with elevated heart rate at the Emergency Department (Pitman et al., 2002). This has been replicated in a non-randomized controlled study (Vaiva et al., 2003). Subsequent RCTs (Nugent et al., 2010; Stein, Kerridge, Dimsdale, & Hoyt, 2007) and a case-control study (McGhee et al., 2009), however, failed to find significant effects of propranolol in preventing PTSD.

Hydrocortisone is another pharmacological intervention that has been proposed as a strategy to prevent PTSD (Aardal-Eriksson et al., 2001; Delahanty et al., 2000; Ehring et al., 2008; McFarlane et al., 1997; McFarlane et al., 2011; Resnick, Yehuda, & Acieno, 1997; Yehuda, Resnick, Schmeidler, Yang, & Pitman, 1998). Lower levels of circulating cortisol have been found to predict PTSD (Aardal-Eriksson et al., 2001; Delahanty et al., 2000; Ehring et al., 2008; McFarlane et al., 1997; McFarlane et al., 2011), although some studies did not confirm this association (Bonne et al., 2003; Resnick et al., 1995; Shalev et al., 2008). Cortisol is assumed to terminate the adrenergic response. As such, low levels of cortisol may lead to prolongation of the acute stress response and strengthening of the consolidation of the fear memory (Yehuda, 2002). In addition, cortisol administration has also been related to impaired memory retrieval (see for an overview, Rimmrele, Besedovsky, Lange, & Born, 2013). Thus, it has been suggested that early administration of glucocorticoids following trauma may counteract and impair memory consolidation and recall. Non-randomized (Schelling et al., 1999) and randomized (Delahanty et al., 2013; Schelling et al., 2001; Schelling et al., 2004; Zohar, Yahalom et al., 2011) controlled trials have demonstrated that hydrocortisone administration after trauma attenuated acute or posttraumatic stress symptoms (Schelling et al., 2004; Zohar, Yahalom et al., 2011) and, in some studies, reduced the incidence of PTSD (Delahanty et al., 2013; Schelling et al., 2001).

Benzodiazepines are frequently prescribed sedatives or anxiolytics during hospitalization (Zatzick & Roy-Byrne, 2006). They act on the neurotransmitter GABA at the GABAA receptor with sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anticonvulsant, and muscle relaxant effects (Page, Curtis, & Walker, 2005). Benzodiazepines are also known for enhancing emotional memory and increasing the risk for PTSD (for a review, see Zohar et al., 2011), and thus far the use of benzodiazepines early after trauma is recommended against (World
Health Organization, 2013). Pre-clinical evidence suggests that acute post-stressor alprazolam administration negatively affects behavioural outcomes to subsequent stress exposure (Matar, Zohar, Kaplan, & Cohen, 2009). Acute benzodiazepine administration was positively associated with PTSD in two small trials of injury victims (Gelpin, Bonne, Peri, Brandes, & Shalev, 1996; Mellman, Byers, & Augenstein, 1998). However, retrospective studies of combat injury patients (Holbrook, Galarneau, Dye, Quinn, & Dougherty, 2010; Schofield, Johnston, & de Mello, 2010) and a prospective study in children with burns (Saxe et al., 2001) did not find significant associations between benzodiazepines during acute trauma care or hospital stay and PTSD outcomes.

Other approaches to pharmacological PTSD prevention have also been explored. Findings from preclinical and clinical studies suggest that early use of opiate analgesics after trauma might prevent or impair traumatic memory consolidation by attenuating noradrenergic activity and dampening fear conditioning by containing the HPA response (Good & Westbrook, 1995; McNally & Westbrook, 2003; Pitman, 1989). Support for this protective effect was found in post-hoc examinations in prospective studies of trauma survivors. Studies in children with burns (Saxe et al., 2001; Stoddard, Jr. et al., 2009) and traumatic injury (Nixon et al., 2010) found positive associations between morphine dosage during hospitalization and greater decline in PTSD symptoms in the first 6 months post-trauma. In addition, a prospective study of 155 adult injury patients reported that morphine dose within the first 48 hrs, but not within the first week, was associated with fewer PTSD symptoms at 3 months (Bryant, Creamer, O'Donnell, Silove, & McFarlane, 2009). A retrospective study of combat injury victims found that morphine during acute trauma care was associated with a reduced risk for a PTSD diagnosis within 24 months following injury (Holbrook et al., 2010).

Recently, one clinical study found that salbutamol, a beta2-adrenergic blocker used to treat acute asthma attacks and respiratory failure or insufficiency after injury, was associated with fewer PTSD symptoms at 6 weeks in 23 MVA victims compared to 232 patients without salbutamol (Kobayashi et al., 2011).

1.6 Design of Trauma TIPS

This thesis describes the results from a large scale multicenter, prospective, longitudinal trial of consecutive traumatic injury patients, called Trauma TIPS. Trauma TIPS stands for The Incidence, Prediction and Prevention of Post-trauma Psychopathology Study, and consisted of the projects Incidence & Prediction and Prevention.
Inclusion in VUmc started in September 2007.

1.6.1

Project I: Incidence & Prediction

The overall aim of this project was to investigate the incidence of posttraumatic psychopathology, such as PTSD, depressive disorders, anxiety disorders and substance use disorders, in a prospective cohort of adult injury victims, and to identify predictors for the development of posttraumatic psychopathology in the year following injury. From September 2005 to March 2009, all adult patients transported by ambulance or trauma helicopter to the Trauma Units of the Academic Medical Center (AMC) and the VU University medical center (VUmc)\(^2\) were approached to participate in a prospective longitudinal study. Patients were included if they were 18 years of age or older, if their injuries were sustained in a traumatic event cf. the A1-criterion for PTSD in the DSM-IV (American Psychiatric Association, 2000), and if they had sufficient understanding of the Dutch language. Patients with injuries due to deliberate self-harm, with an organic brain condition, current psychotic symptoms or disorder, bipolar disorder or depression with psychotic features, with moderate to severe traumatic brain injury (according to the Glasgow Coma Scale score of less than 13; Teasdale & Jennett, 1974), or who permanently resided outside the Netherlands were excluded from participation.

Upon arrival at the Trauma Unit (T0; see Figure 1.1), hospital staff collected blood samples for stress hormone assessment. Research assistants selected eligible patients from the hospitals’ registrations, and contacted them within 72 hours of the injury in-hospital or by telephone for further eligibility assessment. Participants provided oral and written informed consent prior to data collection. A baseline clinical assessment (T1) of medical and psychiatric history and current psychological symptoms occurred at approximately 1 week post-injury. At 4-6 weeks (T2), 3 months (T3), 6 months (T4), and 12 months (T5) post-injury, follow-up clinical and self-report assessments of current psychopathology were performed. Assessments took place at the AMC’s Centre for Anxiety Disorders, at bedside or at the private home of the patient by trained master’s- and doctoral level assessors. Figure 1.1 presents an overview of the study procedures. Results from Project Incidence & Prediction are presented in Chapters 2, 3 and 7. Table 1.1 shows the incidence of PTSD, depressive disorders and anxiety disorders during one year following injury in the entire sample.

\(^2\) Inclusion in VUmc started in September 2007.
Table 1.1. Frequencies (%) of Diagnoses of Psychopathology in Adult Injury Patients (N = 852)

<table>
<thead>
<tr>
<th>Diagnoses of psychopathology</th>
<th>1-Month Follow-Up</th>
<th>3-Month Follow-Up</th>
<th>6-Month Follow-Up</th>
<th>12-Month Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTSD</td>
<td>74 (11.9)</td>
<td>25 (8.9)</td>
<td>39 (8.4)</td>
<td>32 (7.9)</td>
</tr>
<tr>
<td>Depressive disorder</td>
<td>59 (9.6)</td>
<td>14 (5.0)</td>
<td>44 (9.6)</td>
<td>33 (8.2)</td>
</tr>
<tr>
<td>Anxiety disorder†</td>
<td>49 (8.0)</td>
<td>19 (6.8)</td>
<td>46 (10.0)</td>
<td>29 (7.2)</td>
</tr>
<tr>
<td>Any PTSD, depressive or anxiety disorder</td>
<td>125 (19.8)</td>
<td>45 (16.0)</td>
<td>90 (19.4)</td>
<td>63 (15.6)</td>
</tr>
</tbody>
</table>

PTSD: Posttraumatic Stress Disorder.
† Includes: Panic disorder w/out agoraphobia, Generalized Anxiety Disorder, specific phobias, Obsessive Compulsive Disorder, social phobia, adjustment disorder.
The 3-Month Follow-Up was added to the study design at the start of project II to expand the assessments of short term effects of the internet-based intervention. As a consequence, clinical data at this time point is present for a proportion of participants.
Project 1: Incidence & Prediction

Project 2: Prevention

852 Participants

Baseline Clinical Assessment of Psychopathology

T 1: approx. 1-7 days

T 2: 1 Month

T 3: 3 Months

T 4: 6 Months

T 5: 12 Months

151 Intervention

149 Control

778 Clinical Assessment of Psychopathology

304 Clinical Assessment of Psychopathology

607 Clinical Assessment of Psychopathology

448 Clinical Assessment of Psychopathology
1.6.2
*Project II: Prevention*

From September 2007 to March 2009, a RCT was carried out with the aim of testing the effectiveness of a web-based prevention programme for PTSD. A personal log-in code provided access to the intervention website for intervention group patients who were instructed to perform the intervention whenever they wanted within the first month of their injury. Patients in the control condition were not offered any intervention, but had access to usual care, as had intervention group patients. Baseline and follow-up clinical assessments of current psychopathology were similar to those in Project I (see Figure 1.1). Details of the Trauma TIPS internet intervention and results from the RCT on the effectiveness of the program for the prevention of PTSD are described in Chapters 4, 5 and 6.

1.7 Research questions and outline of thesis

The focus of this thesis is on the prediction and prevention of psychological symptoms, especially PTSD symptoms, as a consequence of traumatic injury. The aims of the studies described in this thesis are:

1. to investigate the predictive role of acute post-injury cortisol and DHEAS for acute and chronic PTSD (Chapter 2);

2. to examine the diagnostic accuracy of three early screening instruments for 6-month PTSD (Chapter 3);

3. to develop and test the effectiveness of a web-based early psychological intervention to prevent PTSD in injured trauma survivors (Chapters 4, 5, and 6);

4. to investigate the association between early pharmacotherapy within the initial 48 hours of injury and PTSD at 6 weeks and within the first year after trauma (Chapter 7).

In Chapter 8 (Discussion), I summarize and discuss the results of the studies, the clinical implications and directions for future research.
CHAPTER 2: The Role of Acute Cortisol and DHEAS in Predicting Acute and Chronic PTSD Symptoms

ABSTRACT

Background:
Decreased activation of the hypothalamus-pituitary-adrenal (HPA) axis in response to stress is suspected to be a vulnerability factor for posttraumatic stress disorder (PTSD). Previous studies showed inconsistent findings regarding the role of cortisol in predicting PTSD. In addition, no prospective studies have examined the role of dehydroepiandrosterone (DHEA), or its sulfate form DHEAS, and the cortisol-to-DHEA(S) ratio in predicting PTSD. In this study, we tested whether acute plasma cortisol, DHEAS and the cortisol-to-DHEAS ratio predicted PTSD symptoms at 6 weeks and 6 months post-trauma.

Methods:
Blood samples of 397 adult level-1 trauma center patients, taken at the trauma resuscitation room within hours after the injury, were analyzed for cortisol and DHEAS levels. PTSD symptoms were assessed at 6 weeks and 6 months post-trauma with the Clinician Administered PTSD Scale.

Results:
Multivariate linear regression analyses showed that lower cortisol predicted PTSD symptoms at both 6 weeks and 6 months, controlling for age, gender, time of blood sampling, injury, trauma history, and admission to intensive care. Higher DHEAS and a smaller cortisol-to-DHEAS ratio predicted PTSD symptoms at 6 weeks, but not after controlling for the same variables, and not at 6 months.

Conclusions:
Our study provides important new evidence on the crucial role of the HPA-axis in response to trauma by showing that acute cortisol and DHEAS levels predict PTSD symptoms in survivors of recent trauma.
2.1 INTRODUCTION

Injury victims presenting to an emergency room have an increased risk of developing trauma-related psychopathology, such as posttraumatic stress disorder (PTSD). Prevalence rates of PTSD following a traffic accident, one of the most common injury causing traumatic events (de Vries & Olff, 2009), vary greatly, from 8%-45% at 1 month to 7%-26% at 12 months (for a review, see Heron-Delaney et al., 2013). To explain why some develop PTSD and others do not, studies have examined the role of the hypothalamus-pituitary-adrenal (HPA) axis (Delahanty, Nugent, Christopher, & Walsh, 2005; Delahanty et al., 2000; Delahanty et al., 2003; McFarlane et al., 1997; McFarlane et al., 2011; Resnick et al., 1997; Resnick et al., 1995; Shalev et al., 2008; Yehuda et al., 1998). It has been hypothesized that an insufficient activation of the HPA-axis in response to stress serves as vulnerability for PTSD (Yehuda, 2002; Yehuda, McFarlane, & Shalev, 1998). During acute stress, the hypothalamus secretes corticotrophin-releasing hormone. This in turn stimulates the pituitary gland to release adrenocorticotropic hormone, which leads to the production of glucocorticoids (cortisol) and dehydroepiandrosterone (DHEA) by the adrenal cortex (Vinson et al., 2007). Cortisol suppresses metabolic, immuno- and neurodefensive processes to adequately cope with the stressor, and triggers a negative feedback loop when sufficient circulating levels are reached. Low levels of circulating cortisol have been found to be a vulnerability factor for developing PTSD symptoms, either directly (Delahanty et al., 2003) or indirectly through prior trauma exposure (Resnick et al., 1995; Yehuda et al., 1998). They fail to trigger the negative feedback loop, thus prolonging the adrenergic response, which may exacerbate consolidation of the traumatic memory. This may lead to intrusive symptoms, which may increase the risk for PTSD (Yehuda, 2002).

Whereas high cortisol has catabolic properties, DHEA and its sulfate form DHEAS have been found to possess anabolic, neuroprotective and antiglucocorticoid effects, showing neurogenerative effects in the hippocampus (Karishma & Herbert, 2002) and protection against the neurotoxic effects of cortisol in studies in rodents (Kaminska et al., 2000; Kimonides et al., 1998; Kimonides et al., 1999). This may contribute to an upregulation of HPA-axis responses as well as mitigate possible deleterious effects of high cortisol levels on the brain in PTSD (Rasmusson et al., 2003). As such, it may be hypothesized that dysregulations in the HPA-axis function associated with PTSD may also be evident in an abnormal DHEA-response. DHEAS is much more abundant than DHEA, because DHEAS has longer half-life and lower clearance (Lennartsson et al., 2012). Because DHEAS levels are also more stable and show no diurnal variation (Kroboth et al., 1999), they are often preferred in studies on long term effects of stress. Studies on acute stress, on the other hand, often assess DHEA, since DHEAS serves as a reservoir for DHEA biosynthesis and DHEA rather than DHEAS is expected to respond to acute
psychosocial stress (Izawa et al., 2008; Morgan, III et al., 2004; Oberbeck et al., 1998; Pico-Alfonso et al., 2004; Shirotakie et al., 2009). However, in a recent study, although the response of DHEA was more pronounced, both DHEA and DHEAS were found to increase in response to acute psychosocial stress (Lennartsson et al., 2012). In addition, DHEAS was found to increase in response to low, but not high, intensity military stress exposure (Morgan, III et al., 2004; Taylor et al., 2007). Cortisol and DHEA(S) are often addressed as a ratio, representing the balance between anabolic and catabolic hormones (Maninger et al., 2009). A high ratio of cortisol-to-DHEA(S), or conversely a low DHEA(S)-to-cortisol ratio, represents a catabolic balance. A low cortisol-to-DHEA(S) ratio, or a high DHEA(S)-to-cortisol ratio, reflects an anabolic balance. A higher cortisol-to-DHEA ratio has been linked to a chronic stress response in depressed adolescents and adults (Goodyer et al., 1998; Young et al., 2002), as well as more resilient functioning in both maltreated and non-maltreated children (Cicchetti & Rogosch, 2007), whereas a higher DHEA(S)-to-cortisol ratio was positively correlated with fewer dissociative symptoms after prolonged and extreme training stress (Morgan, III et al., 2004; Taylor et al., 2007). Thus, previous findings are inconclusive with respect to the role of the cortisol-to-DHEA(S) ratio in the onset of psychiatric disorders such as PTSD.

Findings from prospective studies on acute cortisol levels as a predictor for PTSD so far are inconsistent. Some studies have found that low cortisol levels immediately or in the first days following trauma predict PTSD diagnosis (Delahanty et al., 2000; McFarlane et al., 1997) or symptoms (Aardal-Eriksson et al., 2001; Ehring et al., 2008; McFarlane et al., 2011). In some of these studies, however, the association disappeared when controlling for possible confounding variables, such as injury severity and history of PTSD (Delahanty et al., 2000), and time of the accident or blood sampling (McFarlane et al., 1997). Other studies found no direct relationship between initial cortisol and subsequent PTSD (Bonne et al., 2003; Resnick et al., 1995; Shalev et al., 2008). Variations in methodology, for example, when (i.e., immediately post-trauma up to several days after the event) or how (i.e., saliva, urine or plasma) cortisol was measured, might explain these differences. Lack of power due to a small sample size has been referred to by some studies as a possibility for not finding a significant association (Delahanty et al., 2000; Ehring et al., 2008). Therefore, it has been argued that the predictive effect of cortisol should be replicated in large, consecutively recruited samples, taking into account the important confounders. Until now, no prospective studies examining whether the DHEA or DHEAS response is implicated in the development of PTSD have been carried out yet.

In this study, we investigated whether plasma cortisol, DHEAS and cortisol-to-DHEAS ratio, collected immediately following traumatic injury, predicted PTSD symptoms at 6 weeks and 6 months post-trauma in a sample of 397 acutely injured trauma victims. We hypothesized that lower levels of cortisol predict greater PTSD symptoms at 6 weeks and 6 months. Although the role of DHEAS in the development of PTSD is yet unclear, we also expected that lower levels of DHEAS
and a smaller cortisol-to-DHEAS ratio predict PTSD symptoms at 6 weeks and 6 months.

2.2 METHODS AND MATERIALS

2.2.1 Subjects and procedure

Patients were recruited between 2005 and 2009 as part of a large ongoing prospective study of psychopathology following injury. Injury patients presented by the ambulance service at two academic level-1 trauma centers in Amsterdam, The Netherlands, were consecutively included, if they met inclusion criteria of age (18 years and older), having sustained injuries from a traumatic event (cf. A1-criterion of the DSM IV PTSD diagnosis), and mastery of the Dutch language. Patients with injuries due to deliberate self-harm, with an organic brain condition, current psychotic symptoms or disorder, bipolar disorder, depression with psychotic features, with moderate to severe traumatic brain injury (i.e., Glasgow Coma Scale (GCS) score of less than 13; Teasdale & Jennett, 1974), or who permanently resided outside the Netherlands, were excluded. Medical ethical approval was obtained from the institutional review boards of the Academic Medical Center and Vrije Universiteit medical center. Upon arrival at the trauma center and at initial medical examination, medical staff collected blood samples for stress hormone assessment. Research assistants selected eligible patients from the hospitals’ registrations and contacted them within 72 hours of the injury in-hospital or by telephone for participation. Patients provided verbal and written informed consent for the psychological assessments and to analyze the collected blood samples for stress hormones. All clinical assessments were performed at the Center for Anxiety Disorders of the Academic Medical Center, at bedside or at the private home of the patient by trained master and bachelor level psychologists (for more details, see Mouthaan, Sijbrandij, Reitsma, Gersons, & Olff, 2011).

2.2.2 Measures

Cortisol and DHEAS

A 4.5 ml cryovial of blood was stored at -80°C immediately after collection by the trauma center staff at the patient’s initial medical assessment. Cortisol and DHEAS levels (in nmol/L) were analyzed in batch. Cortisol was analyzed by a chemoluminiscence assay using the Immulite 2000 (Siemens, Breda, The Netherlands) with inter-assay and intra-assay coefficients of variation 5.5 and 8.3%.
Injury-related characteristics

Injury severity was assessed using the Injury Severity Score (ISS), a scoring system that provides an overall severity score for patients with traumatic injuries. The ISS ranges from 0 (no injury) to 75 (unsurvivable injury) with a score of 16 and higher indicating severe injury (Copes et al., 1990). The Glasgow Coma Scale (GCS) is a neurological scale to record level of consciousness and consists of three parameters: Best Eye Response (four grades), Best Verbal Response (five grades), Best Motor Response (six grades). Resulting scores are between 3 (deep unconsciousness) and 15 (fully conscious; Teasdale & Jennett, 1974). Both ISS and GCS were assessed by the treating physician at initial medical examination, and were later generated from the hospital trauma registration systems.

Posttraumatic stress disorder

The Clinician Administered PTSD Scale (CAPS; Blake et al., 1995) was used to assess PTSD symptoms at 6 weeks and 6 months. The CAPS is a 30-item semi-structured interview for diagnosing PTSD (Weathers, Keane, & Davidson, 2001). Symptom severity is determined by adding frequency and intensity of the 17 symptoms of intrusion, avoidance and hyperarousal (both ranging from 0 to 4, total scores ranging from 0 to 136). The rule of Weathers et al. (1999) was used to establish a PTSD diagnosis, in which symptoms need at least a frequency of 1 and intensity of 2 with a total score of at least 45 points.

2.2.3 Analyses

As part of a longitudinal database with multiple repeated PTSD assessments, missing data of continuous CAPS outcomes were replaced using multiple imputation (SPSS 21.0), creating five different datasets. In this procedure, the fully conditional
specification approach was used, in which data were imputed on a variable-by-variable basis by specifying an imputation model per variable. This method has been found to work well in practice (van Buuren, 2011). Independent samples t-tests and chi-square tests were used to determine significant associations between demographics and injury-related characteristics and cortisol, DHEAS and cortisol-to-DHEAS ratio. For Pearson correlations and multivariate linear regression analyses, CAPS scores and values for cortisol, DHEAS and cortisol-to-DHEAS ratio were positively skewed and were square root-transformed.

We specified 8 separate multivariate linear regression models for predicting PTSD symptoms. We analyzed whether independent variables cortisol and DHEAS predicted PTSD symptoms at 6 weeks (model 1) and 6 months (model 3). We added gender, age, time of blood sampling, injury severity, trauma history, and ICU admission as covariates to control for possible confounding effects in models 2 (for 6 weeks PTSD) and 4 (for 6 months PTSD). The same procedures were repeated for cortisol-to-DHEAS ratio as independent variable. In models 5 and 7, we tested whether cortisol-to-DHEAS ratio predicted PTSD symptoms at 6 weeks (model 5) and 6 months (model 7). We added the above mentioned covariates gender, age, time of blood sampling, injury severity, trauma history, and ICU admission to control for possible confounding effects (model 6 with PTSD symptoms at 6 weeks and model 8 with PTSD symptoms at 6 months as dependent variables). To examine the role of cortisol, DHEAS and cortisol-to-DHEAS ratio in predicting a PTSD diagnosis at 6 weeks and 6 months, we performed logistic regression analyses with and without the above mentioned covariates. To explore DHEAS’s putative restorative effects, we performed a linear regression analysis of the contribution of DHEAS, controlling for age and gender, to change in PTSD severity from 6 weeks to 6 months. PTSD change scores were computed by subtracting CAPS scores at 6 months from CAPS scores at 6 weeks. All analyses were carried out in SPSS 19.0 with p-values < .05 indicating statistical significance.
2.3 RESULTS

2.3.1 Participants

Of the 1,496 eligible patients who presented at the trauma centers, 852 patients (57%) consented to participate in the ongoing prospective study of which blood samples of 397 patients (46.6%) were collected and analyzed. There were no differences between patients with and without collected blood samples in age, gender, marital status, educational background, country of origin, trauma history, traumatic event, ISS, GCS, time of day of initial medical assessment, or PTSD symptoms at 6 weeks or 6 months. Table 2.1 shows the sociodemographic and clinical characteristics of the 397 participants. The 6 week and 6 month assessments of PTSD symptoms took place at mean 52.3 days (SD = 26.0, \( n = 291, 73.3\% \)) and 214.2 days (SD = 36.1, \( n = 226, 56.9\% \)). Patients not assessed for PTSD at 6 months did not differ from those who were assessed on any of the before mentioned background or clinical characteristics. PTSD prevalence was 10.3% (\( n = 30 \)) at 6 weeks and 6.2% (\( n = 14 \)) at 6 months.
Table 2.1. Sociodemographic and clinical characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>253</td>
<td>63.7</td>
</tr>
<tr>
<td>Married or cohabitating</td>
<td>152</td>
<td>40.2</td>
</tr>
<tr>
<td>College or university degree</td>
<td>80</td>
<td>20.2</td>
</tr>
<tr>
<td>Country of origin: Netherlands</td>
<td>314</td>
<td>83.5</td>
</tr>
<tr>
<td>Traumatic event:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>traffic accident</td>
<td>272</td>
<td>68.5</td>
</tr>
<tr>
<td>fall from height</td>
<td>48</td>
<td>12.1</td>
</tr>
<tr>
<td>work-related accident</td>
<td>43</td>
<td>10.8</td>
</tr>
<tr>
<td>physical abuse</td>
<td>14</td>
<td>3.5</td>
</tr>
<tr>
<td>other: fire, recreational,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>natural disaster, airplane crash</td>
<td>20</td>
<td>5.0</td>
</tr>
<tr>
<td>ICU admission</td>
<td>47</td>
<td>11.8</td>
</tr>
<tr>
<td>Time of blood sampling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>morning (0600-1200h)</td>
<td>104</td>
<td>28.3</td>
</tr>
<tr>
<td>afternoon (1200-1800h)</td>
<td>132</td>
<td>35.9</td>
</tr>
<tr>
<td>evening (1800-2400h)</td>
<td>97</td>
<td>24.4</td>
</tr>
<tr>
<td>night (2400-0600h)</td>
<td>35</td>
<td>8.8</td>
</tr>
<tr>
<td>PTSD diagnosis at 6 weeks</td>
<td>30</td>
<td>10.3</td>
</tr>
<tr>
<td>PTSD diagnosis at 6 months</td>
<td>14</td>
<td>6.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>M</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>42.57</td>
<td>15.48</td>
</tr>
<tr>
<td>Trauma history</td>
<td>2.92</td>
<td>2.19</td>
</tr>
<tr>
<td>ISS</td>
<td>8.76</td>
<td>8.87</td>
</tr>
<tr>
<td>GCS</td>
<td>14.40</td>
<td>2.32</td>
</tr>
<tr>
<td>Plasma cortisol (nmol/L)</td>
<td>714.74</td>
<td>260.87</td>
</tr>
<tr>
<td>Plasma DHEA-S (nmol/L)</td>
<td>4.65</td>
<td>3.40</td>
</tr>
<tr>
<td>CAPS at 6 weeks</td>
<td>21.17</td>
<td>18.51</td>
</tr>
<tr>
<td>CAPS at 6 months</td>
<td>16.33</td>
<td>15.23</td>
</tr>
</tbody>
</table>

PTSD, Posttraumatic Stress Disorder; ISS, Injury Severity Score; GCS, Glasgow Coma Score; DHEA-S, dehydroepiandrosterone-sulfate; ICU, intensive care unit; CAPS, Clinician Administered PTSD Scale.
2.3.2
Univariate analyses of cortisol and DHEAS

Means and standard deviations for cortisol and DHEAS are displayed in Table 2.1. Compared to the reference values, cortisol levels were increased in 76% ($n = 281$) of patients and decreased in 1.4% ($n = 5$). DHEAS was increased in 6.5% ($n = 5$) and decreased in 24% ($n = 91$). Cortisol and DHEAS were positively correlated ($r = .18, p < .001, n = 390$). Cortisol ($F(3,364)=2.26, p = .08$) and DHEAS levels ($F(3,357)=1.68, p = .17$) were not significantly associated with time of day of blood sampling. Cortisol-to-DHEAS ratio, however, was significantly greater during the afternoon compared to evening ($F(3,357)=4.45, p = .004$, mean difference = 81.42, SD = 29.80) and nighttime (mean difference = 133.51, SD = 41.85), indicating higher cortisol relative to lower DHEAS in the afternoon compared to lower cortisol versus higher DHEAS in the evening and night.

Patients who were older ($r = .17, p = .001, n = 397$), severely injured (ISS $\geq 16$; $t(341) = -5.04$, $p < .001$), hospitalized ($t(381) = -5.82$, $p < .001$), and patients who were injured due to falling from a height ($F(4,392)=4.94, p = .001$), had higher mean cortisol levels. DHEAS levels were negatively associated with age ($r = -.39, p < .001, n = 390$) and female gender ($t(388)=4.81, p < .001$). Higher cortisol-to-DHEAS ratios were found for women than for men ($t(388)=3.62, p < .001$) and for hospitalized versus non-hospitalized patients ($t(374) = -2.16, p = .03$). Cortisol-to-DHEAS ratio was positively correlated with age ($r = .45, p < .001, n = 390$).

2.3.3
Prediction of PTSD symptoms

Table 2.2 presents the predictive values of acute cortisol and DHEAS for 6 weeks and 6 months PTSD symptoms. Lower cortisol and higher DHEAS both significantly predicted PTSD symptoms at 6 weeks (model 1). At 6 months, only lower cortisol was a significant predictor of PTSD symptoms (model 3). Cortisol accounted for 2% of the total explained variance for 6-week PTSD symptoms in models 1 and 3. After controlling for the effects of age, gender, time of blood sampling, injury, trauma history, and ICU admission, lower cortisol remained a significant predictor for PTSD symptoms at 6 weeks (model 2) and 6 months (model 4), but DHEAS showed no effects. The outcomes of the models with cortisol-to-DHEAS ratio as a predictor are shown in Table 2.3. A smaller cortisol-to-DHEAS ratio significantly predicted PTSD symptoms at 6 weeks (model 5), but not anymore after inclusion of the covariates (model 6), and not at 6 months (models 7 and 8).
Logistic regression analyses for acute and chronic PTSD diagnoses showed no significant odd’s ratios (OR) for cortisol (6 weeks: OR = .98, 95% CI [.91-1.06], \( p = .68 \), 6 months: OR = .95, 95% CI [.87-1.03], \( p = .24 \)), DHEAS (6 weeks: OR = 1.24, 95% CI [.76-2.00], \( p = .39 \), 6 months: OR = 1.04, 95% CI [.48-2.22], \( p = .93 \)), or cortisol-to-DHEAS ratio (6 weeks: OR = .98, 95% CI [.92-1.04], \( p = .44 \), 6 months: OR = .98, 95% CI [.91-1.07], \( p = .69 \)).

Lastly, change in PTSD symptoms between 6 weeks and 6 months was not significantly predicted by acute DHEAS, controlling for age and gender (\( \beta = .10 \), \( t = 1.47 \), \( p = .15 \); adjusted \( R^2 = .02 \), \( F \) (3, 316) = 3.29, \( p = .03 \)).

Table 2.2. Predictive values of acute cortisol and DHEA-S for 6 week and 6 month PTSD symptoms with and without control variables.

<table>
<thead>
<tr>
<th>PTSD symptoms 6 weeks</th>
<th>PTSD symptoms 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1: ( R^2 = .03 )</strong></td>
<td><strong>Model 2: ( R^2 = .09 )</strong></td>
</tr>
<tr>
<td><strong>Cortisol</strong></td>
<td>-.14**</td>
</tr>
<tr>
<td><strong>DHEA-S</strong></td>
<td>.12*</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>.20**</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>-.05</td>
</tr>
<tr>
<td><strong>Morning</strong></td>
<td>.04</td>
</tr>
<tr>
<td><strong>Evening</strong></td>
<td>.12</td>
</tr>
<tr>
<td><strong>Night</strong></td>
<td>.12</td>
</tr>
<tr>
<td><strong>ISS</strong></td>
<td>.09</td>
</tr>
<tr>
<td><strong>Trauma history</strong></td>
<td>.18*</td>
</tr>
<tr>
<td><strong>ICU admission</strong></td>
<td>-.02</td>
</tr>
</tbody>
</table>

PTSD, posttraumatic stress disorder; DHEA-S, dehydroepiandrosterone-sulfate; ISS, injury severity score; ICU, intensive care unit.

N.B. Beta values of multivariate regression analyses of PTSD symptoms at 6 weeks and 6 months by cortisol and DHEA-S with and without controlling for gender, age, time of blood sampling, injury severity score, trauma history, and ICU admission.

* \( p < .05 \)

** \( p < .01 \)
Table 2.3. Predictive values of acute cortisol-to-DHEA-S ratio for 6 week and 6 month PTSD symptoms with and without control variables.

<table>
<thead>
<tr>
<th></th>
<th>PTSD symptoms 6 weeks</th>
<th>PTSD symptoms 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 5: $R^2 = .03$</td>
<td>Model 6: $R^2 = .09$</td>
</tr>
<tr>
<td></td>
<td>Model 7: $R^2 = .01$</td>
<td>Model 8: $R^2 = .05$</td>
</tr>
<tr>
<td>Cortisol-to-DHEA-S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ratio</td>
<td>-.16**</td>
<td>-.13</td>
</tr>
<tr>
<td>Gender</td>
<td>.19**</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-.05</td>
<td></td>
</tr>
<tr>
<td>Morning</td>
<td>.04</td>
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<tr>
<td>Evening</td>
<td>.12</td>
<td></td>
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<tr>
<td>Night</td>
<td>.13</td>
<td></td>
</tr>
<tr>
<td>ISS</td>
<td>.04</td>
<td></td>
</tr>
<tr>
<td>Trauma history</td>
<td>.18**</td>
<td>.19**</td>
</tr>
<tr>
<td>ICU admission</td>
<td>.01</td>
<td>.01</td>
</tr>
</tbody>
</table>

PTSD, posttraumatic stress disorder; DHEA-S, dehydroepiandrosterone-sulfate; ISS, injury severity score; ICU, intensive care unit.

N.B. Beta values of multivariate regression analyses of PTSD symptoms at 6 weeks and 6 months by cortisol-to-DHEA-S ratio with and without controlling for gender, age, time of blood sampling, injury severity score, trauma history, and ICU admission.

* $p<.05$
** $p<.01$
2.4 DISCUSSION

This study showed that lower plasma cortisol levels in injured patients assessed at the trauma resuscitation room predicted acute and chronic PTSD symptoms, even after controlling for age, gender, time of blood sampling, injury, trauma history, and ICU admission. Higher acute DHEAS levels and a smaller cortisol-to-DHEAS ratio contributed to 6 week PTSD symptoms, but not after controlling for the same factors, and not at 6 months. There were no significant effects of cortisol, DHEAS or cortisol-to-DHEAS ratio on acute or chronic PTSD diagnoses. Lastly, DHEAS did not contribute significantly to PTSD symptom change between 6 weeks and 6 months.

In line with previous studies (Aardal-Eriksson et al., 2001; Delahanty et al., 2000; Ehring et al., 2008; McFarlane et al., 2011), our findings confirm the hypothesis that the development of PTSD may partly be explained by dysfunctioning of the HPA-axis. Moreover, we extended previous results by showing that cortisol is not only a predictor for acute PTSD symptoms, but continues to predict chronic PTSD symptoms at 6 months, even when controlling for relevant trauma and injury characteristics. As proposed, lower levels of circulating cortisol likely prolong the adrenergic response, thereby strengthening the consolidation of the fear memory (Yehuda, 2002). Recent research has also implicated cortisol in the expression of genes relevant to PTSD, such as FKBP5, neuropeptide-Y, and BDNF (see Zoladz & Diamond, 2013, for a review), which points to the necessity for a more comprehensive viewpoint of the influence of stress hormones in general, and cortisol in particular, in the onset of PTSD. As a biomarker for subsequent PTSD symptoms, acute cortisol levels in itself are an interesting target, as they are easily obtainable in injured populations seeking medical assistance and demonstrated a stable effect on acute and chronic PTSD symptoms in our study. However, it is still questionable to what extent acute cortisol levels could predict which individuals go on to develop or not develop PTSD (i.e., positive and negative predictive value), which pertains to the limited variance of PTSD severity explained by acute cortisol as found in our study. In addition, the RIA antibody method used to measure cortisol in our study also may have been suboptimal due to lack of specificity. A recent study using a standard cortisol radioimmunoassay suggested that low cortisol levels predicted poor treatment outcome, whereas use of a more accurate mass spectrometry methodology that measures cortisol and its metabolites separately showed that low levels of a reduced metabolite of cortisol produced by 5alpha reductase, rather than low cortisol, actually predicted poor outcome (Yehuda et al., 2009). Note that 5alpha reductase is also involved in the production of GABAergic reduced metabolite of progesterone (e.g. allopregnanolone) and testosterone (androsterone), both considered to have a conceivable role in PTSD risk (Gillespie et al., 2013).
To our knowledge, our study was the first to investigate the role of DHEAS in the prediction of acute and chronic PTSD. In line with previous cross-sectional studies (Gill, Vythilingam, & Page, 2008; Jogems-Kosterman, de Knijff, Kusters, & van Hoof, 2007; Yehuda, Brand, Golier, & Yang, 2006), higher DHEAS and a smaller cortisol-to-DHEAS ratio were associated with PTSD symptoms at 6 weeks, although not after controlling for background and injury characteristics. Cross-sectional and longitudinal studies on DHEA(-S) and PTSD so far produced highly mixed results, which could indicate a dual effect or performance of DHEA(-S) in trauma-exposed people. This was found in one longitudinal study of refugees: over time, negative events were associated with increases in DHEAS in refugees with PTSD and with decreases in DHEAS levels in those without PTSD (Sondergaard & Theorell, 2003). Moreover, an interaction effect was found between PTSD and depression: in depressed subjects, lower DHEAS was found for PTSD versus non-PTSD, whereas in non-depressed subjects, higher DHEAS was found in PTSD versus non-PTSD (Sondergaard, Hansson, & Theorell, 2002). As DHEA responses are more marked than DHEAS responses to acute stress (Lennartsson et al., 2012), it is possible that DHEA could have played a larger predictive role in our study than DHEAS did. More research is needed to determine the usefulness of DHEA versus DHEAS as a biomarker for subsequent PTSD symptomatology, for example in populations with a higher PTSD prevalence rate, such as victims of rape, combat or interpersonal violence.

This study is the first to show a predictive effect of plasma cortisol, whereas previous studies finding predictive effects for cortisol used saliva or urine samples (Aardal-Eriksson et al., 2001; Delahanty et al., 2000; Ehring et al., 2008; McFarlane et al., 2011). It is possible that our larger sample provided sufficient power for the analyses. Second, it is possible that the timing of our blood draw, within hours of the traumatic event for the entire participant sample, provided sufficient opportunity to witness the acute stress response of the survivors.

In our sample, all patients had endured a physical trauma with the possibility of severe injury. As in previous studies in similar populations (Delahanty et al., 2003; Woolf, 1992), injury severity was significantly positively correlated with acute cortisol levels. It is unclear to what extent our findings may be generalizable to populations without possible severe injury, such as victims of war or rape. However, since we included injury severity as a confounding variable in our analyses, our results show that acute cortisol was an independent predictor for consequent PTSD. Future studies should examine whether acute cortisol displays similar predictive effects on PTSD for injured versus non-injured trauma survivors.

Strengths of our study are that we included a relatively large sample of 397 injured patients, who were assessed at several occasions following trauma using clinical interviews. Limitations may be that blood samples were collected in only half of our originally included sample. A large proportion of blood samples
were missing, most likely due to uninformed hospital staff, use of the blood samples for medical reasons or technical problems in conservation, preparation, transport or laboratory processing. Although our final sample did not differ from the larger sample with respect to baseline variables, selection bias cannot be ruled out. A similar concern is the attrition at follow-up of 22%. Further, although we collected and controlled for various important covariates, among which trauma history, injury severity and ICU admission, we did not account for other possible confounders, such as nicotine use, oral contraceptive use, experienced pain or alcohol or drug use at the time of blood sampling. Nicotine and oral contraceptives have been shown to suppress cortisol reactivity (Fu et al., 2007; Reynolds et al., 2013). Alternately, pain, alcohol and opiate drug use were found to increase the cortisol response to acute stress (Coventry et al., 2001; Ehring et al., 2008; Stankiewicz, Swiergiel, & Lisowski, 2013). Furthermore, studies have shown that smoking is an independent risk factor for mental health problems in a post-disaster sample (Olff et al., 2006; van der Velden, Grievink, Olff, Gersons, & Kleber, 2007), and pain moderates the relationship between cortisol and the development of PTSD in a sample of injury victims (Ehring et al., 2008). Since we had no information about these variables, we do not know whether they may have influenced the association between cortisol level and PTSD symptoms. Finally, we measured cortisol and DHEAS at only one occasion and had no information on day curves of stress hormones.

Future studies may be focused on elucidating whether low cortisol and increased DHEAS levels are pre-trauma vulnerability factors for PTSD or associated with the trauma. Moreover, while psychotherapy may be associated with restoring HPA-axis abnormalities (Olff, de Vries, Guzelcan, Assies, & Gersons, 2007), interventions targeting the HPA-axis more directly by glucocorticoid augmentation are promising (Yehuda, Bierer, Pratchett, & Malowney, 2010). A recent pilot study on hydrocortisone administration immediately after trauma shows promise to the prevention of the development of PTSD (Zohar, Juven-Wetzler et al., 2011).

In summary, our study provides important new evidence on the crucial role of the HPA-axis in response to trauma by showing that cortisol and DHEAS levels predict PTSD symptoms in survivors of recent trauma.
CHAPTER 3: Comparing Screening Instruments to Predict Posttraumatic Stress Disorder

ABSTRACT

Background:
Following traumatic exposure, a proportion of trauma victims develops posttraumatic stress disorder (PTSD). Early PTSD risk screening requires sensitive instruments to identify everyone at risk for developing PTSD in need of diagnostic follow-up.

Aims:
This study compares the accuracy of the 4-item SPAN, 10-item Trauma Screening Questionnaire (TSQ) and 22-item Impact of Event Scale-Revised (IES-R) in predicting chronic PTSD at a minimum sensitivity of 80%.

Method:
Injury patients admitted to a level-I trauma centre (N = 311) completed the instruments at a median of 23 days and were clinically assessed for PTSD at 6 months. Areas under the curve and specificities at 80% sensitivity were compared between instruments.

Results:
Areas under the curve in all instruments were adequate (SPAN: 0.83; TSQ: 0.82; IES-R: 0.83) with no significant differences. At 80% sensitivity, specificities were 64% for SPAN, 59% for TSQ and 72% for IES-R.

Conclusion:
The SPAN, TSQ and IES-R show similar accuracy in early detection of individuals at risk for PTSD, despite differences in number of items. The modest specificities and low positive predictive values found for all instruments could lead to relatively many false positive cases, when applied in clinical practice.
3.1 INTRODUCTION

A proportion of individuals exposed to a traumatic event develops psychopathology, such as posttraumatic stress disorder (PTSD; de Vries & Olff, 2009). PTSD consists of symptoms of intrusion, avoidance, and hyperarousal. It is a disabling disorder which may lead to chronic psychiatric morbidity and loss of normal daily functioning (Neria, Nandi, & Galea, 2008; O’Donnell et al., 2004). Traumatic injury is one of the most common traumatic events worldwide, accounting for 9% of global mortality (Peden, McGee, & Sharma, 2002). Reported rates of PTSD within the first 6 months of injury range between 10-20% (de Vries & Olff, 2009; O’Donnell et al., 2004; Zatzick et al., 2002). Early interventions for everyone involved in the traumatic event are unsuccessful in preventing PTSD (e.g., psychological debriefing; Sijbrandij et al., 2006), whereas there is evidence that early treatment of acute PTSD with trauma-focused cognitive behavioural therapy can ward off a chronic course of PTSD (Roberts et al., 2009; Sijbrandij et al., 2007). To identify trauma survivors at risk for PTSD in need of early treatment, the use of self-report instruments has been proposed (Sijbrandij et al., 2013), such as the SPAN (Meltzer-Brody et al., 1999), the Trauma Screening Questionnaire (TSQ; Brewin et al., 2002) and the Impact of Event Scale-Revised (IES-R; Weiss & Marmar, 1997). These instruments may be used as selection tools as part of a “triage” (Bossuyt, Irwig, Craig, & Glasziou, 2006) or “screen and treat” (Brewin et al., 2008) strategy. Only those individuals scoring above the cut-off are referred for further diagnostics. If the instrument is sufficiently accurate, such a strategy may save resources and costs (Bossuyt et al., 2006).

In evaluating the accuracy of early screening instruments, its sensitivity (i.e., the probability that someone with PTSD has a positive test result) and specificity (i.e., the probability that someone without PTSD has a negative result) are important. The higher the sensitivity, the lower the specificity, and vice versa. In studies of diagnostic accuracy, an optimal cut-off point is usually chosen based on the trade-off between sensitivity and specificity (Smits et al., 2007). However, the post-hoc nature in choosing an optimal cut-off has resulted in many different cut-offs reported across studies and populations. This limits comparability between screening instruments, and may complicate the professionals’ choice for an early PTSD risk screening instrument. Related to sensitivity and specificity, but more important for clinical practice, are the positive predictive value (PPV) and the negative predictive value (NPV) of a screening instrument. The PPV refers to the proportion of people scoring positive on the screening instrument who indeed have or will develop PTSD, whereas the NPV refers to the proportion of people scoring negative on the screener who do not have or will not develop PTSD. PPV and NPV are both dependent on the population prevalence of a disorder. Typically, when the prevalence of a disorder in the population is low, as is the case in PTSD after injury (10-20%, (de Vries & Olff, 2009; O’Donnell et al., 2004; Zatzick et al., 2002), PPV will be low and NPV will be high.
Which levels of sensitivity and specificity are acceptable, depends on the aim of administering the screening instrument and the costs and benefits of the decision based on the screening instrument (Smits et al., 2007). Thus, there are no standard sensitivity and specificity levels that are considered acceptable. However, with respect to early PTSD risk screening after injury, a few recommendations can be made. First, in the early phase following traumatic injury, sensitivity may be important, to identify as many cases as possible that may be referred for more extensive diagnostic examination. In addition, it has been argued that in populations with a low condition prevalence, more sensitive screening instruments may be especially useful in selecting individuals for further assessment because PPV in that population will be low whereas NPV will be high (Baldessarini, Finklestein, & Arana, 1983). Since previous studies in injury victims have shown that sensitivities of early PTSD risk screening instruments vary between 80% to 90% (for a review, see O’Donnell et al., 2008), it may be argued that for being acceptable as an early PTSD risk screener, an instrument should at least have a sensitivity of 80%. To illustrate, when 10% of a trauma population of 1,000 individuals will develop PTSD, 80% sensitivity would imply that 80 PTSD cases will be correctly detected and 20 PTSD cases remain unnoticed by the test. An important question, then, is to understand which early PTSD risk screening instrument performs best at this sensitivity level?

Until now, most of the early PTSD risk screening instruments were developed to predict acute PTSD, but were not evaluated on their accuracy in predicting a chronic PTSD diagnosis. Yet, from a clinical and cost-effectiveness perspective we want to pick out the individuals with the worst long term prognosis and focus our resources on them. In this study, we will compare the diagnostic performance of three well-established PTSD self-report instruments when predicting PTSD at 6 months after injury at 80% sensitivity, aiming to evaluate whether the two shorter instruments, the SPAN (Meltzer-Brody et al., 1999) and the TSQ (Brewin et al., 2002), perform as well as the longer instrument, the IES-R (Weiss & Marmar, 1997).

3.2 METHOD

3.2.1 Ethics statement

Medical ethical approval was obtained from the local institutional review boards of the Academic Medical Centre and the VU medical centre, Amsterdam, The Netherlands.
3.2.2 Participants

Participants were recruited from September 2005 to March 2009 for participation in a prospective study on the psychiatric morbidity following traumatic injury (for more details on the setting, see also Mouthaan et al., 2011). All adult patients presenting at a level-1 trauma centre in Amsterdam, The Netherlands, with injuries sustained in a traumatic event according to the DSM-IV A1-criterion for PTSD (American Psychiatric Association, 2000) and with sufficient understanding of the Dutch language were eligible for participation. Patients were excluded if they had injuries due to deliberate self-harm, an organic brain condition, current psychotic symptoms or disorder, bipolar disorder or depression with psychotic features, moderate to severe traumatic brain injury (according to the Glasgow Coma Scale score of less than 13; Teasdale & Jennett, 1974), or if they permanently resided outside the Netherlands.

3.2.3 Procedure

Research assistants selected eligible patients for participation from the hospitals’ registrations and contacted them within 72 hours of the injury in-hospital or by telephone. Participants provided oral and written informed consent prior to data collection and completed an extensive clinical and self-report examination of psychological symptoms, including the index tests described in this study, within 8 weeks of their injury. All patients received clinical assessments of PTSD at 6 months. These were performed at the Centre for Anxiety Disorders of the Academic Medical Centre, at bedside or at the private home of the patient by master’s- and doctoral level assessors who were blind to the outcomes of the baseline tests. Formal training in the Clinician Administered PTSD Scale (CAPS; Blake et al., 1995) was provided to all interviewers by the original translators of the Dutch version of the CAPS 5.0 of the Research Centre for Military Mental Health Care, Utrecht, The Netherlands, and by experienced clinicians from the Centre for Anxiety Disorders of the Academic Medical Centre, Amsterdam, The Netherlands.

3.2.4 Measures

PTSD self-report instruments (index tests)

The 4-item SPAN (Startle, Physiological arousal, Anger, and Numbness) is derived from the 17-item Davidson Trauma Scale (DTS), which assesses frequency and severity of PTSD symptoms over the past week (Zlotnick, Davidson, Shea, & Pearlstein, 1996). The items are rated on a 5-point scale from 0 (not at all distressing)
to 4 (extremely distressing) with a total score range of 0-16. The Dutch translation of the DTS, including the SPAN items, has been previously reported to show high agreement with the Structured Interview for PTSD (SI-PTSD; Davidson, Malik, & Travers, 1997; Sijbrandij, Olff, Opmeer, Carlier, & Gersons, 2008). In our sample, the SPAN correlated moderately (Pearson $r = .65$, $p < .001$) with a concurrent CAPS assessment that was collected as a part of the larger prospective study (Mouthaan et al., 2011). Missing items were replaced with the mean item response (1 case with 1 missing item). Previous studies found sensitivity varying between 0.79-0.84 and specificity varying between 0.80-0.91 in relation to a concurrent PTSD diagnosis (Chen, Shen, Tan, Chou, & Lu, 2003; Meltzer-Brody et al., 1999; Seo et al., 2011). The only prospective study of the SPAN found a cut-off of 10 at 1 week post-trauma to be predictive of 2 month PTSD with a sensitivity and specificity of 0.86 (Sijbrandij et al., 2008).

The TSQ is a 10-item self-report scale with a yes/no-response format and assesses the presence of 5 intrusion items (e.g., “Upsetting dreams about the event”) and 5 hyperarousal items (e.g., “Difficulty falling or staying asleep”) over the past week (Brewin et al., 2002). It was adapted from the PTSD Symptom Scale-Self-Report Version (PSS-SR; Foa, Riggs, Dancu, & Rothbaum, 1993). The TSQ, translated into Dutch by the Research Group Psychotrauma of the Centre for Anxiety Disorders, shows adequate agreement with a concurrent CAPS assessment in the present study (Pearson $r = .72$, $p < .001$). Missing data were replaced with the scale mean (6 cases with 1 missing item). At a cut-off of 6 symptoms in any combination the TSQ showed a sensitivity/specificity of 0.86/0.93 in predicting PTSD in rail crash survivors at 6-12 months post-trauma and a sensitivity/specificity of 0.76/0.97 in crime victims within 1 month post-trauma (Brewin et al., 2002). Walters et al. (2007) replicated this cut-off in a sample of emergency unit patients with a sensitivity/specificity of 0.85/0.89 for future PTSD at 1 month and of 0.88/0.78 for 6 month PTSD. At a cut-off of 7, the Dutch version of the TSQ showed a sensitivity and specificity of 0.87 and 0.69 respectively in a sample of civilian trauma survivors for future PTSD at 1 month (Dekkers, Olff, & Naring, 2010).

The 22-item IES-R measures intrusion (8 items, e.g., “Any reminder brought back feelings about it”), avoidance (8 items, e.g., “I tried not to talk about it”), and hyperarousal (6 items, e.g., “I felt watchful and on guard”; Weiss & Marmar, 1997). The items are scored on a 5-point scale, from 0 (not at all) to 4 (extremely), with respect to how distressing each item has been in the past week. Total scores range from 0-88 with higher scores representing greater severity. In the present study, both the subscales and the total score of the Dutch IES-R, translated by the Research Group Psychotrauma of the Centre for Anxiety Disorders, show moderate to adequate similarities with the subscales and total score of the CAPS (Intrusion: $r = .79$, Avoidance: $r = .57$, Hyperarousal: $r = .65$, total score: $r = .75$, all $p < .001$). Missing responses were replaced with the individual subscale mean (18 cases with 1 missing item, 6 cases with 2 missing items and 1 case with 3 missing
items). Proposed cut-offs to indicate probable concurrent presence of PTSD were 19-20 in adolescent floods and mudslides survivors with a sensitivity/specificity of 0.86/0.84 (Chen et al., 2011), 22 in treatment-seeking substance abusers with a sensitivity/specificity of 0.92/0.57 (Rash, Coffey, Baschnagel, Drobes, & Saladin, 2008) and in psychiatric patients at a sensitivity/specificity of 0.95/0.80 (Adkins, Weathers, McDevitt-Murphy, & Daniels, 2008), 24/25 in survivors of terrorist and natural disasters with a sensitivity of 0.83 and 1.00 and specificity of 0.67 and 0.84 (Asukai et al., 2002), 33 in treatment-seeking and community-sample military veterans with a sensitivity/specificity of 0.91/0.82 (Creamer, Bell, & Failla, 2003), and an item mean score of 1.6, which corresponds to a cut-off score of 35, in acute lung injury survivors with a sensitivity/specificity of 1.00/0.85 (Bienvenu, Williams, Yang, Hopkins, & Needham, 2013).

Clinical interview

The 30-item semi-structured interview of the CAPS was used to obtain the final diagnosis of PTSD (Blake et al., 1995). The CAPS is generally considered to be the best reference standard for diagnosing PTSD (Weathers et al., 2001). Frequency and intensity of the 17 DSM-IV symptoms of PTSD are scored from 0-4, with higher scores indicative of more severe symptoms. The internal consistency of the scales in the Dutch translation of the CAPS is good to excellent (Intrusion: $\beta=0.63$, Avoidance: $\beta=0.78$, Hyperarousal: $\beta=0.79$, CAPS total: $\beta=0.89$; Hovens et al., 1994). In the current study, the CAPS subscales and total score showed similar high internal consistency (Intrusion: $\beta=.91$, Avoidance: $\beta=.83$, Hyperarousal: $\beta=.86$, CAPS total: $\beta=.95$). Missing items were replaced with the mean item response of the corresponding subscale (5 cases with 1 missing item, 1 case with 2 missing items and 1 case with 3 missing items). Inter-rater reliability was high (ICC=.98, 95% CI=.95-.99). We used the rule of Weathers et al. (1999) to establish a PTSD diagnosis, in which symptoms need at least a frequency of 1 and intensity of 2 with a total score of at least 45 points.

3.2.5 Analyses

Receiver operating characteristic (ROC) curves were computed for the total scores of the SPAN, the TSQ and the IES-R in relation to the 6 month PTSD diagnosis as the reference standard. As our main analysis, we performed paired t-tests to test for significant differences in areas under the curve (AUCs) using the method of Hanley and McNeil (Hanley & McNeil, 1983), which accounts for the paired data (subjects received all instruments under evaluation) within our study. Across all analyses,
p-values of $P=0.05$ (two-tailed) were considered to indicate statistical significance. Second, to illustrate the clinical implications of the three self-report instruments in predicting PTSD, we compared the values for specificity at 80% sensitivity. We calculated the exact specificity for 80% sensitivity by means of linear interpolation between the two data points directly before and after the 80% sensitivity. PPV, NPV and cut-off values are reported that correspond most closely to 80% sensitivity.

### 3.3 RESULTS

#### 3.3.1 Participant characteristics

Of the total study sample of 852 consecutively included injury patients, 311 patients (36.5%) were included in the final sample. Patients who did not complete any of the index tests (38.7%, $n=330$) or did not attend the 6 month assessment of PTSD (24.8%, $n=211$) were excluded from the final sample. Figure 3.1 shows a flow chart of the study sample. Patients completed the SPAN, TSQ and/or the IES-R at a median of 23 days post-injury (Inter Quartile Range=10-16) and were clinically assessed for a final diagnosis of PTSD at 6 months. Compared to the excluded patients ($n=541$), participants were older (mean=44.9 (s.d.=15.9) versus mean=42.6 (s.d.=15.8); $t=-2.1$, d.f.=850, $P=.037$), more often female (39.9% versus 32.9%; $\chi^2=4.2$, d.f.=1, $P=.041$), more often had a Dutch cultural background (89.3% versus 76.0%; $\chi^2=21.9$, d.f.=1, $P<.001$), and were less often diagnosed with PTSD at 6 months (5.8% versus 13.7%; $\chi^2=8.4$, d.f.=1, $P=.004$).

Eighteen patients (5.8%) of the final sample were diagnosed with 6 month PTSD. In addition, 22 patients (7.1%) were diagnosed with major depressive episode (MDE) and 24 (7.8%) with an anxiety disorder (AD) other than PTSD. Of the patients with PTSD, nine were diagnosed with comorbid MDE, two with comorbid AD and one with both. Thirty-seven patients reported having had contact with a professional mental health caregiver (i.e., psychologist, psychiatrist, social worker, victims aid worker) in the past 6 months, four of which were diagnosed with 6 month PTSD. Sixty-five patients in the final sample (20.9%) were offered a brief web-based early intervention within the first month of injury, aimed at preventing PTSD symptoms, as part of a randomized controlled trial (Mouthaan et al., 2013). Except for more prior traumatic experiences ($t=-2.05$, d.f.=308, $P=0.011$), there were no baseline differences between patients with and without PTSD. Table 3.1 presents baseline characteristics of participants and differences in baseline variables for patients with and without 6 month PTSD.
Table 3.1. Baseline characteristics of the total sample and participants with and without 6 month PTSD.

<table>
<thead>
<tr>
<th>Variables</th>
<th>All participants (n = 311)</th>
<th>PTSD (n = 18)</th>
<th>Non-PTSD (n = 293)</th>
<th>P&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (s.d.)</td>
<td>44.9 (15.9)</td>
<td>40.8 (10.4)</td>
<td>45.2 (16.1)</td>
<td>0.256</td>
</tr>
<tr>
<td>Male gender, No. (%)</td>
<td>187 (60.1)</td>
<td>12 (66.7)</td>
<td>175 (59.7)</td>
<td>0.559</td>
</tr>
<tr>
<td>College or university degree, No. (%)</td>
<td>75 (24.3)</td>
<td>6 (33.3)</td>
<td>69 (23.7)</td>
<td>0.624</td>
</tr>
<tr>
<td>Married or cohabitating, No. (%)</td>
<td>131 (42.1)</td>
<td>8 (44.4)</td>
<td>123 (42.0)</td>
<td>0.837</td>
</tr>
<tr>
<td>Country of origin:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Netherlands, No. (%)</td>
<td>276 (89.3)</td>
<td>13 (76.5)</td>
<td>263 (90.1)</td>
<td>0.078</td>
</tr>
<tr>
<td>Prior traumatic events, mean (s.d.)</td>
<td>2.9 (2.2)</td>
<td>4.2 (1.7)</td>
<td>2.8 (2.2)</td>
<td>0.011</td>
</tr>
<tr>
<td>Traumatic event, No. %:</td>
<td></td>
<td></td>
<td></td>
<td>0.382</td>
</tr>
<tr>
<td>Road traffic accident</td>
<td>200 (64.3)</td>
<td>13 (72.2)</td>
<td>187 (63.8)</td>
<td></td>
</tr>
<tr>
<td>Fall from height</td>
<td>47 (15.1)</td>
<td>-</td>
<td>47 (16.0)</td>
<td></td>
</tr>
<tr>
<td>Work-related accident</td>
<td>36 (11.6)</td>
<td>3 (16.7)</td>
<td>33 (11.3)</td>
<td></td>
</tr>
<tr>
<td>Assault/abuse</td>
<td>8 (2.6)</td>
<td>1 (5.6)</td>
<td>7 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Other (e.g., burn accident, plane crash,</td>
<td>20 (6.4)</td>
<td>1 (5.6)</td>
<td>19 (6.5)</td>
<td></td>
</tr>
<tr>
<td>recreational accident)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital admission, No. (%)</td>
<td>204 (70.3)</td>
<td>10 (58.8)</td>
<td>194 (71.1)</td>
<td>0.284</td>
</tr>
<tr>
<td>Days hospitalized, mean (s.d.)</td>
<td>5.3 (8.4)</td>
<td>4.8 (8.6)</td>
<td>5.3 (8.4)</td>
<td>0.810</td>
</tr>
<tr>
<td>ICU stay, No. (%)</td>
<td>31 (10.5)</td>
<td>1 (5.9)</td>
<td>30 (10.8)</td>
<td>0.524</td>
</tr>
<tr>
<td>Injury Severity Score, mean (s.d.)</td>
<td>9.7 (9.8)</td>
<td>6.6 (7.1)</td>
<td>9.9 (9.9)</td>
<td>0.181</td>
</tr>
<tr>
<td>Glasgow Coma Score, mean (s.d.)</td>
<td>14.3 (2.3)</td>
<td>14.1 (3.2)</td>
<td>14.3 (2.3)</td>
<td>0.680</td>
</tr>
</tbody>
</table>

PTSD, Posttraumatic Stress Disorder; ICU, Intensive Care Unit.

<sup>a</sup> Chi-square tests were used to test for differences in categorical variables and independent samples t tests were used for continuous measures.
3.3.2 Accuracy of the SPAN, TSQ and IES-R as screening instruments for PTSD

AUCs of the SPAN (0.83, 95% CI=0.66-1.00), TSQ (0.82, 95% CI=0.66-0.98) and IES-R (0.83, 95% CI=0.72-0.94) were adequate (see Figure 3.2). There were no statistical significant differences between the AUCs of the SPAN, TSQ and IES-R ($P_{SPAN-TSQ}=0.84$, $P_{SPAN-IES-R}=0.97$, $P_{TSQ-IES-R}=0.85$). Figure 3.2 shows the ROC curves of the original data points of sensitivity and specificity values of the SPAN, TSQ and IES-R for 6 month PTSD using linear interpolation between the data points.

The specificity of the SPAN at 80% sensitivity was 64% (Table 3.2). This specificity indicates that in a population of 1,000 patients and assuming a prevalence of PTSD of 6%, the number of subjects receiving a false positive SPAN result will be 338. The cut-off most adjacent to 80% sensitivity was 4. PPV at this cut-off was 8% and NPV 99%, indicating an 8% chance of 6 month PTSD at a positive score and a 99% chance of no PTSD at a negative score. At 80%
sensitivity, the TSQ’s specificity was 59%, indicating that out of a 1,000 patients, 385 patients would unjustly score positive. The cut-off for the TSQ that most closely corresponded to 80% sensitivity was 5 (PPV=0.19, NPV=0.98). The specificity of the IES-R at 80% sensitivity was 72%, which means 263 false positives. A cut-off of 23 corresponded best with this sensitivity (PPV=0.15, NPV=0.99). There were no significant differences in specificities between tests.

Figure 3.2. ROC curves of the SPAN, TSQ and IES-R for 6 month PTSD.

Note: ROC curves represent original sensitivity and specificity values using linear interpolation between the observed data points. ROC, Receiver Operating Characteristic; SPAN, Startle, Physiological Arousal, Anger & Numbness; TSQ, Trauma Screening Questionnaire; IES-R, Impact of Event Scale-Revised; PTSD, posttraumatic stress disorder.
Table 3.2. Specificity values of the SPAN, the TSQ and the IES-R at 80% sensitivity, and corresponding cut-off values, PPVs and NPVs.

<table>
<thead>
<tr>
<th>Index test</th>
<th>Specificity†</th>
<th>Accuracy for corresponding cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cut-off</td>
</tr>
<tr>
<td>SPAN</td>
<td>0.64</td>
<td>4</td>
</tr>
<tr>
<td>TSQ</td>
<td>0.59</td>
<td>5</td>
</tr>
<tr>
<td>IES-R</td>
<td>0.72</td>
<td>23</td>
</tr>
</tbody>
</table>

SPAN, Startle, Physiological Arousal, Anger & Numbness; TSQ, Trauma Screening Questionnaire; IES-R, Impact of Event Scale-Revised; PPV, positive predictive value; NPV, negative predictive value. † Values for specificity were calculated using linear interpolation at 80% sensitivity.

3.3 DISCUSSION

3.3.1 Summary of the findings and comparison to previous studies

In this study, we compared the accuracy of three widely used early PTSD risk screening instruments in predicting a PTSD diagnosis at 6 months in injury victims. The results showed that with AUCs varying between 0.82-0.83, all instruments adequately distinguished between individuals with and without PTSD at 6 months. As we aimed for high sensitivity (80%) in order for these instruments to not miss potential clinical cases of PTSD, the specificities were modest for all instruments. This implies that while the instruments are adequate in identifying PTSD cases, they are poor in identifying non-cases. Thus, the instruments could well be used as a first selection step of possible cases, but a second, more comprehensive, diagnostic examination is needed to identify individuals in need of treatment. Importantly, the specificities did not significantly differ between tests, suggesting that the briefer, SPAN and TSQ, are as accurate as the longer, IES-R.

Our results concerning the accuracy of the SPAN, TSQ and IES-R are in line with those found in other studies that focused on screening for future PTSD (O’Donnell et al., 2008). Specificity results are often lower in replication studies as compared to the original validation studies, in which the items of the instruments are selected based on the performance in that particular population (Brewin, Fuchkan, Huntley, & Scragg, 2010; Dekkers et al., 2010; O’Donnell et al., 2012; Shalev,
Freedman, Peri, Brandes, & Sahar, 1997). Our proposed cut-offs of 4 for SPAN, 5 for TSQ and 23 for IES-R, best corresponding to 80% sensitivity, slightly differ from the cut-offs previously published (Adkins et al., 2008; Asukai et al., 2002; Bienvenu et al., 2013; Brewin et al., 2002; Chen et al., 2003; Chen et al., 2011; Creamer et al., 2003; Dekkers et al., 2010; Meltzer-Brody et al., 1999; Rash et al., 2008; Seo et al., 2011; Sijbrandij et al., 2008; Walters, Bisson, & Shepherd, 2007). Our cut-off of 4 for the SPAN is much lower than found in a previous study administering the SPAN at 10 days after the trauma (Sijbrandij et al., 2008). Perhaps the later timing of administration in our study (i.e., 3 weeks following trauma) explains this difference. At 3 weeks most initial PTSD symptoms, such as re-experiencing and hyperarousal symptoms that are usually found in the first weeks after trauma (O’Donnell et al., 2008), are likely to have decreased naturally. Previous cut-offs reported for the TSQ were 6 (Brewin et al., 2002; Walters et al., 2007) and 7 (Dekkers et al., 2010). Our cut-off of 23 for the IES-R is the first prognostic cut-off to be published, but matches the range of diagnostic cut-offs of 22 to 25 found previously (Chen et al., 2011; Rash et al., 2008; Adkins et al., 2008), with the exception of studies of veterans (Creamer et al., 2003) and acute lung injury victims (Bienvenu et al., 2013) who reported cut-offs of 33 and 35 respectively.

It is important to consider that a PTSD incidence at 6% is low, which leads to low PPVs. In our sample, the highest chance of someone with a positive result developing PTSD at 6 months was 19%. It is an issue found in several previous screening studies, especially within injury populations (Adkins et al., 2008; O’Donnell et al., 2008; Sijbrandij et al., 2008; Walters et al., 2007). As our PPVs imply, at most only one in five persons scoring positive on the instruments will actually develop PTSD. This hampers the usefulness of screening initiatives in these types of population. Among patients who did not complete the early PTSD risk screening instruments (n = 330), PTSD prevalence was double that of the final sample (13.7%). This could indicate a reluctance to screening or research participation among patients with a higher risk of later PTSD. This issue has also been raised previously (Brewin et al., 2010) and limits the generalizability of the findings to samples with a higher PTSD prevalence.

Previous studies have shown good results in identifying individuals at risk for depressive and anxiety disorders using screeners of 5, 3, 2 or even a single item (Cuijpers, Smits, Donker, ten Have, & de Graaf, 2009; Donker, van Straten, Marks, & Cuijpers, 2010; van Ballegooijen et al., 2012). Our finding that the short instruments perform equal to the longer one are in line with these results. However, comparable to our results, these screeners generally suffered from moderate to low specificity (44% to 77%; Cuijpers et al., 2009; Donker et al., 2010; van Ballegooijen et al., 2012). Thus, it may be worthwhile to evaluate the diagnostic accuracy of even shorter early PTSD risk screening instruments than in the current study, but only when followed by a comprehensive clinical evaluation, to rule out any false positives as a result of the lower specificity.
3.3.2
Strengths and limitations

A strength of our study is that we tested the accuracy of three instruments that are already in use globally in various populations and practices. Our study employed a comparative accuracy design, meaning that all patients received all tests under evaluation as well as the best available reference standard. Such a design has both higher validity and greater efficiency than comparing instruments between samples. Higher validity comes from the fact that all external factors can be kept constant when comparing the instruments; efficiency is enhanced because of the within patient comparisons that can be made similar to a paired t-test. This knowledge helps us make informed decisions on which instrument to best choose in a certain situation or population. Because these instruments do not rely on information specific to a particular trauma population (e.g., injury characteristics or the context in which the trauma occurred), but instead on symptoms, they may be useful for multiple groups or situations. A strong point of our sample is that, compared to other studies of screening in acutely traumatised populations (O’Donnell et al., 2008; Sijbrandij et al., 2008; Walters et al., 2007), ours included a heterogeneous, consecutively included sample of injury victims, reflecting the broad range of injury victims of a level-1 trauma centre. We included various accident and assault victims, admitted to the hospital for a long period or immediately released. Finally, this study was the first to provide a prognostic cut-off for the IES-R and the first to examine the Dutch versions of the TSQ and the SPAN in a prospective design and using a consecutively included sample.

A limitation is that the screening instruments were administered quite late, at around 3 weeks following injury. This limits the generalizability of our findings to screening efforts in the immediate aftermath of traumatic events. Additionally, we were unable to collect a clinical PTSD diagnosis of 211 patients at 6 months, whose results on the index tests could not be included. However, post-hoc analyses revealed no significant differences in demographics, trauma history or scores on the screening instruments between participants and these dropouts. The determination of specificity values was hampered due to the relatively small sample size in the study. The total number of patients with a final diagnosis of PTSD was relatively low in this study. This hampered in particular the exact determination of cut-off values to obtain a specific value of sensitivity. Due to the low PTSD incidence in our sample, the ROC curves were surrounded with considerable uncertainty, which may have led to small, but potentially significant, differences between instruments remaining undetected.
3.3.3 Clinical implications

An important clinical implication of our study is that shorter instruments perform as well as longer ones in early PTSD risk screening. The use of shorter instruments may enhance the response rate to these screening instruments (Edwards et al., 2009). This means more individuals could be monitored or even referred for follow-up. Our results also imply that early screening cannot be used in clinical practice without adequate diagnostic follow-up. As a triage strategy, early screening can assist in filtering out anyone in need of PTSD treatment, without having to conduct time-consuming clinical interviews in low-risk individuals. This may not be problematic, since mental health treatment is usually preceded by a more thorough clinical interview.

3.3.4 Research implications

Future studies should investigate the potential disadvantages of early screening, such as the hazard of stigmatizing individuals when wrongly identifying them as potential PTSD cases. Lastly, the design and method of our study of comparing the diagnostic accuracy within the same patients and at a fixed sensitivity level should also be replicated in trauma populations with a higher PTSD prevalence, such as victims of rape or violence (Bisson, Weltch, Maddern, & Shepherd, 2010), to examine whether the instruments perform equally accurate in samples with a higher proportion of PTSD cases.
CHAPTER 4: Design and Pilot Study of an Internet-Based Preventive Intervention for PTSD

ABSTRACT

In the prevention of posttraumatic stress disorder (PTSD) after severe traumatic injury, easily applicable, accessible, cost-efficient early interventions are needed that use well-established techniques for decreasing acute psychological stress reactions. Whereas most studies delivered cognitive behavioral techniques face-to-face or as a curative treatment, we incorporated them into a brief internet-based early intervention to reduce acute psychological distress and prevent long-term symptoms of PTSD in trauma victims. By means of interactive elements, visual and auditory materials, the intervention contains psychoeducation, modeling, in vivo exposure, stress management and social support. In this article, we describe the design of the program and the outcomes of an initial feasibility study among trauma patients \((n = 5)\) and healthy controls \((n = 5)\). The participants reviewed the program as useful and clear. Neither patients nor controls experienced adverse psychological reactions after completing the intervention. The results show that the intervention is well-received and feasible for implementation in severely injured trauma survivors.
4.1 INTRODUCTION

Following traumatic injury, many patients find themselves facing more than their physical recovery. Previous studies have shown that sizeable percentages of trauma patients develop psychiatric symptoms as a result of their traumatic experiences, such as posttraumatic stress disorder (PTSD). One to six months post-injury, reported rates of PTSD vary from 17.5% to 42% (Ehlers, Mayou, & Bryant, 1998; Harvey & Bryant, 1998; Michaels et al., 1999; O’Donnell, Creamer, Pattison, & Atkin, 2004; Shalev et al., 1998; Yehuda, McFarlane, & Shalev, 1998). PTSD is a severe and disabling disorder associated with considerable personal suffering and psychobiological abnormalities due to a deregulated stress system, functional impairment, and a high economic impact (Walker et al., 2003).

To prevent the development of PTSD in trauma victims, several types of brief early interventions have been developed. The most frequently applied early psychological intervention after trauma, the single-session psychological debriefing, does not prevent the onset of PTSD and may even increase the risk for PTSD in some survivors (Rose, Bisson, & Wessely, 2003; Sijbrandij, Olff, Reitsma, Carlier, & Gersons, 2006; van Emmerik, Kamphuis, Hulsbosch, & Emmelkamp, 2002). It has been suggested that the emphasis on expressing emotions related to the trauma, which is a usual part of most acute interventions following psychological trauma, may exacerbate and sustain arousal, which may cause PTSD symptoms to escalate rather than to decrease (Sijbrandij et al., 2006). Therefore, recent guidelines advocate against the use of such trauma-focused early interventions for everyone involved in the traumatic event (National Institute for Clinical Excellence; NICE, 2005). Up to date, no evidence-based alternatives exist to prevent PTSD in trauma-affected populations shortly after the traumatic event.

Instead, it has been suggested that future early interventions in trauma populations should focus on reducing hyperarousal and consist of ‘psychological first aid’, such as psychoeducational materials about normal and abnormal reactions to trauma and about the various available care options (Gray & Litz, 2005). Lacking thorough research, psychological first aid still remains an evidence-informed, rather than an evidence-based intervention. Stronger support has been found for the use of trauma-focused cognitive behavioral therapy (CBT) in the treatment of Acute Stress Disorder (ASD) and acute PTSD in injury populations (see Roberts, Kitchiner, Kenardy, & Bisson, 2009, for an overview). Cognitive behavioral techniques include psychoeducation about individual reactions to traumatic events, stress management techniques (i.e. relaxation exercises), exposure, and cognitive restructuring. Although trauma-focused CBT usually consists of 4 to 5 sessions, there is some evidence indicating that only 1 CBT session is useful in the treatment of PTSD in Turkish earthquake survivors (Basoglu, Salcioglu, & Livanou, 2007). In addition, a recent pilot feasibility study in which a single exposure therapy session was delivered to injury victims in the emergency department (ED) within 24 hours after experiencing trauma, showed that patients receiving this intervention were rated lower on clinician-
rated global severity of symptoms than patients in the assessment-only condition (Rothbaum et al., 2008).

The internet may provide a useful medium in delivering early interventions to recently trauma-exposed populations. E-Mental health interventions are considered a cost-effective variant of traditional interventions (Kaltenthaler et al., 2006). In addition, the accessibility of the internet, its interactivity and low-threshold could be beneficial features in the delivery of care to injured trauma survivors. For the treatment of chronic posttraumatic stress symptoms, several internet-based interventions have been developed, demonstrating feasibility (Litz, Williams, Wang, Bryant, & Engel, 2004) and efficacy (Hirai & Clum, 2005; Lange et al., 2003). However, few initiatives have yet been undertaken using the internet as a medium for the prevention of PTSD. A pilot study of a preventive internet-intervention that addresses mental health (among which PTSD) and substance abuse in disaster populations showed to be feasible (Ruggiero et al., 2006).

In the next section, we will describe the design and core elements of the internet-based early psychological intervention “Trauma TIPS”, which we developed for the prevention of PTSD in injured trauma survivors. The intervention is targeted at decreasing acute psychological stress reactions in traumatic injury patients within the first month following their injury. In addition, we will present the results of an initial feasibility study.

4.1.1 Design of the Trauma TIPS early intervention

The script for Trauma TIPS was written by the authors from the Center for Anxiety Disorders, Research group Psychotrauma of the Academic Medical Center in Amsterdam, the Netherlands. The intervention was produced by the University of Amsterdam’s Audiovisual Center. The Trauma TIPS internet-intervention is an internet program of about 30 minutes duration with interactive elements and visual and auditory materials. Since patients use the web program within the first month after experiencing a traumatic event, which may be one of the most hectic and stressful periods in their lives, we considered keeping the design and lay-out of the web pages as simple and straightforward as possible. To achieve this, the toolbar of the program remained visible at the top of every page of the website. In addition, at the left and right hand bottoms of every web page, the buttons “back” and “next” respectively were present at all times, allowing patients to leave and enter sections at any time they wish. Trauma TIPS was accessed on a secure https://-website. Each patient was assigned a personal login name to log into the program. If a patient had forgotten his or her login name, he or she could click on a “forgot your login name?” button upon which the mail server automatically replied the login name to their preregistered email address. With Active Server Pages (ASP) HTML codes
were generated at the server, selecting the web pages using the data generated by each patient. In a Microsoft Access database relevant information was filed, such as the responses to the online anxiety instrument we added to our program (see description of the program below), and the total amount of time patients spent interacting with the various elements of the program. The video and audio fragments in the intervention were put on a streaming media server to allow for immediate viewing after clicking on them, without prior downloading.

The Trauma TIPS intervention consisted of the following steps, corresponding to the buttons in the navigation bar at the top of each page (see Figure 4.1):

(1) Introduction: explanation of the goal of the intervention and operating instructions;
(2) Questions 1: a pre-test of state anxiety;
(3) Trauma: this module consists of three sections:
   a. Trauma Unit: a video feature in which a brief overview of the procedures at the Trauma Unit was presented. In addition, the head of the Trauma Unit explained that stress reactions are very common after traumatic injury, but that the intensity may vary across individuals.
   b. Experiences: three video features of Trauma Unit patients (re-enacted by actors) who briefly disclosed their experiences after the accident. Based on the distribution of sex, age and trauma mechanism in our hospital’s trauma records, we presented three patients: a male survivor of an industrial accident (“Piet”; 51 years); a male survivor of a motor vehicle accident (“Mike”; 31 years); and a female survivor of an assault (“Esther”; 35 years).
   c. Tips: a summary list of five tips for coping with common physical and psychological reactions after a traumatic event was presented. The tips corresponded to the suggestions of the actors during the three video features of the Trauma Unit patients;
(4) Exercises: two audio features of approximately 7 minutes duration each with instructions for stress management techniques were presented. The stress management techniques were relaxation exercises based on breathing retraining and muscle relaxation, developed by external experts and staff members of the Amsterdam Academic Medical Center;
(5) Questions 2: a post-test of state anxiety;
(6) End of the program: information about other sources of available help was provided. Participants were given the opportunity to contact the main investigator of the project for additional support or information on professional help. Patients could also leave their remarks and suggestions about the program at a separate remarks section. The remarks were only visible for the project researchers.

Figure 4.1. Flow chart of the Trauma TIPS intervention
4.1.2

Cognitive behavioral elements of the intervention

The main cognitive behavioral elements of the intervention were: information/psychoeducation, modeling, in vivo exposure, social support, and stress management. Below, we will briefly outline the distinctive cognitive behavioral elements and we will discuss evidence to support their use in acutely injured trauma survivors.

Information and psychoeducation. First, information about the usual natural decline in symptoms of distress after experiencing a traumatic event was given in the video feature of the trauma unit professional (step 3a) and in the three video features of the patients (step 3b), who described their initial psychological reactions to the trauma, such as feeling tensed, difficulties concentrating or sleeping, and feeling tired. All patients emphasized that they were moderately distressed at first, but that they improved as time went by. In addition, suggestions for coping strategies were provided in the patients’ videos, such as seeking social support for emotional or practical reasons, seeking distraction, resuming normal daily activities (i.e. work, social events), and to self-expose to normal daily routines that may be feared or avoided, such as driving a car. Furthermore, the following 5 tips (step 3c) were provided: 1. Symptoms of distress, such as thinking back about what happened, not feeling up to much, insomnia are common, but often spontaneously decline; 2. Seek support with other people, for emotional or practical help; 3. Seek distraction in activities; 4. Resume daily activities at one’s own pace; 5. When many symptoms of distress are present, when a participant is worried or when symptoms do not decrease, participants were advised to contact a staff member of the Trauma TIPS team, or a staff member of the Trauma unit. Contact details were provided on the final page.

Note, however, that recent studies evaluating the use of psychoeducation in the immediate aftermath of severe injury, showed that psychoeducation does not contribute to reductions in symptoms of PTSD and may even worsen existing psychological symptoms (Ehlers et al., 2003; Scholes, Turpin, & Mason, 2007; Turpin, Downs, & Mason, 2005). One study in emergency room patients with panic attacks found that psychoeducation coupled with exposure instructions was more effective than psychoeducation alone in decreasing panic symptoms (Swinson, Soulis, Cox, & Kuch, 1992). In a recent systematic review on the efficacy of psychoeducation in the prevention of PTSD, Wessely et al. (2008) suggested that the type of psychoeducation provided so far may not have been optimal. Instead of sensitizing victims by summing up all possible stress reactions, the authors stated that psychoeducation should include constructive information to stimulate the expectancy of resilience, and promote help seeking, if necessary (Wessely et al., 2008). In our Trauma TIPS intervention, we adhered to these recommendations by not mentioning all possible stress symptoms patients may or may not develop, and by emphasizing return to normal routine.
**Modeling**, i.e. visually showing behavior with the intent to transfer knowledge on wanted behavior patterns, may facilitate behavior change (Bandura, 1969). It has been used previously in an early video-based intervention for rape victims (Resnick, Acierno, Holmes, Kilpatrick, & Jager, 1999). In Trauma TIPS, modeling was incorporated by showing three patients, enacted by actors, who briefly told their experiences after the accident. Even though the patients told their own story of how they have coped with the aftermath of trauma, the videos had several commonalities. Each patient conveyed information on how to cope with commonly occurring physical and psychological difficulties after traumatic injury. The videos also showed the patients successfully engaging in activities to reduce avoidance behaviors. For instance, one of the videos presented a trauma victim driving a car again after he initially had fear of driving by himself.

**In vivo exposure** elements in the Trauma TIPS intervention were embedded within the three video clips of the patients. In these clips, the patients explained how they gradually encountered activities and situations that provoked anxiety. The purpose of the in vivo exposure tips was to stimulate patients to pick up their normal routine and to prevent avoidance behavior. As already mentioned earlier, of all the elements of the Trauma TIPS intervention, exposure was the element with the strongest empirical evidence.

**Social support** is strongly related to a more favorable PTSD symptom course (Brewin, Andrews, & Valentine, 2000; Ozer, Best, Lipsey, & Weiss, 2003). Recent commentaries indeed suggested that, as part of early intervention, trauma victims should be stimulated to use their own social network (see Gray & Litz, 2005). In the Trauma TIPS intervention, social support was presented in the video clips of the patients as a successful coping strategy. We recommended patients to actively seek support with other people in the form of coping tips (see Information and psychoeducation).

**Stress management** was presented in the form of two audio clips of approximately 7 minutes duration, each with instructions for stress management techniques. The first clip (“Muscle relaxation”) focused on progressive muscle relaxation through breathing retraining. The second clip (“Safe place”) was an exercise that focuses on decreasing stress or tension levels by imagining a safe and secure place while retraining breathing. The main purpose for the exercises was to decrease acute distress levels and help patients regain a sense of control. Relaxation therapy was not regarded as an effective stand-alone treatment for PTSD, but was usually provided as an effective anxiety-reducing tool within a larger framework of CBT treatments for early symptoms of PTSD and acute stress disorder as well as chronic PTSD (Foa, Keane, Friedman, & Cohen, 2008).
4.1.3
Pilot study for feasibility and acceptability of the intervention

To evaluate the feasibility of the intervention and its effects on acute anxiety and early PTSD symptoms, we performed an initial pilot study of the intervention. We hypothesized that the intervention was acceptable to the patients and feasible for implementation in the intended population. Second, we hypothesized that the specific parts of the intervention would not cause or aggravate adverse short-term psychological reactions (i.e. anxiety, posttraumatic stress symptoms).

4.2 MATERIALS AND METHODS

4.2.1
Participants

In December, 2006 and January, 2007, five eligible consecutively admitted trauma patients (4 males, 1 female; age in years: M = 34.4, SD = 19.5, Mdn = 23.0, range = 40; 2 patients had up to four years of highschool, 3 had five or more years of highschool) of the Level I Trauma Center of the Academic Medical Center in the Netherlands were included in the study. Four patients were admitted following a motor vehicle accident and one after a work-related accident. None of the patients endured severe physical injuries (Injury Severity Score: M = 4.6, SD = 4.3, Mdn = 6.0, range = 9) and all were released from hospital care immediately (n = 1) or after a few days (n = 4) (number of days in hospital care: M = 3.0; SD = 2.9; Mdn = 2.0, range = 7). Five healthy control subjects were included, who matched the patients in terms of gender (4 males, 1 female), educational level (2 up to four years highschool, 3 five or more years highschool), and age (M = 34.6, SD = 19.8, Mdn = 23.0, range = 41). Patients under the age of 18 years, with suicidal ideation, with psychotic, bipolar, or organic disorders, or depressive disorder with psychotic characteristics, with a Glasgow Coma Score < 13 at the time of the intervention, without access to the internet, or who were physically unable to perform the intervention, were deemed ineligible for the study.

4.2.2
Measures

State anxiety

The State Trait Anxiety Inventory (STAI; Spielberger, 1983; Van der Ploeg, Defares, & Spielberger, 1980) was used to assess state anxiety online at pre- and post-intervention. The STAI is a well-established questionnaire containing 20 items on a 4-point Likert scale (1=very much to 4=not at all).
Posttraumatic stress symptoms

Patients completed the Impact of Event Scale-Revised (IES-R; Weiss & Marmar, 1997), a well-established questionnaire for assessing posttraumatic stress symptoms, at baseline assessment and at 1 month post-trauma. The IES-R consists of 22 items distributed over 3 subscales that represent the 3 symptom clusters of PTSD: Intrusion (8 items), Avoidance (8 items), and Hyperarousal (6 items). The sum of all items represents a total score of PTSD symptoms. Scores on the items range from 0 (not at all) to 4 (very much). Because we were especially interested in the acute psychological reactions after trauma and post-intervention, patients completed an additional assessment of intrusive and hyperarousal symptoms at 24 hours post-intervention.

4.2.3
Feasibility and satisfaction

The feasibility and acceptability of the intervention was measured by assessing the participants’ opinions on clarity and usefulness of all the individual parts of the intervention. Scores were rated on 4-point Likert scales ranging from 1 (not clear at all, not useful at all) to 4 (clear, useful). Participants could also indicate suggestions or improvements for the intervention. Furthermore, patient satisfaction was assessed on a 4-point Likert scale with scores ranging from 1 (very unsatisfied) to 4 (satisfied).

4.2.4
Procedure

After written and oral informed consent, patients completed a self-report assessment of PTSD symptoms. Next, personal log-in names for the internet-based intervention were provided to all participants. State anxiety was assessed online immediately prior to and following the program. Within 24 hours of completing the intervention the participants were contacted face-to-face or by telephone by clinicians for an evaluation of feasibility of the intervention. Patients completed post-assessments of current PTSD symptoms at 24 hours after the program and again at 1 month post-trauma.
4.2.5
Statistical analyses

Means and standard deviations of all questions on feasibility were computed. Means, medians and ranges of demographic characteristics and outcome variables are presented. To compare means between pre-intervention and post-intervention assessments of state anxiety and PTSD symptoms within patients and healthy control subjects, paired one sample t-tests were used. Level of significance was set at $p < .05$. Data were analyzed using SPSS (version 12.0.1).

4.3 RESULTS

4.3.1
State anxiety

Table 4.1 shows the individual and mean scores of the participants on the STAI at pre- and post-intervention. No significant differences were found between pre- and post-intervention assessments for both patients and controls. All mean scores were equal to norms of male and female student populations, male army draftees, or ex-radiotherapy patients (van der Ploeg et al., 1980).

4.3.2
Posttraumatic stress symptoms

Table 4.1 also shows the individual and mean scores of the patients on posttraumatic stress symptoms. Although all mean scores of the patients decreased with time, no significant differences were found between any of the mean scores on posttraumatic stress symptoms.

4.3.3
Feasibility

Overall, the patients and the controls evaluated the intervention as clear and useful, although some sections were preferred above others. Most comments were focussed on the sections containing the pre- and post-intervention assessments of state anxiety and the stress management exercises. Regarding the assessments of state anxiety, the participants commented that they contained too much overlap between the questions (3 patients and 3 controls) and too many questions (1 patient, 3 controls). Regarding the stress management and relaxation exercises, some participants (1 patient, 1 control) had difficulty concentrating on the exercises enough to perform them seriously. Others (2 patients, 2 controls) thought the exercises were very relaxing and would try them again. One control had difficulty
listening to the voice and concentrating on the exercise. About the video of the trauma professional, the participants’ comments were that the information was calming, soothing, clear and informative (4 patients, 5 controls), helpful for themselves (2 patients, 2 controls), or helpful for other patients (3 patients, 3 controls). The opinions of the participants about the videos of the patients were that they were interesting (2 controls), soothing (1 patient), diverse (1 control), and easy to relate to (2 controls). According to the participants, the video of the work-related accident provided helpful information about coping with the aftermath of injury both physically and psychologically (2 patients, 4 controls) and on how to regain their normal routine after an accident (1 patient and 2 controls). Three patients thought the information and the specific story of the video of the car accident was clear and insightful. The information in the video of the assault victim was easy to understand (2 patients, 2 controls), interesting (1 patient), and provided good tips for relaxation (2 controls). The tips summarized after the experiences of the patients were evaluated as calming and easy to understand and apply (3 patients, 5 controls). Two patients and 3 controls felt the tips were helpful and worth trying themselves, and 1 patient and 1 control already applied them in their own situation. At the end of the program, the participants rated the possibility of providing remarks and the contact information as useful and necessary (3 patients, 3 controls). Suggestions for improvement concerned resolving technical difficulties, such as automatically being logged out and having to log in again and re-answering all questions, and changing the questions of the pre- and post-intervention assessment.

4.4 DISCUSSION

In this article, we described the Trauma TIPS intervention. Based on well-established cognitive behavioral techniques, we designed an internet program for injured trauma victims with the aim of reducing acute hyperarousal and anxiety symptoms to prevent the development of PTSD on the long term. In order to evaluate its feasibility for further study and implementation and to ensure that the elements of the intervention did not cause or aggravate adverse psychological reactions, we conducted an initial pilot study. The results show that the internet-based intervention was feasible and acceptable and had no immediate adverse psychological reactions for the patients or the control subjects. The individual sections or steps in the program were generally evaluated as clear and useful. The participants showed satisfaction with the end product. The results also suggest some adjustments to the intervention that were implemented after the completion of the pilot study. For instance, most participants felt that the 20-item STAI, which we used to assess distress, was too long to complete twice immediately before and after the intervention. Therefore, we replaced the STAI as an online outcome measure with a more time-efficient instrument for assessing state anxiety, a single item Visual Analogue Scale (VAS), to place less demand on participants. With regard to the relaxation exercises, we chose
another voice-over that was more neutral to listeners, as some of the participants criticized the original voice. Lastly, all technical difficulties were addressed and eliminated to minimize any inconvenience for future participants.

Since the current study was carried out as a pilot feasibility study, there are a few important limitations. First, we included a small number of participants. Thus, at present no conclusions with respect to efficacy of the Trauma TIPS intervention may be drawn yet. In addition, we assessed symptoms of PTSD only up to one month after the trauma. Further assessments on later time points should be made to examine the long-term psychological effects of the intervention. Finally, the five trauma-exposed patients in this pilot exhibited low levels of anxiety and PTSD severity. The safety and efficacy of the Trauma TIPS in patients with higher levels of distress and arousal remains to be tested.

Currently, Trauma TIPS is under evaluation in a randomized controlled trial in 300 injured patients admitted to the Trauma Units of the Academic Medical Center and the Free University Medical Center in Amsterdam. In this trial, we compare effectiveness of Trauma TIPS to usual care prevents with respect to the prevention of (symptoms of) PTSD, anxiety and depression, and the reduction of health care costs. If the intervention indeed proves to be effective in preventing PTSD, it may be added to the standard care for trauma patients in Level I Trauma Centers and at emergency departments in peripheral hospitals. The e-mental health approach holds promise for the acute psychological care for trauma victims due to its low-threshold nature, easy application, possibilities for wide distribution, and low burden on financial and personnel costs.
Table 4.1. Individual and mean scores on state anxiety (STAI) at pre- and post-intervention of controls and patients, and on posttraumatic stress symptoms (IES-R) at baseline, 24 hrs post-intervention and 1 month post-trauma of patients.

<table>
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<th></th>
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<td>3</td>
<td>4</td>
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<tr>
<td>- Baseline</td>
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<td>8</td>
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STAI = State Trait Anxiety Inventory (Spielberger, 1983); IES-R = Impact of Event Scale-Revised (Weiss & Marmar, 1997) Note. Paired sample t-tests results: baseline-1 month: total IES-R: mean difference = 9.0, 95% CI: -10.7 to 28.7, $p = .19$; intrusion: mean difference = 7.3, 95% CI: -4.4 to 19.1, $p = .12$; hyperarousal: mean difference = 1.0, 95% CI: -11.4 to
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<td>52</td>
<td>29</td>
<td>30</td>
<td>37</td>
<td>39</td>
<td>37.4 (9.2)</td>
<td>37.0 [23]</td>
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<td>Post-intervention</td>
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<td></td>
<td>37.0 [23]</td>
<td>39</td>
<td>31</td>
<td>31</td>
<td>35</td>
<td>48</td>
<td>35.6 (14.9)</td>
<td>30.0 [37]</td>
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<td><strong>PTSD symptoms (IES-R)</strong></td>
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<tr>
<td>Avoidance</td>
<td>0.3 (4.7)</td>
<td>3.0 [3]</td>
<td>1.0 [11]</td>
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<tr>
<td>Hyperarousal</td>
<td>3.3 (2.2)</td>
<td>3.0 [5]</td>
<td>1.8 (1.0)</td>
<td>.0 (.0)</td>
<td>2.0 (4.0)</td>
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<tr>
<td>Total</td>
<td>9.8 (7.4)</td>
<td>9.0 [15]</td>
<td>.5 [8]</td>
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<td>24 hrs</td>
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<tr>
<td>Intrusion</td>
<td>6.0 (4.7)</td>
<td>1.0 [3]</td>
<td>1.0 [11]</td>
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<tr>
<td>Hyperarousal</td>
<td>3.0 (4.7)</td>
<td>.0 [1]</td>
<td>.0 [0]</td>
<td>.0 [8]</td>
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<tr>
<td>Total</td>
<td>3.3 (2.2)</td>
<td>1.0 [3]</td>
<td>1.0 [11]</td>
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<tr>
<td>Intrusion</td>
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<tr>
<td>Hyperarousal</td>
<td>3.0 (4.7)</td>
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<td>Total</td>
<td>9.8 (7.4)</td>
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<td>.5 [8]</td>
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13.4, \( p = .76 \); avoidance: mean difference = .7, 95% CI: -.8 to 2.1, \( p = .18 \); baseline-24 hrs post-intervention: intrusion: mean difference = 0.0; hyperarousal: mean difference = 1.5, 95% CI: -1.3 to 4.3, \( p = .12 \); 24 hrs post-intervention-1 month: intrusion: mean difference = 7.3, 95% CI: -4.4 to 19.1; hyperarousal: mean difference = -1.0, 95% CI: -14.1 to 12.1, \( p = .78 \).
CHAPTER 5: Design of a Randomized Controlled Trial of the Effectiveness of an Internet-Based Early Preventive Intervention for PTSD

ABSTRACT

Background:
Injured trauma victims are at risk of developing Posttraumatic Stress Disorder (PTSD) and other post-trauma psychopathology. So far, interventions using cognitive behavioural techniques (CBT) have proven most efficacious in treating early PTSD in highly symptomatic individuals. No early intervention for the prevention of PTSD for all victims has yet proven effective. In the acute psychosocial care for trauma victims, there is a clear need for easily applicable, accessible, cost-efficient early interventions.

Objective:
To describe the design of a randomised controlled trial (RCT) evaluating the effectiveness of a brief internet-based early intervention that incorporates CBT techniques with the aim of reducing acute psychological distress and preventing long-term PTSD symptoms in injured trauma victims.

Method:
In a two armed RCT, 300 injured trauma victims from two Level-1 trauma centers in Amsterdam, the Netherlands, will be assigned to an intervention or a control group. Inclusion criteria are: being 18 years of age or older, having experienced a traumatic event according to the diagnostic criteria of the DSM-IV and understanding the Dutch language. The intervention group will be given access to the intervention’s website (www.traumatips.nl), and are specifically requested to log-in within the first month post-injury. The primary clinical study outcome is PTSD symptom severity. Secondary outcomes include symptoms of depression and anxiety, quality of life, and social support. In addition, a cost-effectiveness analysis of the intervention will be performed. Data are collected at 1 week post-injury, prior to first log-in (baseline), and at 1, 3, 6 and 12 months. Analyses will be on an intention-to-treat basis.

Discussion:
The results will provide more insight into the effects of preventive interventions in general, and internet-based early interventions specifically, on acute stress reactions and PTSD, in an injured population, during the acute phase after trauma. We will discuss possible strengths and limitations.

Trial registration
Netherlands Trial Register NTR318
5.1 BACKGROUND

Victims of traumatic injury are prone to several psychiatric sequelae of their traumatic exposure. One to six months post-injury, reported rates of posttraumatic stress disorder (PTSD) vary from 17.5% to 42% (see O’Donnell et al., 2003, for a review). Comorbidity is very prevalent, with rates of major depressive disorder (MDD) up to 53%, rates of anxiety disorder other than PTSD of 25%, and rates of substance use disorder of 20% in injured patients with a PTSD diagnosis.

So far, interventions aiming for the prevention of post-trauma psychopathology have not proven effective. One of the most frequently applied early interventions in the last decades was the trauma-focused psychological Critical Incident Stress Debriefing or Management (CISD or CISM; (Mitchell, 1983). Research has shown that CISD is not efficacious in preventing PTSD, and can even increase the risk for PTSD symptoms (Rose, Bisson, Churchill, & Wessely, 2002); (Sijbrandij et al., 2006). It has been suggested that its emphasis on expressing emotions related to the trauma may exacerbate and sustain arousal, which may cause PTSD symptoms to escalate (Sijbrandij et al., 2006). Current PTSD guidelines advocate against the use of these trauma-focused early interventions for everyone involved in the traumatic event (Impact, 2007; National Institute for Clinical Excellence (NICE), 2005). Furthermore, in a recent Cochrane review, the authors found no convincing evidence that psychosocial interventions can prevent psychological, social or physical disability after traumatic injury (De Silva et al., 2009).

Early psychotherapeutic treatments based on trauma-focused cognitive behavioural therapy (TF-CBT) have consistently shown efficacy in the treatment of Acute Stress Disorder (ASD) and acute PTSD (see Roberts, Kitchiner, Kenardy, & Bisson, 2009, for a meta-analysis). TF-CBT techniques include psychoeducation about individual reactions to traumatic events, stress management techniques, in vivo and imaginal exposure, and cognitive restructuring. TF-CBT for ASD or acute PTSD is typically delivered after a minimum of 2 weeks post-injury and consists of 4 to 5 sessions. More recently, briefer versions of TF-CBT, aimed at the prevention of PTSD in less symptomatic individuals have been developed. A recent pilot feasibility study showed positive results in offering a single imaginal exposure therapy session to injured emergency department victims within 24 hours after trauma: compared to assessments only, patients in the intervention condition were rated lower on clinician-rated global severity of symptoms (Rothbaum et al., 2008). Techniques from CBT have also been successfully implemented in internet-based preventive interventions for depressive symptoms in adolescents (Van Voorhees et al., 2009), mood problems in the workplace (Billings, Cook, Hendrickson, & Dove, 2008), and for enhancing stress management and promoting healthy behaviours in college students (Chiauzzi, Brevard, Thum, Decembrele, & Lord, 2008).

Following large-scale, or even individual, traumatic incidents, adequate delivery of mental health services can be impeded by many practical and financial factors. Especially in considering preventive mental health strategies, there is only
a small time window and delivering the needed services to those affected can be
time consuming and costly. The internet may be a useful medium in delivering
early interventions to recently trauma-exposed populations. It is possible to use
the interactivity of the internet to tailor interventions to specific needs, and for users
to access them where-ever and whenever they please. With rapidly expanding
evidence, e-Mental Health interventions are considered a cost-effective alternative
for traditional face-to-face interventions (Kaltenthaler et al., 2006). Several internet-
based interventions have demonstrated feasibility (Litz, Williams, Wang, Bryant, &
Engel, 2004) and efficacy (Hirai & Clum, 2005; Lange et al., 2003) in the treatment
of chronic (symptoms of) PTSD. Yet, few studies have used the internet as a
medium for preventive interventions for PTSD. So far, only one pilot study of a
preventive internet-intervention that addresses mental health (among which PTSD)
and substance abuse in disaster populations is documented (Ruggiero et al., 2006).
Recently, the design and content of Afterdeployment.org, a web-based self-care
management programme for military personnel returning from Afghanistan and
their families, was published (Ruzek et al., 2011). Primarily meant to use parallel or
as an addition to psychological treatment, the programme could also be used in
an early post-trauma context to supplement face-to-face preventive help.

We created a brief, internet-based early intervention, named Trauma TIPS. The
intervention fits within a universal prevention strategy, aimed at an unselected
trauma-affected population (i.e., injured trauma victims). The main aim of Trauma
TIPS is to decrease acute levels of distress, anxiety and arousal, and thereby
preventing the development of PTSD symptoms, by offering information on
successful coping and instructions for self-exposure to fearful situations to prevent
avoidance behaviour and by providing stress management techniques to increase
self-control of acute arousal symptoms. Another key element of the intervention is
stimulating seeking social support. Below, we will describe these elements in more
detail.

Psychoeducation.

Information constitutes an important element in the Trauma TIPS intervention. In
many mental health interventions, patients are provided with psychoeducation to
increase their knowledge of their condition and change their attitudes and skills in
improving their health (Creamer & O’Donnell, 2008). Psychoeducation alone was
not found effective in preventing PTSD (see Wessely et al., 2008, for a review). To
explain this, it is suggested that only listing possible stress reactions after trauma
could sensitise victims. Psychoeducation should entail constructive information to
stimulate the expectancy of resilience and to promote help seeking (Wessely et
al., 2008). In the Trauma TIPS intervention, psychoeducation is conveyed through
patient models and in textual ‘tips’. The emphasis is on recovery, transferring
knowledge on successful coping and how to pick up normal routine, instead of
focusing on the traumatic event or symptoms. Information is also provided where
to seek contact if symptoms remain over the next weeks.
**In vivo exposure.**

With in vivo exposure, the individual exposes himself to a frightening stimulus to diminish the anxiety response and to counteract avoidance behaviour (Foa, Keane, Friedman, & Cohen, 2009). In vivo exposure has been thoroughly studied in the early treatment of injury victims with ASD and acute PTSD (Bisson et al., 2004; Bryant, Harvey, Dang, Sackville, & Basten, 1998; Bryant, Moulds, Guthrie, & Nixon, 2003; Bryant et al., 2005). In the Trauma TIPS intervention, tips for in vivo exposure exercises are presented in the videos: the patient models explain and show how they gradually encountered activities and situations that provoked anxiety, which decreased after a few times.

**Relaxation.**

Relaxation therapy is not regarded as an effective stand-alone treatment for PTSD, but is used as an anxiety-reducing technique within CBT treatments for ASD and PTSD to reduce and regain control over physical arousal and distress (Bisson et al., 2004; Bryant et al., 1998; Foa et al., 2009; Sijbrandij et al., 2007). In our intervention, instructions for stress management techniques (relaxation and breathing retraining exercises) are presented in two audio clips of approximately 7 minutes duration each: (a) “Muscle relaxation” focuses on progressive muscle relaxation through breathing retraining; b) “Safe place” is an exercise that focuses on decreasing stress or tension levels by imagining a safe and secure place while retraining breathing.

**Social support.**

Perceived lack of social support is a strong predictor for chronic PTSD (Brewin, Andrews, & Valentine, 2000; Ozer et al., 2003). Positive social support is also found to enhance psychosocial adjustment after trauma (see, among others, Forbes & Roger, 2011; King, King, Fairbank, Keane, & Adams, 1998). Promoting social support is an integral part of the Trauma TIPS intervention, both as textual coping advice (a ‘tips’ section) and shown by the patients models (i.e. when anxious or distressed, a patient model calls a friend). The intervention also features a forum for peer support which allows patients to write to communicate with other trauma survivors about their experiences.

In this paper, we describe the design of a RCT evaluating the effectiveness of our brief early intervention.
5.2 METHOD

5.2.1 Participants

Our study population will consist of patients receiving medical treatment for acute physical injuries at the Level-1 trauma centers of the Academic Medical Center (AMC) and Vrije Universiteit medical center (VUmc) hospitals in Amsterdam, the Netherlands. Inclusion criteria are: having sustained physical injuries from a traumatic event meeting the A1-Criterion of PTSD of the DSM-IV (American Psychiatric Association, 2000), aged 18 years of age or older, and mastery of the Dutch language. Exclusion criteria are: being injured due to deliberate self-harm, suffering from an organic brain condition, current psychotic symptoms or disorder, bipolar disorder or depression with psychotic features, moderate to severe traumatic brain injury (according to the Glasgow Coma Scale score of less than 13; Teasdale & Jennett, 1974), and permanently residing outside the Netherlands.

5.2.2 Study design

In our RCT, participants will be randomised to the Trauma TIPS intervention group or a control group without the intervention. Randomisation is on a 1:1 basis, stratified for center, using varying block sizes. The randomisation and allocation of patients is done by an independent research worker with no further role in the data collection process. The study protocol has been reviewed and approved by the Medical Ethics Committees of the AMC hospital (registration no. 05-054# 05.17.0504) and VUmc hospital (registration no. 06/039).

5.2.3 Intervention

The Trauma TIPS intervention is featured on an interactive website (www.traumatips.nl), created and owned by the authors from the Research Group Psychotrauma. The intervention consists of six steps (see Figure 5.1). Step 1, ‘Introduction and log-in’, highlights the goal of the programme and provides basic instructions. In step 2, patients rate their current levels of anxiety and arousal on two Visual Analogue Scales (VASs). The third step, ‘Trauma and Experiences’, shows videos of the surgical head of the trauma center, explaining the procedures at the center and the purpose of the programme, and of three patient models, who briefly tell about their experiences after their injury. Patients are free to watch any, every or no videos. At the end of this step, a short textual summary is provided of five tips for coping with common physical and psychological reactions after injury or trauma. The tips correspond to the information and instructions in the patient videos. Step
4 presents two audio clips with instructions for stress management techniques. Patients are free to perform the exercises at will. In step 5, patients again rate their anxiety and arousal on two VASs. At the end of the program (step 6), patients can give suggestions or remarks about the programme or contact the research team by email, and obtain regular contact information for assistance or professional help. Via a link to a moderated web forum, patients can share experiences for peer

Figure 5.1. Individual steps in the Trauma TIPS internet-intervention

INTRODUCTION

QUESTIONS 1

TRAUMA

TRAUMA UNIT (video): Professional explains procedures at the unit and the program

TRAUMA UNIT (video): 3 patients tell about coping with the aftermath of trauma

TIPS (text): A short summary of coping information from previous videos

EXERCISES

STRESS MANAGEMENT (audio): 2 stress management and relaxation exercises

QUESTIONS 2

END OF THE PROGRAM

- care options
- remarks section
- instructions for practice

Note. Figure previously published in Mouthaan et al. (2011), described in Chapter 4.
support. The total programme takes about 30 minutes to complete. Elaborate descriptions of the key principles and the design of the internet programme can be found elsewhere (Mouthaan et al., 2011; Mouthaan, Sijbrandij, & Olff, 2010; Sijbrandij, Mouthaan, & Olff, 2008).

The patients in the control condition are not offered access to the Trauma TIPS intervention, but are allowed standard care, as are all patients in the study. Standard care consists of incidental, non-protocolised talks with trauma center personnel or a patient’s general physician (GP). The frequency of these contacts and other professional care will be registered throughout the participation process.

5.2.4
Procedure

Adult injury patients are selected from the hospital registries and contacted in-hospital (when admitted) or via telephone (when discharged) within 72 hours post-injury to assess eligibility based on language skills and adverse medical or psychiatric conditions. After informed consent, a baseline assessment (T0) of clinically diagnosed and self-reported symptoms of PTSD, depression and anxiety, coping behavior, and social support takes place at ca. 1 week post-injury. At 1 month (T1), 3 months (T2), 6 months (T3) and 12 months (T4) post-injury, follow-up clinical and self-report assessments of current psychopathology are performed. Table 5.1 presents an overview of the instruments per assessment. All assessments take place at the outpatient clinic of the Center for Anxiety Disorders, AMC, at bedside (in case of hospital stay) or at the private home of the patient.

Patients allocated to the intervention group receive personal log-in codes to enter the intervention’s website, along with instructions to perform the intervention at will. To test a possible practical application of the intervention in a hospital environment, hospitalised patients and patients without access to the internet or a personal computer are visited by research assistants with a laptop. Because we aim at preventing (rather than treating) PTSD symptoms, patients are specifically instructed to log on within the first month after their injury. All interviewers will be qualified clinicians or Masters-level psychology students, trained by the research groups who developed the Dutch versions of the clinical interviews (i.e. M.I.N.I. and CAPS, see Assessments). Patients will be instructed to withhold information regarding their randomisation outcome from the interviewers to ensure blindness for condition. Any questions about the intervention or the randomisation process can be addressed to the independent researcher in charge of the randomisation. The independent researcher keeps track of the log-ins of the patients. Electronic and telephone reminders will be sent to encourage (early) log-in. Figure 5.2 shows the trial’s flow chart.
Figure 5.2. Trial flowchart of the participant flow for this trial.

1. **Recruitment**
2. **Screening for eligibility**
   - **Informed consent**
3. **Baseline assessment (T0)** at 1 wk. post-injury
4. **Randomization**
5. **Trial arm 1: Intervention group**
   - **Follow-up assessment (T1)** at 1 mo. post-injury
   - **Follow-up assessment (T2)** at 3 mo. post-injury
   - **Follow-up assessment (T3)** at 6 mo. post-injury
   - **Follow-up assessment (T4)** at 12 mo. post-injury
6. **Trial arm 2: Control group**
   - **Follow-up assessment (T1)** at 1 mo. post-injury
   - **Follow-up assessment (T2)** at 3 mo. post-injury
   - **Follow-up assessment (T3)** at 6 mo. post-injury
   - **Follow-up assessment (T4)** at 12 mo. post-injury
5.2.5
Assessments

Table 5.1 provides an overview of the instruments used at the individual assessments. We will describe the instruments in more detail below.

5.2.5.1
Clinical assessments

Demographic and trauma variables

Basic demographic and trauma-related information, i.e. age, sex, mechanism of injury, Injury Severity Score (ISS; Baker, O’Neill, Haddon, Jr., & Long, 1974) and Glasgow Coma Scale (GCS; Teasdale & Jennett, 1974), are obtained from the hospital registries during the initial selection of participants. Further data on demographics, such as education and marital status, and specifics of the traumatic event will be collected during the first contact with the patients. The ISS is an anatomical scoring system that provides an overall severity score for patients with multiple injuries. The ISS index ranges from 0 (no injury) to 75 (unsurvivable injury) with a score of 16 and higher indicating severe injury (Copes et al., 1990). The Glasgow Coma Scale (GCS) is a neurological scale to record level of consciousness and consists of three parameters: Best Eye Response (four grades), Best Verbal Response (five grades), Best Motor Response (six grades). Resulting scores are between 3 (deep unconsciousness) and 15 (fully conscious). In general, brain injury is classified as: Severe (GCS ≤ 8), Moderate (GCS 9-12) and Mild (GCS 13-15; Teasdale & Jennett, 1974).

Clinician Administered PTSD Scale

The Clinician Administered PTSD Scale counts as the golden standard to establish a PTSD diagnosis (CAPS; Blake et al., 1995). It is a 30-item structured interview that corresponds to the DSM-IV criteria for PTSD. The CAPS can be used to make a current or lifetime diagnosis or to assess symptoms over the past week. By adding frequency and intensity (both ranging from 0 to 4) of intrusion, avoidance and hyperarousal symptoms, the symptom severity or diagnosis of PTSD as a whole can be determined. The internal consistency of the scales in the Dutch translation of the CAPS is good to excellent; with alpha’s of .63 for re-experiencing, .78 for avoiding and numbing, .79 for hyperarousal and .89 for all 17 core PTSD symptoms (Hovens et al., 1994).
The M.I.N.I. International Neuropsychiatric Interview-Plus (M.I.N.I.-Plus version 5.0; (Sheehan et al., 1998) is used to diagnose mood disorders (i.e., major depressive episode, (hypo-)manic episode), anxiety disorders (i.e., panic disorder, social phobia, generalized anxiety disorder), alcohol and other substance abuse and psychotic disorders. Each module starts with screening questions which, if positive, lead to further examination of the criteria for a specific diagnosis. For purposes of this study, a module on ASD was created by authors JM and MS, based on DSM-IV diagnostic criteria. The M.I.N.I.-Plus has reasonable to good interrater reliability (Cohen’s kappa = .43 for current drug dependence to .84 for major depressive episode) and reasonable to very good concurrent validity with the SCID-P (Cohen’s kappa = .43 for current drug dependence to .90 for major anorexia; (Sheehan et al., 1998). Research on the validation of the Dutch translation of the M.I.N.I.-Plus is currently being performed (van Vliet & de Beurs, 2007).

5.2.5.2
Self-report measures

Impact of Event Scale-Revised

The Impact of Event Scale-Revised (IES-R; Weiss & Marmar, 1997) is a 22-item questionnaire that assesses the severity of PTSD symptoms of intrusion (eight items), avoidance (eight items), and hyperarousal (six items). Items are scored on a 5-point scale, from 0 (not at all) to 4 (extremely), corresponding to how distressing each item has been in the past week. Total scores range from 0 to 88 with higher scores representing more severe symptoms. The subscales were found to have a high degree of intercorrelation (r’s = .52-.87) and high internal consistency (Intrusion: Cronbach’s alpha = .87-.94; Avoidance: Cronbach’s alpha = .84-.87; Hyperarousal: Cronbach’s alpha = .79-.91; Creamer et al., 2003; Weiss & Marmar, 1997). The validation of the Dutch version of the IES-R is currently in preparation for publication (Mouthaan, Sijbrandij, & Olff, 2011).

Hospital Anxiety and Depression Scale

The severity of depressive and anxiety symptoms is assessed using the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). The items in the two subscales depression (7 items) and anxiety (7 items) are scored on a 4-point scale from 0 to 3. Total scores per subscale range from 0 to 21, with higher scores indicating greater symptomatology. The test-retest reliability of the two scales is high (Pearson’s r’s = .86 and .91; Spinhoven et al., 1997).
**Quality of life and functional status**

Quality of life and functional status will be assessed using the World Health Organisation Quality of Life-Abbreviated scale (WHOQOL-Bref; WHOQOL GROUP, 1998) and the Euroqol 6-Dimensions (EQ-6D; Hoeymans, van Lindert, & Westert, 2005). The WHOQOL-Bref is a 26-item questionnaire measuring quality of life on four domains: physical health (seven items), psychological health (six items), social relationships (three items) and environment (eight items). Items are scored on 5-point scales from 1 (worse outcome) to 5 (best outcome). Total scores range from 4 to 20 with higher scores indicating better quality of life. The EQ-6D is based on the earlier EQ-5D (Brooks, 1996), a generic measure of health status that provides a simple descriptive profile. The original EQ-5D dimensions of mobility, self-care, usual activities, pain/discomfort and anxiety/depression are supplemented by a dimension on cognitive functioning (memory, concentration, coherence, IQ). All dimensions are single items with three possible answers. The EQ-5D provides an index value for health states. It is a valid and frequently used instrument for assessing generic quality of life and health status (Dolan, 1997).

**Coping**

The Dutch questionnaire ‘Utrechtse Coping Lijst’ (UCL; Schreurs & van de Willige, 1988) assesses coping behaviour when confronted with problems or demanding events. It has 47 items in seven scales: active approach (seven items), palliative reaction (eight items), avoidance (eight items), seeking social support (six items), passive reaction pattern (seven items), expression of emotions (three items) and reassuring thoughts (five items). All items are rated on 4-point scales from 1 (seldom or never) to 4 (very often). High scores correspond with making use of the concerning coping styles. The internal consistencies of the scales are good, with Cronbach’s alpha’s from 0.64 to 0.82 (Schreurs & van de Willige, 1988).

**Social support**

Social support is measured using the Dutch questionnaire ‘Sociale Steun Lijst – Discrepancies’ (SSL-d; van Sonderen, 2011). It assesses satisfaction with received social support, more specific the extent to which the received support equals the needs of the individual. The SSL-d features 34 items in six subscales: everyday emotional interactions (four items), emotional support during problems (eight items), appreciation support (six items), instrumental interactions (seven items), social companionship (five items) and informative support (four items). Answers range from 1 (would like it to happen more often) to 4 (happens too often, would like less). Items are summed for total scale scores (range 0-136), with high scores corresponding to more satisfaction with experienced social support. The reliability of the scales is good (Cronbach’s alpha’s: 0.83-0.96; van Sonderen, 2011).
Costs associated with psychiatric illness

The TiC-P (Trimbos/IMTA questionnaire for Costs associated with Psychiatric illness; Hakkaart-van Roijen, van Straten, Donker, & Tiemens, 2002) is administered to compare direct and indirect costs of possible psychopathology between groups. Direct costs are measured by assessing the frequency of contacts with mental health care professionals (i.e., GP, psychologist, social worker). Medication and hospital or clinic admissions for mental health problems are also part of direct costs. Indirect costs are calculated as production losses due to the effects of psychological problems by the Short Form Health and Labour Questionnaire (SF-HLQ; van Roijen, Essink-Bot, Koopmanschap, Bonsel, & Rutten, 1996), which includes absence from paid work, production losses without absence from paid work and hindrance in paid and unpaid work.

5.2.5.3
Online assessments

Pre- and post-intervention anxiety and arousal

Anxiety and arousal during the intervention are assessed using two pre- and two post-intervention VASs featured in the intervention (see subparagraph Intervention). Patients in the intervention condition are asked to indicate their current levels of anxiety and arousal from 0 (no anxiety or arousal) to 100 (worst anxiety or arousal).

Web-related behaviour

Every step or click made in the intervention is automatically logged for the purpose of evaluating the influence of web-related behaviour on the effectiveness of the programme. Besides the number of logins, we also register the total time logged in, and the number of times and total time spent on the videos and the exercises.

5.2.6
Sample size

The main outcome measure to assess the intervention’s effectiveness in preventing PTSD symptoms is the difference in the total CAPS score between the intervention and control condition at 12 months post-injury. We expect to find a small to medium effect size of Cohen’s $d = .35$, which is equivalent to a difference of 5.5 points on the CAPS. To demonstrate this difference, we require a total of 134 patients or more in each group (alpha=5%, power=80%). This calculation is based on a standard
deviation of 16 for CAPS scores, derived from a published study using the CAPS as a continuous outcome in a similar research population (Conlon, Fahy, & Conroy, 1999). Anticipating possible attrition of study participants, we aim for 150 patients in each group.

5.2.7
Data analysis

Descriptive statistics will be used to describe and examine differences in demographic, trauma-related and baseline clinical characteristics between the two intervention arms. The main analysis to assess the intervention’s effectiveness on preventing PTSD is the difference in CAPS scores between the two arms of the trial. Differences in scores at twelve months will be compared using an analysis of covariance with the baseline assessment as a covariate. In addition, a repeated measurement analysis will be performed in which the CAPS scores at 1, 3 and 6 months will be included to describe trends over time. All analyses will be on an intention-to-treat basis. Results are expressed as differences in scores between the two arms together with 95% confidence intervals. Reductions on the VASs are measured by scoring the differences on arousal and anxiety prior to and after the intervention (VAS scores before – VAS scores after). All analyses will be performed using SPSS 18.0.

5.3 DISCUSSION

This RCT represents a unique study of an internet-based early intervention aimed at reducing acute distress levels and preventing the development of PTSD symptoms. We expect that it will generate new scientific information on the effectiveness of preventive interventions in general, internet-based interventions and CBT techniques specifically, in the acute phase following trauma, targeted at a trauma-affected sample with varying levels of injury.

From a practical standpoint, several possible limitations may affect the trial. Patients can encounter technical difficulties in performing the internet-intervention. We anticipated for these difficulties by pilot testing the functionality of the program and its individual steps (Mouthaan et al., 2011). At the end of the intervention, patients can (electronically or otherwise) contact the research team about the content or working of the programme. The research team will also hold weekly updates of the functionality of the programme, to ensure that any problems with the website are resolved quickly. Another problem may be the accessibility of our web-programme. An unknown proportion of patients do not own a personal computer with private
access to the internet. These patients will be visited by a research assistant to perform the intervention on a laptop. Finally, some patients will not be capable to perform the intervention, such as patients with insufficient understanding of the Dutch language, patients with little computer skills, or patients who are physically unable to perform a computerized intervention (e.g., severely injured Intensive Care patients).

As a result of the information and advice provided in the intervention, it is possible that patients in the intervention condition will actually show more use of mental health care for psychological symptoms after their injury than control patients. It could also be that the intervention increases awareness of psychological well-being after trauma, which could possibly result in higher symptomatology within the intervention group. Although our pilot results indicated that the intervention did not aggravate acute anxiety or stress symptoms in recently injured trauma victims (Mouthaan et al., 2011), the RCT will show us the longer term effects.

A particular strength of the trial is that it is embedded within a larger ongoing prospective cohort study (Trauma TIPS) which started in 2005 with the general aim to study the incidence and prediction of psychiatric symptoms in 2,000 injured trauma victims. Advantageously, many of the practical necessities are already arranged, such as having trained staff for the inclusion of research participants and for performing the assessments. In addition, we are better able to realistically predict the rate of inclusion and the amount of time needed. A steady 15 patients per center per month are included in the prospective trial. Because in the RCT patients have to be open to randomization to either the intervention or the control group and be able to participate within the first month after trauma, we expect to realistically include 10 patients per center per month, with a total inclusion time of 15 months.

If the intervention proves effective in counteracting early distress symptoms and consequently preventing PTSD, it may be implemented in the standard care for trauma patients in Level-1 trauma centers and at emergency departments. In addition, the general public will be informed about the availability of the intervention via posters and leaflets in hospital casualty and emergency departments and in GP waiting rooms and possibly via the media or cross-links on other relevant websites. Further, it might be worthwhile to adapt the intervention to other trauma populations, especially considering the current lack of effective interventions available for all trauma survivors irrespective of their symptom levels. The low-threshold nature, easy application, possibilities for wide distribution, and low burden on financial and personnel costs make e-Mental Health solutions promising for the acute psychosocial care for trauma victims. We expect the results of the RCT at the end of 2011.
<table>
<thead>
<tr>
<th>Clinical instruments</th>
<th>Hospital Admission Follow-up</th>
<th>1-Month Follow-up</th>
<th>3-Month Follow-up</th>
<th>6-Month Follow-up</th>
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<tr>
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<tr>
<td>M.I.N.I.-Plus</td>
<td>-</td>
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<td>ISS</td>
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<th>Self-report instruments</th>
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<tr>
<td>IES-R</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<td>SSL-d</td>
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<td>-</td>
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<td>-</td>
</tr>
<tr>
<td>TiC-P</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>X</td>
</tr>
</tbody>
</table>

N.B.: CAPS = Clinician Administered Posttraumatic Stress Disorder Scale (Blake et al., 1995); M.I.N.I.-Plus = M.I.N.I. International Neuropsychiatric Interview-Plus (Sheehan et al., 1998); ISS = Injury Severity Score (Baker et al., 1974); GCS = Glasgow Coma Scale score (Teasdale & Jennett, 1974); IES-R = Impact of Event Scale-Revised (Weiss & Marmar, 1997); HADS = Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983); WHOQOL-Bref = World Health Organisation Quality of Life-Abbreviated scale (WHOQOL GROUP, 1998); EQ-6D = Euroqol 6-Dimensions (Hoeymans et al., 2005); UCL = Utrechtse Coping Lijst (Schreurs & van de Willige, 1988); SSL-d = Sociale Steun Lijst- Discrepancies (van Sonderen, 2011); TiC-P = Trimbos/IMTA questionnaire for Costs associated with Psychiatric illness (Hakkaart-van Roijen et al., 2002).
CHAPTER 6: Internet-Based Early Intervention to Prevent Posttraumatic Stress Disorder in Injury Patients: Randomized Controlled Trial

ABSTRACT

Background:
Posttraumatic stress disorder (PTSD) develops in 10-20% of injury patients. We developed a novel, self-guided Internet-based intervention (called Trauma TIPS) based on techniques from cognitive behavioral therapy (CBT) to prevent the onset of PTSD symptoms.

Objective:
To determine whether Trauma TIPS is effective in preventing the onset of PTSD symptoms in injury patients.

Method:
Adult, level 1 trauma center patients were randomly assigned to receive the fully automated Trauma TIPS Internet intervention ($n = 151$) or to receive no early intervention ($n = 149$). Trauma TIPS consisted of psychoeducation, in vivo exposure, and stress management techniques. Both groups were free to use care as usual (nonprotocolized talks with hospital staff). PTSD symptom severity was assessed at 1, 3, 6, and 12 months post injury with a clinical interview (Clinician-Administered PTSD Scale) by blinded trained interviewers and self-report instrument (Impact of Event Scale-Revised). Secondary outcomes were acute anxiety and arousal (assessed online), self-reported depressive and anxiety symptoms (Hospital Anxiety and Depression Scale), and mental health care utilization. Intervention usage was documented.

Results:
The mean number of intervention logins was 1.7: SD 2.5, median (MDN) 1, inter quartile range (IQR)=1-2. Thirty-four patients in the intervention group did not log in (22.5%), 63 (41.7%) logged in once, and 54 (35.8%) logged in multiple times (Mean 3.6, SD 3.5, Mdn 3, IQR=2-4). On clinician-assessed and self-reported PTSD symptoms, both the intervention and control group showed a significant decrease over time ($P<.001$) without significant differences in trend. PTSD at 12 months was diagnosed in 4.7% of controls and 4.4% of intervention group patients. There were no group differences on anxiety or depressive symptoms over time. Post hoc analyses using latent growth mixture modeling showed a significant decrease in PTSD symptoms in a subgroup of patients with severe initial symptoms ($n = 20$) ($P<.001$).
Conclusions:
Our results do not support the efficacy of the Trauma TIPS Internet-based early intervention in the prevention of PTSD symptoms for an unselected population of injury patients. Moreover, uptake was relatively low since one-fifth of individuals did not log in to the intervention. Future research should therefore focus on innovative strategies to increase intervention usage, for example, adding gameplay, embedding it in a blended care context, and targeting high-risk individuals who are more likely to benefit from the intervention.


6.1 INTRODUCTION

Posttraumatic stress disorder (PTSD) develops after trauma exposure, such as violence, disasters, and injury (O’Donnell et al., 2004; Rees et al., 2011). PTSD’s lifetime prevalence in adults is 7-8% (de Vries & Olff, 2009; Kessler, Chiu, Demler, Merikangas, & Walters, 2005), whereas the conditional prevalence rate after exposure to violence or injury ranges from 10-56% (Bryant et al., 2010; de Vries & Olff, 2009; Rees et al., 2011). PTSD symptoms include intrusions of the traumatic event, avoidance of stimuli related to the event, emotional numbness, and hyperarousal (American Psychiatric Association, 2000). Until now, efforts to prevent PTSD onset, for example, psychological debriefing, have been unsuccessful (De Silva et al., 2009; Rose et al., 2003). Early treatment of PTSD, or its precursor Acute Stress Disorder, with 4-5 sessions of trauma-focused cognitive behavioral therapy (CBT) was found to be efficacious in preventing chronic PTSD (Roberts et al., 2009). CBT consists of imaginal exposure to the traumatic incident, aimed at extinction of the original fear associations (Foa & Kozak, 1986), and stress-management techniques and cognitive restructuring to correct irrational beliefs (Foa, Riggs, & Gershuny, 1995). A recent randomized controlled trial found evidence for the effectiveness of 3 sessions of prolonged (imaginal) exposure, starting within 12 hours of the traumatic event, in counteracting later symptoms of PTSD and depression (Rothbaum et al., 2012). It is yet unclear whether CBT-techniques administered as a single session early intervention are efficacious in preventing PTSD.

We developed Trauma TIPS, a brief self-guided Internet intervention based on established CBT techniques. Trauma TIPS aims to decrease acute levels of
distress, anxiety, and arousal, known to predict PTSD (Sijbrandij et al., 2006), and to prevent the onset of PTSD symptoms by providing information on successful coping, instructions for self-exposure to fearful situations, and stress management techniques. The exponential growth of global Internet use contributes to the feasibility of e-mental health interventions, which are considered a cost-effective alternative to traditional interventions (Kaltenthaler et al., 2006). Although both self-guided and therapist-assisted Internet-based CBT programs have been successful in the treatment of PTSD (Andrews, Cuijpers, Craske, McEvoy, & Titov, 2010), there is a great lack of study into whether these programs may prevent PTSD. Preliminary evidence from one previous study on the efficacy of a self-guided Internet-based psychoeducational program for injured children and their parents showed greater anxiety reductions in children who had completed the program compared to those who had not (Cox et al., 2010).

Our study examined whether Trauma TIPS prevents the onset of PTSD symptoms in injury patients compared to care as usual. In addition, we evaluated whether Trauma TIPS prevented symptoms of depression and anxiety and led to a decrease in mental health care utilization during the first year after injury.


6.2 METHODS

6.2.1 Trial Design

This study was an assessor-blinded randomized controlled trial (RCT) comparing a brief Internet-based early psychological intervention with a care-as-usual control group in 2 trauma centers (see Multimedia Appendix 1 for the CONSORT E-HEALTH Checklist of the trial).

6.2.2 Participants

Injury patients transported by ambulance or helicopter to the level 1 trauma centers of the Academic Medical Center (AMC) and VU University Medical Center (VUmc) in Amsterdam, the Netherlands, were eligible for inclusion. These patients were suspected to suffer from possible severe injuries that required specialized acute medical care. Inclusion criteria were age 18 years or older, proficiency in Dutch, and having experienced a potential traumatic event (cf. Criterion A1 DSM-IV PTSD diagnosis; American Psychiatric Association, 2000). According to this criterion, the person has experienced, witnessed, or been confronted with an event or events that involve actual or threatened death or serious injury, or a threat to the physical integrity of oneself or others. Exclusion criteria were the injury resulted from deliberate self-harm (organic brain condition, psychotic disorder, bipolar disorder, or depression with psychotic features; cf. DSM-IV; American Psychiatric Association, 2000); moderate to severe traumatic brain injury (TBI) (according to a Glasgow Coma Score (GCS) (Teasdale & Jennett, 1974) less than 13); and permanent residency outside the Netherlands.

6.2.3 Interventions

Trauma TIPS (www.traumatips.nl, archived by WebCite® at http://www.webcitation.org/6FeK0io9X) (for screenshots see Multimedia Appendices 2 and 3) was created and is owned by the authors from the Research Group Psychotrauma (Mouthaan et al., 2011). It is based on CBT techniques of psychoeducation, stress management/relaxation techniques, and in vivo exposure. It consists of 6 steps, including: introduction to the program and basic operating instructions; assessments of acute anxiety and arousal using Visual Analogue Scales (VASs) at pre- and postintervention; video features of the trauma center’s surgical head explaining the procedures at the center and the purpose of the program, and of 3
patient models sharing their experiences after their injury; a short textual summary of 5 coping tips for common physical and psychological reactions after trauma; audio clips with instructions for stress management techniques; contact information for program assistance or professional help for enduring symptoms; and a Web forum for peer support. The introduction page shows the logos of the academic hospitals involved in the study, as well as the logos of the funders of the study. The full design and content of the intervention are described elsewhere (Mouthaan et al., 2011; Mouthaan et al., 2011). Total duration of the program was approximately 30 minutes. Care as usual, available to patients from both groups, consisted of incidental, nonstructured talks with trauma center staff or with a patient’s general practitioner (GP), either directly following injury or during the course of the trial.

6.2.4 Study Procedures

The local institutional review boards provided medical ethical approval. Patients were contacted in hospital or via telephone within 72 hours post injury to assess eligibility and to schedule a baseline assessment. Informed consent was obtained face-to-face directly prior to the baseline assessment at approximately 1 week post injury. Patients were randomly allocated to (1) the Trauma TIPS intervention or (2) a control group with no intervention, but access to care as usual. Randomization was performed by a research member independent of data collection in a 1:1 ratio by a computerized program, TENALEA Clinical Trial Data Management System (NKI/AVL Biometrics department, Amsterdam), using random block sizes (with maximum block size 6), stratified by study center. Intervention group patients received personal log-in codes for the intervention’s website, along with instructions to perform the intervention at will, but at least once within the first month. Electronic and telephone reminders were sent to encourage (early) log-in, but patients were free to access the intervention as they pleased, to underscore the intervention’s voluntary nature and self-guiding principles. Research assistants visited patients with a laptop in case of hospitalization or a lack of Internet or computer access. Follow-up assessments were scheduled at 1, 3, 6, and 12 months post injury. The assessments took place at the AMC’s Center for Anxiety Disorders, at bedside in the hospital or at the private home of the patient. Patients were asked not to share information about the randomization to the assessors, to ensure that they were blind to the allocated interventions. No reimbursement was given.
6.2.5

Outcomes

Trained assessors at the master’s and doctoral levels performed the data collection. The main outcome measure was PTSD symptom severity on the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995). The structured interview assesses the frequency and intensity (ranging from 0-4) of the 17 DSM IV symptoms of PTSD (total scores range from 0-136). Scores are added to represent PTSD symptom severity or a diagnosis. The internal consistency of the Dutch translation of the CAPS is good to excellent (Hovens et al., 1994). Presence of a PTSD diagnosis was computed using the established rule of Weathers et al. (1999).

The Mini International Neuropsychiatric Interview (MINI-Plus, version 5.0; Sheehan et al., 1998), a semistructured clinical interview, was used to obtain DSM IV diagnoses of major depressive disorders (MDD) and anxiety disorders other than PTSD. Each module starts with screening questions, which, if positive, lead to a further examination of the disorder’s criteria.

We assessed self-reported PTSD severity with the Impact of Events Scale-Revised (IES-R; Weiss & Marmar, 1997). The 22 items are scored on a 5-point scale, from 0 (not at all) to 4 (extremely). Total scores range from 0-88 with higher scores representing more severe symptoms. The IES-R shows high internal consistency (Creamer et al., 2003; Weiss & Marmar, 1997).

Self-reported severity of depressive and anxiety symptoms was assessed using the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). The item scores in the 2 subscales depression (7 items) and anxiety (7 items) range from 0-3 (total scores per subscale ranging from 0-21). Higher scores indicate greater symptomatology. The test-retest reliability of the 2 scales is high (Spinhoven et al., 1997).

The Trimbos/iMTA questionnaire for Costs associated with Psychiatric illness (TiC-P; Hakkaart-van Roijen et al., 2002) was used to evaluate direct and indirect health costs. Direct costs include contacts with mental health professionals (eg, GP, psychologist, social worker), medication use, and admissions for mental health problems. Indirect costs were calculated as production losses due to psychological problems by the Short Form Health and Labour Questionnaire (SF-HLQ; van Roijen et al., 1996).

At the beginning and after completion of Trauma TIPS, patients indicated acute anxiety and arousal levels from 0 (no anxiety or arousal) to 100 (worst anxiety or arousal) on 2 online VASs (Mouthaan et al., 2011; Mouthaan et al., 2011).

Website activity was recorded to evaluate usage characteristics, such as number of log-ins and total amount of login time.
6.2.6
Sample Size

To demonstrate a difference of at least 5.5 points on the CAPS between the groups at 12 months, equivalent to a small to medium effect size of Cohen’s $d=.35$, 134 patients or more per condition were required (Cronbach’s $\alpha=.05$, power=80%, SD 16; Conlon et al., 1999). Anticipating possible attrition of study participants, we included 150 patients per condition.

6.2.7
Analyses

Differences in baseline characteristics between the study groups, patients lost to follow-up vs patients not lost to follow-up and patient groups with varying intervention usage were tested using independent sample t-tests and Chi-square tests (Bonferroni adjusted $P$ value=.005). Missing data were imputed using general purpose multivariate imputation procedure (ICE: sequential regression imputation method), creating 50 different datasets. All analyses were performed using these 50 datasets and then pooled by combining the individual results. Due to their positive skewness, CAPS and IES-R values were square root transformed. Stata version 11.2 was used for all repeated measures analyses of PTSD symptoms (CAPS, IES-R) and depressive and anxiety symptoms (HADS-A, HADS-D). The effects of time of measurement, group, and the group-by-time interaction were analyzed with linear mixed models. For all regression models, a robust variance estimator was used. Estimated values (adjusted) and 95% confidence intervals (CIs) are presented throughout the paper unless otherwise specified. Finally, as a post hoc analysis, we applied latent growth mixture modelling (LGMM) (Muthén & Muthén, 2010; Preacher, Wichman, MacCallum, & Briggs, 2008) to explore possible latent subgroups within the 2 groups by use of the software Mplus (Version 6.11) (Muthen & Muthen, 2000) using a Bayesian estimator (Elliott, Gallo, Ten Have, Bogner, & Katz, 2005; Lynch, 2007). Across all analyses, two-tailed tests are reported with Cronbach’s $\alpha=.05$. 
Table 6.1. Participant characteristics at baseline.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Internet intervention $n = 151$</th>
<th>Control with usual care $n = 149$</th>
<th>$P$-value$^a$</th>
</tr>
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<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>44.18 (15.76)</td>
<td>43.49 (16.00)</td>
<td>.54</td>
</tr>
<tr>
<td>Sex (male), n (%)</td>
<td>89 (58.9)</td>
<td>91 (61.1)</td>
<td>.73</td>
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<td>Post-high school education, n (%)</td>
<td>37 (24.7)</td>
<td>43 (29.1)</td>
<td>.71</td>
</tr>
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<td>Unemployed, n (%)</td>
<td>41 (27.5)</td>
<td>29 (19.5)</td>
<td>.13</td>
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<tr>
<td>Married/ cohabitating, n (%)</td>
<td>82 (54.3)</td>
<td>81 (54.4)</td>
<td>.54</td>
</tr>
<tr>
<td>Dutch cultural background, n (%)</td>
<td>127 (84.1)</td>
<td>122 (83.0)</td>
<td>.88</td>
</tr>
<tr>
<td>Prior traumatic event, mean (SD)</td>
<td>2.99 (2.42)</td>
<td>2.93 (2.20)</td>
<td>.80</td>
</tr>
<tr>
<td>Hospital admission, n (%)</td>
<td>100 (66.7)</td>
<td>105 (70.9)</td>
<td>.46</td>
</tr>
<tr>
<td>Days hospitalized, mean (SD)</td>
<td>5.30 (8.02)</td>
<td>4.57 (7.36)</td>
<td>.20</td>
</tr>
<tr>
<td>ICU admission, n (%)</td>
<td>13 (8.7)</td>
<td>13 (8.8)</td>
<td>.97</td>
</tr>
<tr>
<td>Injury Severity Score, mean (SD)</td>
<td>10.45 (8.59)</td>
<td>10.21 (9.87)</td>
<td>.33</td>
</tr>
<tr>
<td>Glasgow Coma Scale, mean (SD)</td>
<td>14.48 (1.91)</td>
<td>14.72 (1.42)</td>
<td>.08</td>
</tr>
<tr>
<td>Traumatic event, n (%)</td>
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<td>.11</td>
</tr>
<tr>
<td>Traffic accident</td>
<td>99 (65.6)</td>
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<td>Work-related accident</td>
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<tr>
<td>Fall</td>
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<td>Other</td>
<td>10 (6.6)</td>
<td>10 (6.7)</td>
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<td>Psychological assessment tools, mean (SD)</td>
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<tr>
<td>Impact of Event Scale-Revised</td>
<td>17.60 (16.82)</td>
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<tr>
<td>Hospital Anxiety and Depression Scale-Depression</td>
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<tr>
<td>Hospital Anxiety and Depression Scale-Anxiety</td>
<td>4.36 (3.90)</td>
<td>4.87 (4.33)</td>
<td>.21</td>
</tr>
</tbody>
</table>

$^a$ Independent $t$ test for difference between groups for continuous measures and Chi-square test for differences between groups in categorical characteristics.
6.3 RESULTS

6.3.1 Baseline Characteristics

Recruitment and follow-up took place from September 2007 to June 2010. Figure 6.1 shows the flow of patients through the trial. Participants were significantly older (mean age 43.8, SD 15.9) than patients who refused participation (mean age 40.1, SD 16.3, $P=.01$). Table 6.1 shows the baseline characteristics of participants. There were no differences in baseline characteristics or attrition rate between the study groups. Patients lost to the 12-month follow-up were more often unmarried than patients who were not lost to follow-up ($P=.001$).
Figure 6.1. Flow of participants through the trial

Randomized ($n = 300$)

Assigned to Receive Intervention ($n = 151$)
- Logged Into the Program as Assigned ($n = 117$)
- Did Not Log Into the Program ($n = 34$)

Assigned to Control Condition ($n = 149$)
- Received Intervention as Assigned ($n = 149$)

1-mo Assessment
- Assessed ($n = 115$)
- Unable to Attend Current Assessment ($n = 12$)
- Could not be located ($n = 9$)
- Refused Assessment ($n = 13$)

3-mo Assessment
- Assessed ($n = 91$)
- Unable to Attend Current Assessment ($n = 19$)
- Could not be located ($n = 16$)
- Cumulative Refused Assessment ($n = 23$)

6-mo Assessment
- Assessed ($n = 72$)
- Unable to Attend Current Assessment ($n = 27$)
- Could not be located ($n = 26$)
- Cumulative Refused Assessment ($n = 24$)

12-mo Assessment
- Assessed ($n = 69$)
- Could not be located ($n = 53$)
- Cumulative Refused Assessment ($n = 27$)

Included in Primary Analysis ($n = 151$)

Included in Primary Analysis ($n = 149$)
6.3.2

**Intervention Usage**

Most intervention group patients logged in on the intervention’s website once \( (n = 63, 41.7\%) \). Fifty-four patients (35.8%) logged in multiple times (mean 3.6, SD 3.5, Median 3, IQR=2-4). Thirty-four patients (22.5%) did not log in (ie, nonusers) and provided the following reasons: not interested anymore (2), occupied with rehabilitation (1), too busy (1), on holiday (1), too much on my mind (1), tired (1), difficulty concentrating (1), postconcussion symptoms (1), broken back (1), husband deceased (1), or no explanation (22). The average number of log-ins for the entire group was 1.7 (SD 2.5). The average login time was 20.8 minutes (SD 26.3). There were no differences in attrition or outcome measures between nonusers \( (n = 34) \) and users of the intervention \( (n = 117) \), or between patients with a single log-in \( (n = 63) \) versus multiple log-ins \( (n = 54) \). The only differences were that more nonusers than users had a nonDutch cultural background \( (P = .003) \) and that patients with multiple log-ins were significantly older (mean age 48.0, SD 14.6) than those with a single log-in (mean age 39.6, SD 14.1, \( P = .001 \)).

From pre- to postintervention, the majority of intervention group patients reported no change in acute anxiety (55.9%, \( n = 38 \)) and arousal (63.2%, \( n = 43 \)) on the VASs. Seven patients reported an increase (10.3%), and 23 (33.8%) and 18 (26.5%) patients reported a reduction in anxiety and arousal respectively.

6.3.3

**Main Outcomes**

Table 6.2 shows the results of the intention-to-treat analyses for PTSD, anxiety, and depressive symptoms. Mixed-model analysis of PTSD symptom severity of the CAPS showed a significant effect of time \( (P<.001) \), but no significant group differences over time (12-month follow-up, Internet intervention group: estimated means 13.0, 95% CI 11.2 - 14.8; control group: estimated means 13.0, 95% CI 11.4 - 14.6, \( P=.63 \)). On the mixed-model analysis of self-reported PTSD symptoms (IES-R), we found a similar significant time effect \( (P<.001) \) and no group differences over time (12-month follow-up, Internet intervention group: estimated means 7.6, 95% CI 6.4 - 8.7; control group: estimated means 7.8, 95% CI 6.4 - 9.2, \( P=.76 \)). Figure 6.2 presents the estimated CAPS and IES-R means over time. For depressive and anxiety symptoms, we found no effects of time or group over time in mixed-model analyses (12 month HADS-D, Internet intervention group: estimated means 3.3, 95% CI 2.4 - 4.2; control group: estimated means 3.0, 95% CI 2.2 - 3.7, \( P=.72 \); 12 month HADS-A, Internet intervention group: estimated means 4.1, 95% CI 3.5 - 4.8; control group: estimated means 3.7, 95% CI 3.0 - 4.3, \( P=.53 \)).

PTSD was diagnosed in 9.2% of patients at 1 month \( (n = 21) \), 7.6% at 3 months \( (n =14) \), 7.5% at 6 months \( (n = 11) \), and 4.5% at 12 months \( (n = 6) \). MDD was diagnosed in 7.6% of patients at 1 month \( (n = 17) \), 2.7% at 3 months \( (n = 5) \),
7.6% at 6 months ($n=11$), and 6.8% at 12 months ($n=9$). Ten patients (4.4%) were diagnosed with an anxiety disorder at 1 month, 11 patients (6.0%) at 3 months, 14 patients (9.7%) at 6 months, and 10 patients (7.6%) at 12 months. Chi-square analyses showed no group differences in prevalence of any of the psychiatric diagnoses.

Mental health care utilization at 12 months was similar for both groups, such as visits to a GP ($P=.35$), company doctor ($P=.95$), mental health specialists ($P=.52$), hospital admissions ($P=.70$), or medication use ($P=.57$). The groups also did not differ with respect to employment status ($P=.70$), working hours ($P=.89$), and work absence ($P=.81$). Due to the absence of significant group differences, the direct and indirect costs for mental health use were not calculated.

6.3.4 Completer Analyses

In completers-only analyses ($n=117$ intervention group and $n=149$ control group patients), excluding nonusers ($n=34$), results were similar to the intention-to-treat results for all outcome measures.

Figure 6.2. Trends in observed PTSD symptom severity (CAPS and IES-R) per intervention group.
Table 6.2. Outcomes of intention-to-treat linear mixed models for PTSD, depressive and anxiety symptoms.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Internet intervention $n = 151$</th>
<th>Control with usual care $n = 149$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinician assessed PTSD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>symptoms (CAPS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 month follow-up</td>
<td>17.7 (16.7 to 18.7)</td>
<td>20.2 (19.1 to 21.3)</td>
</tr>
<tr>
<td>3 month follow-up</td>
<td>14.3 (13.2 to 15.5)</td>
<td>16.8 (15.1 to 18.6)</td>
</tr>
<tr>
<td>6 month follow-up</td>
<td>14.5 (13.2 to 15.8)</td>
<td>15.7 (14.3 to 17.1)</td>
</tr>
<tr>
<td>12 month follow-up</td>
<td>13.0 (11.2 to 14.8)</td>
<td>13.0 (11.4 to 14.6)</td>
</tr>
<tr>
<td><strong>Patient reported PTSD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>symptoms (IES-R)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 month follow-up</td>
<td>10.6 (9.6 to 11.7)</td>
<td>12.4 (11.1 to 13.7)</td>
</tr>
<tr>
<td>3 month follow-up</td>
<td>9.7 (8.0 to 11.4)</td>
<td>11.8 (10.1 to 13.5)</td>
</tr>
<tr>
<td>6 month follow-up</td>
<td>8.2 (6.9 to 9.6)</td>
<td>9.8 (8.1 to 11.5)</td>
</tr>
<tr>
<td>12 month follow-up</td>
<td>7.6 (6.4 to 8.7)</td>
<td>7.8 (6.4 to 9.2)</td>
</tr>
<tr>
<td><strong>Anxiety symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(HADS-A)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 month follow-up</td>
<td>4.6 (3.9 to 5.2)</td>
<td>4.8 (4.1 to 5.5)</td>
</tr>
<tr>
<td>3 month follow-up</td>
<td>4.0 (3.5 to 4.5)</td>
<td>4.3 (3.8 to 4.9)</td>
</tr>
<tr>
<td>6 month follow-up</td>
<td>3.9 (3.2 to 4.6)</td>
<td>4.6 (3.7 to 5.4)</td>
</tr>
<tr>
<td>12 month follow-up</td>
<td>4.1 (3.4 to 4.8)</td>
<td>3.7 (3.0 to 4.3)</td>
</tr>
<tr>
<td><strong>Depressive symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(HADS-D)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 month follow-up</td>
<td>3.6 (3.2 to 4.0)</td>
<td>4.1 (3.5 to 4.6)</td>
</tr>
<tr>
<td>3 month follow-up</td>
<td>3.5 (3.0 to 4.0)</td>
<td>3.9 (3.4 to 4.5)</td>
</tr>
<tr>
<td>6 month follow-up</td>
<td>4.1 (3.5 to 4.8)</td>
<td>4.5 (3.6 to 5.4)</td>
</tr>
<tr>
<td>12 month follow-up</td>
<td>3.3 (2.4 to 4.2)</td>
<td>3.0 (2.2 to 3.7)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Significance levels are indicated by $F$ for $p$-values less than .05.
<table>
<thead>
<tr>
<th>Time</th>
<th>Group</th>
<th>Group x Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>P</td>
</tr>
<tr>
<td>Clinician assessed PTSD symptoms (CAPS)</td>
<td>6.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1 month follow-up</td>
<td>17.7 (16.7 to 18.7)</td>
<td>20.2 (19.1 to 21.3)</td>
</tr>
<tr>
<td>3 month follow-up</td>
<td>14.5 (13.2 to 15.5)</td>
<td>16.8 (15.1 to 18.6)</td>
</tr>
<tr>
<td>6 month follow-up</td>
<td>14.5 (13.2 to 15.8)</td>
<td>15.7 (14.3 to 17.1)</td>
</tr>
<tr>
<td>12 month follow-up</td>
<td>13.0 (11.2 to 14.8)</td>
<td>13.0 (11.4 to 14.6)</td>
</tr>
<tr>
<td>15.7</td>
<td>&lt;.001</td>
<td>1.9</td>
</tr>
<tr>
<td>Patient reported PTSD symptoms (IES-R)</td>
<td>15.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1 month follow-up</td>
<td>10.6 (9.6 to 11.7)</td>
<td>12.4 (11.1 to 13.7)</td>
</tr>
<tr>
<td>3 month follow-up</td>
<td>9.7 (8.0 to 11.4)</td>
<td>11.8 (10.1 to 13.5)</td>
</tr>
<tr>
<td>6 month follow-up</td>
<td>8.2 (6.9 to 9.6)</td>
<td>9.8 (8.1 to 11.5)</td>
</tr>
<tr>
<td>12 month follow-up</td>
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<td>7.8 (6.4 to 9.2)</td>
</tr>
<tr>
<td>2.2</td>
<td>.07</td>
<td>0.3</td>
</tr>
<tr>
<td>Anxiety symptoms (HADS-A)</td>
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<td>.07</td>
</tr>
<tr>
<td>1 month follow-up</td>
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<td>4.8 (4.1 to 5.5)</td>
</tr>
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<td>3 month follow-up</td>
<td>4.0 (3.5 to 4.5)</td>
<td>4.3 (3.8 to 4.9)</td>
</tr>
<tr>
<td>6 month follow-up</td>
<td>3.9 (3.2 to 4.6)</td>
<td>4.6 (3.7 to 5.4)</td>
</tr>
<tr>
<td>12 month follow-up</td>
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<td>2.5 (1.7 to 3.3)</td>
</tr>
<tr>
<td>2.3</td>
<td>.054</td>
<td>0.3</td>
</tr>
<tr>
<td>Depressive symptoms (HADS-D)</td>
<td>2.3</td>
<td>.054</td>
</tr>
<tr>
<td>1 month follow-up</td>
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<td>4.1 (3.5 to 4.6)</td>
</tr>
<tr>
<td>3 month follow-up</td>
<td>3.5 (3.0 to 4.0)</td>
<td>3.9 (3.4 to 4.5)</td>
</tr>
<tr>
<td>6 month follow-up</td>
<td>4.1 (3.5 to 4.5)</td>
<td>4.5 (3.6 to 5.4)</td>
</tr>
<tr>
<td>12 month follow-up</td>
<td>3.3 (2.4 to 4.2)</td>
<td>3.7 (3.0 to 4.3)</td>
</tr>
</tbody>
</table>

*Data are expressed as mean (95% CI).*
6.3.5
Latent Subgroups

Post hoc LGMM analyses of self-reported PTSD symptoms (IES-R) revealed 2 latent subgroups per study group based on PTSD symptom severity at baseline, resulting in a low symptomatic control subgroup \( n = 94 \) and intervention subgroup \( n = 105 \), and a high symptomatic control subgroup \( n = 15 \) and intervention subgroup \( n = 20 \). The main difference between the groups was the slope of the high symptomatic subgroups, which showed a significant decrease in the intervention subgroup \( P < .001 \), but not in the control subgroup \( P = .32 \). Table 6.3 shows the outcomes of the LGMM analyses.

Table 6.3. Outcomes of latent growth mixture modeling analyses for self-reported PTSD severity (IES-R).

<table>
<thead>
<tr>
<th>Latent subgroups</th>
<th>Internet intervention</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>( n )</td>
<td>mean (95% CI)</td>
<td>( P )</td>
</tr>
<tr>
<td>Low symptomatic subgroup</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>105</td>
<td>9.0 (6.9 to 11.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Slope</td>
<td></td>
<td>-1.0 (-1.4 to -0.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>High symptomatic subgroup</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>20</td>
<td>41.2 (35.0 to 50.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Slope</td>
<td></td>
<td>-3.6 (-5.2 to -2.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Control with usual care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>-------------------------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>mean (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Low symptomatic subgroup</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>105</td>
<td>9.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>(6.9 to 11.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>-1.0</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(-1.4 to -0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High symptomatic subgroup</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>20</td>
<td>41.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>(35.0 to 50.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>-3.6</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(-5.2 to -2.1)</td>
<td></td>
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</tbody>
</table>
In this paper, we presented the results of a randomized clinical trial comparing a self-guided Internet-based prevention program vs usual care in the prevention of PTSD symptoms in injury patients. PTSD symptoms decreased over time without a significant difference between the Internet intervention group and the control group. Moreover, there were no differences between groups with respect to the number of PTSD and MDD diagnoses, and with respect to the severity of depression and anxiety at 12 months. An important finding is that participants were reluctant to use the intervention. In fact, one in five patients in the intervention group lacked any exposure to the intervention. Based on these results, there are currently no indications that offering a voluntary, information-based prevention program via the Internet to unselected injury victims is useful in preventing PTSD symptoms.

The low adherence rates were comparable to those found in similar self-help Internet-based interventions (Christensen, Griffiths, & Farrer, 2009). In part, this nonusage was a consequence of a deliberate design choice to allow patients freedom in performing the intervention, having learned from adverse effects of debriefing interventions found previously to be noneffective or even harmful (Rose et al., 2003; Sijbrandij et al., 2006). However, in order to induce changes in behavior and affect, true exposure to an intervention is necessary, which entails accessing the intervention website, staying on the intervention website to actually use it, and revisiting the intervention website, in case of a repetitive design (Crutzen, Cyr, & de Vries, 2011). As possible reasons for dropping out of or not adhering to online treatment programs, previous studies reported time constraints, lack of motivation, technical or computer-access problems, depressive episode or physical illness, the lack of face-to-face contact, a preference for taking medication, perceived lack of treatment effectiveness, improvement in condition, and burden of the program (Christensen et al., 2009). Strategies to increase uptake of Trauma TIPS may be a more structured peer-support forum, more interactive elements to the intervention, such as quizzes or knowledge questions, automated feedback on the acute anxiety and arousal assessments, or monetary incentive (Brouwer et al., 2011; Crutzen et al., 2011; Donkin et al., 2011). Moreover, a more strict approach to intervention adherence for inclusion in our study (eg, a minimum number of log-ins or log-in time required for participation) may have resulted in greater benefits. However, note that we found no differences in outcomes between users and nonusers or between participants with single versus multiple use. Finally, it is possible that the idea of a computerized program did not match the acute needs of the injury victims, resulting in some of them not using it. Previous studies investigating needs of victims after the September 11, 2001, terrorist attacks and the 2005 London bombings showed that only very few people (< 1%) reported a need for professional mental health support in the acute posttrauma phase, and most (71-87%) turned to loved ones or others for support (Rubin & Wessely, 2013; Schuster et al., 2001).
Another explanation for not finding a significant effect of the intervention may be the low overall PTSD symptom level. Only 9.2% of patients developed PTSD at 1 month, which decreased to 4.5% at 12 months. Beforehand, we expected that 19% of participants would have developed PTSD at 3 months (Conlon et al., 1999). This unexpectedly low PTSD incidence left little room for symptom improvement for the whole group. Additionally, the relatively low symptom levels may have caused participants to experience little personal incentive to access and use the intervention. Support for this comes from our post hoc subgroup analyses that suggested that the Trauma TIPS intervention was effective in reducing PTSD symptoms in individuals with high initial symptom levels. Because this subgroup was small ($n = 20$), these results must be interpreted with caution.

Internet interventions may not be suitable for all individuals. Common points of criticism are that the mainly information-driven formats pose a disadvantage to people with lesser reading or language skills, do not meet the needs of the elderly or persons with limited computer skills or experience, and that it is difficult to appeal to a culturally diverse audience in a single format, as possibly illustrated in our sample of more nonusers having a non-Dutch cultural background (Christensen et al., 2009). On the other hand, the rapid developments in Internet applications, especially via mobile technology, provide more possibilities to reach populations who were earlier underserved in eHealth care (Eysenbach, 2011; Istepanaian & Zhang, 2012).

One limitation of our study was missing data due to patient dropout or failure to complete self-report instruments. We do not know to what extent attrition may have biased our results, although besides marital status, we found no differences between participants and dropouts. In addition, our sample may not have been fully representative of the entire level 1 trauma center population, since we excluded patients with moderate-severe TBI, who did not master the Dutch language, or who were unable to meet our time requirements for logging in.

As a clinical implication of our study, future comparable Internet-based early interventions should be aimed at individuals with high initial symptoms. These individuals may be accurately identified within the first weeks following trauma with early screening tools for PTSD (O'Donnell et al., 2008; Shalev et al., 1997; Sijbrandij et al., 2008). Stepped care programs for acutely traumatized individuals have recently shown to be feasible (Zatzick et al., 2011). The results of our study show that an e-mental health approach could well be a first step in the acute aftercare of highly distressed trauma victims, since Trauma TIPS was indeed effective in a latent subgroup of participants experiencing high levels of PTSD symptoms at baseline. For those victims whose symptoms remain, our self-guided early intervention could be followed by more specialized or traditional curative face-to-face treatment as
part of a blended care strategy (Cucciare, Weingardt, Greene, & Hoffman, 2012). Future studies may determine the effectiveness of applying interventions such as Trauma TIPS to individuals with high levels of distress. They may also evaluate whether incorporation of strategies to increase adherence, for instance a motivating interviewing module or increasing the fun by adding serious gaming components to Trauma TIPS, may increase its effectiveness.

In conclusion, our study found no evidence for preventing the development of PTSD symptoms by offering a voluntary, information-based prevention program via the Internet to unselected injury trauma victims. Future research may focus on innovative strategies to increase intervention usage and targeting high-risk individuals who are more likely to benefit from the intervention.
CHAPTER 7: The role of early pharmacotherapy in the development of posttraumatic stress disorder symptoms after traumatic injury: An observational cohort study in consecutive patients.

ABSTRACT

Background:
Pharmacological intervention during traumatic memory consolidation has been suggested to prevent posttraumatic stress disorder (PTSD). We investigated the association between opiate analgesics, beta-adrenergic blockers, corticosteroids and benzodiazepines, administered within the first 48 hrs of traumatic injury, and the risk of developing PTSD symptoms at 6 weeks posttrauma.

Methods:
The use of opiate analgesics, beta-adrenergic blockers, corticosteroids and benzodiazepines within 48 hrs post-injury was documented based on hospital charts for 629 level 1 trauma center patients. PTSD symptoms were assessed using structured clinical interviews. Primary outcome was 6-week PTSD symptoms. Secondary outcomes were PTSD diagnoses at 6 weeks and during 1 year posttrauma.

Results:
Linear regression analyses showed that opiate administration within 48 hrs was negatively associated with PTSD symptoms at 6 weeks ($\beta=-0.14, p=.009$) after controlling for demographic and injury-related characteristics and concurrent pharmacotherapy. Fewer patients with opiates had a PTSD diagnosis at 6 weeks ($p=.047$) and during 1 year posttrauma ($p=.013$) than patients with none of the specified pharmacotherapies. Low prescription frequency of beta-blockers, corticosteroids and benzodiazepines precluded further examination regarding their role in the development of PTSD symptoms.

Conclusions:
This study suggests a possible beneficial influence of opiate administration within 48 hrs posttrauma on the development of PTSD symptoms. Future studies may evaluate the effectiveness of in-hospital opiate analgesics compared to placebo in preventing PTSD and may focus on the mechanisms underlying the effect of opiates in preventing PTSD.
Posttraumatic stress disorder (PTSD) is a disabling disorder with a reported lifetime prevalence of around 7% (de Vries & Olff, 2009; Kessler et al., 2005). PTSD is characterized by symptoms of intrusion (e.g., involuntary memories and nightmares), avoidance of trauma-related thoughts or external reminders, negative alterations in cognition and mood and alterations in arousal and reactivity (e.g., sleep disturbance, concentration problems, hypervigilance; American Psychiatric Association, 2013). Efforts to prevent the onset of PTSD with psychological interventions were not successful (Rose et al., 2003), and psychological debriefing may even increase PTSD symptoms (Sijbrandij et al., 2006). It has been suggested that emphasizing the recall of emotions and details associated with the event early after trauma may exacerbate PTSD symptom development and interfere with natural recovery (Sijbrandij et al., 2006). This has shifted attention to pharmacological intervention as an alternative, neurobiological way to promote the natural recovery from traumatic stress. Of most interest are beta-adrenergic blockers, corticosteroids, opiate analogues and benzodiazepines.

**Beta-adrenergic blockers:** One proposed neurobiological pathway is that the hyperadrenergic state, that occurs after trauma exposure, may cause an overconsolidation of the traumatic memory (Pitman, 1989). This is revealed in intrusions that in turn may cause a re-release of glucocorticoids and catecholamines which further enhance the consolidation of the traumatic memory. Evidence for this positive feedback loop comes from studies that found that the onset of PTSD is associated with increased heart rate variability (Bryant, Marosszeky, Crooks, & Gurka, 2004; O'Donnell, Creamer, Elliott, & Bryant, 2007; Shaikh et al., 2012; Zatzick et al., 2005), urinary (nor)epinephrine (Delahanty et al., 2005; Delahanty et al., 2000; Delahanty et al., 2003), and a dysregulated cortisol response (Aardal-Eriksson et al., 2001; Delahanty et al., 2000; Ehring et al., 2008; McFarlane et al., 2011; Mouthaan, Sijbrandij, Luitse et al., 2014). Medication that acts on the hyperadrenergic state may prevent this positive feedback loop (Pitman, 1989), and subsequent PTSD. Beta-adrenergic antagonists, or beta-blockers, such as propranolol, interfere with the binding to the receptor of epinephrine and other stress hormones. Animal studies found that increased (nor)adrenaline levels in the body and the brain during encoding and consolidation led to increased memory performance, while beta-adrenergic blockade in the same phase reduced memory performance (for a review, see van Stegeren, 2008). A randomized controlled trial (RCT) in individuals with acute medical trauma and elevated heart rate at the emergency room found that psychophysiological responses (as measured with fear-potentiated startle to trauma scripts) were lower at 3 months following trauma in the propranolol than in the placebo group (Pitman et al., 2002). A non-randomized controlled study found fewer PTSD symptoms in the 2-month follow-up in eleven injury patients with propranolol compared to eight patients without propranolol or placebo (Vaiva et al., 2003). Subsequent RCTs (Nugent et al., 2010; Stein et
al., 2007) and a case-control study (McGhee et al., 2009), however, failed to find significant effects of propranolol in preventing PTSD. As a confirmation of these findings, a recent animal study found that immediate post-stressor propranolol administration did not prevent PTSD-like behavioral responses, despite reductions in physiological stress responses and long term memory performance (Cohen et al., 2011).

**Corticosteroids:** Hydrocortisone is another pharmacological intervention that has been proposed as a strategy to prevent PTSD (Aardal-Eriksson et al., 2001; Delahanty et al., 2000; Ehring et al., 2008; McFarlane et al., 1997; McFarlane et al., 2011; Resnick et al., 1997; Yehuda et al., 1998). The rationale behind the use of hydrocortisone to prevent PTSD is the assumed involvement of a dysregulated HPA-axis in the onset of PTSD symptoms. Lower levels of circulating cortisol are assumed to prolong the adrenergic response, thereby strengthening the consolidation of the fear memory (Yehuda, 2002). Thus, it has been argued that the administration of glucocorticoids counteracts and impairs memory consolidation and recall. In animals, corticosterone administration following a stressor reduced extreme disruptive and PTSD-like behavior and improved resilience to subsequent trauma (Cohen et al., 2006; Cohen, Matar, Buskila, Kaplan, & Zohar, 2008). In humans, non-randomized (Schelling et al., 1999) and randomized (Delahanty et al., 2013; Schelling et al., 2001; Schelling et al., 2004; Zohar, Yahalom et al., 2011) controlled trials have demonstrated that hydrocortisone administration after medical trauma was associated with a lower risk for PTSD symptom development. This suggests the possibility of the HPA-axis to return to homeostasis by early glucocorticoid administration.

**Opiate analgesics:** In addition to beta-blockers and hydrocortisone, other approaches to pharmacological PTSD prevention have also been explored. Findings from preclinical studies suggest that early use of opiate analgesics after trauma might prevent or impair traumatic memory consolidation by attenuating noradrenergic activity and dampening fear conditioning by containing the HPA response (Good & Westbrook, 1995; McNally & Westbrook, 2003; Pitman, 1989). Support for this protective effect was found in post-hoc examinations in prospective studies of trauma survivors. Studies in children with burns (Saxe et al., 2001; Stoddard, Jr. et al., 2009) and traumatic injury (Nixon et al., 2010) found positive associations between morphine dosage during hospitalization and greater decline in PTSD symptoms in the first 6 months posttrauma. In addition, a prospective study of 155 adult injury patients reported that morphine dose within the first 48 hrs, but not within the first week, was associated with fewer PTSD symptoms at 3 months (Bryant et al., 2009). A retrospective study of combat injury victims found that receiving morphine during acute trauma care was associated with a reduced risk for a PTSD diagnosis within 24 months following injury (Holbrook et al., 2010).
Benzodiazepines: Benzodiazepines are frequently prescribed sedatives or anxiolytics during posttrauma hospitalization (Zatzick & Roy-Byrne, 2006). They act on the neurotransmitter GABA at the GABA<sub>A</sub> receptor with sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anticonvulsant, and muscle relaxant effects (Page et al., 2005). Benzodiazepines are also known for enhancing emotional memory, which acutely after trauma may impact traumatic memory consolidation and worsen PTSD symptoms (for a review, see Zohar, Juven-Wetzler et al., 2011). Acute benzodiazepine administration was positively associated with PTSD in two small trials of injury victims (Gelpin et al., 1996; Mellman et al., 1998). These findings, along with pre-clinical evidence that acute post-stressor alprazolam administration negatively affects behavioral outcomes to subsequent stress exposure (Matar et al., 2009), suggest a negative effect of benzodiazepines on natural recovery following trauma. Retrospective studies of combat injury patients (Holbrook et al., 2010; McGhee et al., 2009) and a prospective study in children with burns (Saxe et al., 2001) did not find significant associations between benzodiazepines during acute trauma care or hospital stay and PTSD outcomes.

In this prospective study, we examined whether the administration of beta-blockers, corticosteroids, opiate analgesics and benzodiazepines within the first 48 hrs posttrauma was associated with PTSD symptom development in a naturalistic sample of injury patients. We expected that early administration of beta-blockers, corticosteroids and opiate analgesics was associated with lower levels of PTSD, but that benzodiazepine administration was associated with higher levels of PTSD at follow-up.

7.2 MATERIALS AND METHODS

7.2.1 Subjects and procedure

Consecutive injury patients who were transported by ambulance or trauma helicopter to the level-1 trauma center of the Academic Medical Center in Amsterdam, The Netherlands, between September 2005 and March 2009, were eligible for the study, if (a) they were 18 years of age or older, (b) their injuries were sustained in a traumatic event cf. the A1-criterion of the DSM-IV PTSD diagnosis (American Psychiatric Association, 2000), and (c) they mastered the Dutch language. Patients were excluded if their injuries were due to deliberate self-harm, if they suffered from an organic brain condition, current psychotic symptoms or disorder, bipolar disorder, depression with psychotic features, if they had moderate to severe traumatic brain injury (i.e., Glasgow Coma Scale (GCS) score of less than 13; Teasdale & Jennett, 1974), or if they permanently resided outside the Netherlands. Medical ethical approval was obtained from the institutional review board of the Academic Medical Center. Research assistants selected eligible patients from the hospital’s registration
system and contacted them within 72 hrs of the injury in-hospital or by telephone for participation. Patients provided verbal and written informed consent after complete description of the study. Psychological assessments were performed at the Center for Anxiety Disorders of the Academic Medical Center, at bedside or at the patients home by trained master and bachelor level psychologists at several time points during the first year following trauma (for more details, see Mouthaan et al., 2011). Trauma Unit staff assessed injury severity and Glasgow Coma Score at the time of initial medical examination. PTSD symptom severity at 6 weeks was considered the main outcome in this study. Secondary outcomes were PTSD diagnosis at 6 weeks and during the first year after trauma.

7.2.2 Measures

Predictor variables

All medications prescribed in-hospital up to 48 hrs posttrauma were obtained from the hospital records by research assistants and the main researcher. For this study, any medication from the following categories was scored as absent/present:

- beta-adrenergic blockers (i.e., sotalol, bisoprolol, metoprolol, atenolol, nebivolol, carvedilol, labetalol);
- systemic corticosteroids (i.e., hydrocortisone, prednisone, dexamethasone, betamethasone, methylprednisolone, prednisolone);
- opiate analgesics (i.e., morphine, fentanyl, pethidine, tramadol);
- benzodiazepines (i.e., oxazepam, diazepam, clorazepate, lorazepam, temazepam, midazolam, flunitrazepam, zopiclone, zolpidem).

Injury severity was assessed using the Injury Severity Score (ISS), ranging from 0 (no injury) to 75 (unsurvivable injury) with a score of 16 and higher indicating severe injury (Copes et al., 1990). The Glasgow Coma Scale (GCS) is a neurological scale to record level of consciousness and consists of three parameters: Best Eye Response (four grades), Best Verbal Response (five grades), Best Motor Response (six grades). Resulting scores are between 3 (deep unconsciousness) and 15 (fully conscious; Teasdale & Jennett, 1974).

Posttraumatic stress symptoms and disorder

PTSD symptoms and diagnosis were assessed using the Clinician Administered PTSD Scale (CAPS; Blake et al., 1995). The CAPS is a well-established 30-item semi-structured interview for diagnosing PTSD (Weathers et al., 2001). Symptom severity is determined by adding frequency and intensity of the 17 symptoms of intrusion, avoidance and hyperarousal (both ranging from 0 to 4, total scores
ranging from 0 to 136). The rule of Weathers et al. (1999) was used to establish a PTSD diagnosis, in which symptoms need at least a frequency of 1 and intensity of 2 with a total score of at least 45 points.

7.2.3 Analysis

Descriptive statistics were used to compute frequencies, percentages, means and standard deviations for demographic and clinical characteristics and pharmacotherapy categories. As part of a longitudinal database with multiple repeated PTSD assessments, missing data of continuous CAPS outcomes were replaced using multiple imputation (SPSS 21.0), creating five different datasets. In this procedure, the fully conditional specification approach was used, in which data were imputed on a variable-by-variable basis by specifying an imputation model per variable. This method has been found to work well in practice (van Buuren, 2011).

Our main model to examine whether the early use of specific pharmacological treatment was associated with higher or lower levels of PTSD symptoms was based on the CAPS measurement at 6 weeks. Examination of the frequency of pharmacotherapy within 48 hrs posttrauma showed that that beta-blockers (3.8%), corticosteroids (2.2%) and benzodiazepines (7.8%) were prescribed only rarely. As a consequence, further linear regression analysis was performed for the main effect of opiate analgesics only. However, concurrent prescription of beta-blockers, corticosteroids and benzodiazepines was controlled for in these analyses. We applied the following modeling strategy to gain insight in the relationship between the use of opiate analgesics and PTSD symptoms. In step 1, we examined the univariate model of opiate analgesics. Next, in consecutive steps, we examined the change in beta, 95% CI and p-value when controlling for demographics, e.g., age, gender (step 2), injury- and trauma-related characteristics, e.g., Emergency Department heart rate, ISS, GCS, type of traumatic event (i.e., dummy variables of traffic accident, physical abuse, work-related accident, fall from height and other) (step 3), and concurrent pharmacotherapy categories within 48 hrs posttrauma (step 4).

In addition, a chi-square test was performed to examine whether patients with opiate analgesics in the initial 48hrs of hospital care had a higher or lower risk of receiving a PTSD diagnosis at 6 weeks and in the year following the trauma. Only patients with opiate analgesics and no concurrent pharmacotherapy (i.e., beta-blockers, corticosteroids or benzodiazepines) were included in the chi-square analysis, and were compared to patients who received no medication from any of the specified pharmacotherapy categories. All analyses were carried out in SPSS 21.0 with p-values < .05 indicating statistical significance.
7.3 RESULTS

7.3.1 Participants

Of 1,583 eligible injury patients, 629 patients (39.7%) were included in the final sample, 437 patients (27.6%) did not respond to our participation requests, 403 (25.5%) refused or withdrew from the study before the baseline assessment and 114 (7.2%) met exclusion criteria (see Figure 7.1 for a flow chart). Table 7.1 shows demographic, injury and clinical characteristics of the participant sample. Of the total sample, 456 patients (72.5%) were assessed for PTSD at 6 weeks, at a median of 45 days (Inter Quartile Range = 36-62), and 530 patients (84.3%) were assessed for PTSD within the first year after trauma. PTSD prevalence was 12.3% at 6 weeks (n = 56) and 15.7% during 1 year after injury (n = 83). Within the patients assessed for PTSD at 6 weeks, more patients were administered beta-blockers than among those not assessed at 6 weeks (n = 22, 4.8%, versus n = 2, 1.2%; $\chi^2(1)$=4.60, $p = .034$). There were no other significant differences between patients with or without a PTSD assessment at 6 weeks or within the first year posttrauma on any baseline demographic or injury-related characteristic. Concurrent medication administrations are presented in Supplementary Table 1.

7.3.2 Associations between early pharmacotherapy and development of PTSD

Table 7.2 presents the results from the stepwise linear regression analysis of opiate analgesics on 6-week PTSD symptoms. In the full model (step 4), controlling for demographics, injury characteristics and concurrent early pharmacotherapy, administration of opiate analgesics within 48 hrs posttrauma was negatively associated with PTSD symptoms. Significantly fewer patients with early opiates (8 of 121 patients; 6.6%) developed PTSD at 6 weeks than patients without any of the specified pharmacotherapy categories (37 of 274 patients; 13.5%; $\chi^2(1)$=3.95, $p=.047$). Similarly, 12 of 138 patients with opiates (8.7%) were diagnosed with PTSD during 1 year after injury compared to 57 of 322 patients who did not receive pharmacotherapy (17.7%) ($\chi^2(1)$=6.15, $p=.013$).
Figure 7.1. Flow chart of study participants

2,020 adult injured trauma patients

1,583 eligible patients contacted

629 patients included

456 patients assessed for PTSD at 6 weeks (72.5%)

173 not available for 6 week assessment

530 patients assessed for PTSD within 1 year (84.2%)

99 not available for 12 month assessment

20 withdrew

437 did not respond

114 met exclusion criteria:
- physically or mentally not stable/weak (32)
- severe psychiatric symptoms (30)
- non-Dutch speaking (23)
- dementia (18)
- insufficient cognitive skills (11)

383 refused

456 patients assessed for PTSD at 6 weeks

287 not eligible:
- deceased (108)
- living abroad (95)
- self-inflicted injuries or suicide attempt (73)
- permanent brain damage (11)

150 could not be located
Table 7.1. Demographic, injury-related and clinical characteristics of the study sample (N = 629)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>416</td>
<td>66.1</td>
</tr>
<tr>
<td>Age in years (Mean, SD)</td>
<td>43.6</td>
<td>15.8</td>
</tr>
<tr>
<td>Married or cohabitating</td>
<td>227</td>
<td>38.7</td>
</tr>
<tr>
<td>College or university degree</td>
<td>125</td>
<td>19.9</td>
</tr>
<tr>
<td>Country of origin: Netherlands</td>
<td>477</td>
<td>81.8</td>
</tr>
<tr>
<td>Prior traumatic events (Mean, SD)</td>
<td>2.9</td>
<td>2.2</td>
</tr>
<tr>
<td>Traumatic event:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traffic accident</td>
<td>401</td>
<td>63.8</td>
</tr>
<tr>
<td>Fall from height</td>
<td>94</td>
<td>14.9</td>
</tr>
<tr>
<td>Work-related accident</td>
<td>64</td>
<td>10.2</td>
</tr>
<tr>
<td>Physical abuse</td>
<td>30</td>
<td>4.8</td>
</tr>
<tr>
<td>Other (e.g., fire, recreational, natural disaster, airplane crash)</td>
<td>40</td>
<td>6.4</td>
</tr>
<tr>
<td>ISS (Mean, SD)</td>
<td>8.7</td>
<td>8.6</td>
</tr>
<tr>
<td>GCS (Mean, SD)</td>
<td>14.3</td>
<td>2.5</td>
</tr>
<tr>
<td>Admitted to hospital</td>
<td>441</td>
<td>70.3</td>
</tr>
<tr>
<td>Admitted to ICU</td>
<td>83</td>
<td>13.2</td>
</tr>
<tr>
<td>Categories of early pharmacotherapy:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>24</td>
<td>3.8</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>14</td>
<td>2.2</td>
</tr>
<tr>
<td>Opiate analgesics</td>
<td>217</td>
<td>34.5</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>49</td>
<td>7.8</td>
</tr>
<tr>
<td>CAPS at 6 weeks (Mean, SD)</td>
<td>21.7</td>
<td>20.7</td>
</tr>
<tr>
<td>PTSD diagnosis at 6 weeks</td>
<td>56</td>
<td>12.3</td>
</tr>
<tr>
<td>PTSD diagnosis during 1 year post-trauma</td>
<td>83</td>
<td>15.7</td>
</tr>
</tbody>
</table>

ISS, Injury Severity Score; GCS, Glasgow Coma Score; ICU, intensive care unit; CAPS, Clinician Administered PTSD Scale; PTSD, Posttraumatic Stress Disorder.

* Values represent frequencies and percentages, unless otherwise specified.
### Table 7.2. Stepwise linear regression results of the effects of opiate analgesics on 6-week PTSD symptoms.

<table>
<thead>
<tr>
<th>Step</th>
<th>Model Description</th>
<th>Beta</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1: Univariate model</td>
<td>- .10</td>
<td>-.20,.01</td>
<td>.04</td>
<td></td>
</tr>
<tr>
<td>Step 2: Univariate model + demographic characteristics</td>
<td>- .10</td>
<td>-.20,.00</td>
<td>.045</td>
<td></td>
</tr>
<tr>
<td>Step 3: Univariate model + demographic + injury characteristics</td>
<td>- .12</td>
<td>-.22,.02</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>Step 4: Univariate model + demographic + injury characteristics + concurrent pharmacotherapy</td>
<td>- .14</td>
<td>-.24,.04</td>
<td>.01</td>
<td></td>
</tr>
</tbody>
</table>

Demographic characteristics (Step 2): age, gender; Injury characteristics (Step 3): emergency department heart rate, ISS, GCS, dummy-coded traumatic event variables (traffic accident, physical abuse, work-related accident, fall from height, other traumatic event); Concurrent pharmacotherapy (Step 4): beta-blockers, corticosteroids, benzodiazepines.

N.B.: Step 1, $R^2_{adj}$=.01; Step 2, $\Delta R^2$=.02; Step 3, $\Delta R^2$=.11; Step 4, $\Delta R^2$=.01.

### Supplementary Table 7.1. (Concurrent) Pharmacotherapy Administration Within 48 Hrs Post-Injury.

<table>
<thead>
<tr>
<th>Pharmacotherapy</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neither opiate analgesics, beta-blockers, corticosteroids or benzodiazepines</td>
<td>387</td>
<td>45.4</td>
</tr>
<tr>
<td>Opiate analgesics (alone or in combination)</td>
<td>217</td>
<td>34.5</td>
</tr>
<tr>
<td>Opiates alone</td>
<td>163</td>
<td>25.9</td>
</tr>
<tr>
<td>Benzodiazepines (alone or in combination)</td>
<td>49</td>
<td>7.8</td>
</tr>
<tr>
<td>Benzodiazepines alone</td>
<td>12</td>
<td>1.9</td>
</tr>
<tr>
<td>Beta-blockers (alone or in combination)</td>
<td>24</td>
<td>3.8</td>
</tr>
<tr>
<td>Beta-blockers alone</td>
<td>6</td>
<td>1.0</td>
</tr>
<tr>
<td>Corticosteroids (alone or in combination)</td>
<td>14</td>
<td>2.2</td>
</tr>
<tr>
<td>Corticosteroids alone</td>
<td>6</td>
<td>1.0</td>
</tr>
</tbody>
</table>
7.4 DISCUSSION

In this study, we examined whether early posttrauma administration of pharmacotherapy was associated with the development of PTSD symptoms at 6 weeks following injury. The results showed that patients who were administered opiates within 48 hrs (34.5%) developed less PTSD symptoms at 6 weeks, after controlling for relevant demographic and injury characteristics and concurrent early pharmacotherapy. In a similar vein, PTSD incidence at 6 weeks and during the first year following trauma was lower in patients who were administered opiate analgesics within 48 hrs, than in patients who were not administered any of the pre-specified types of pharmacotherapy. Because beta-blockers (3.8%), corticosteroids (2.2%) and benzodiazepines (7.8%) were rarely prescribed, their role in the development of PTSD was not examined further.

Our findings are in line with previous studies in injured populations that reported associations between morphine prescription and lower levels of PTSD symptoms or lower PTSD incidence in the months following injury (Bryant et al., 2009; Holbrook et al., 2010; Nixon et al., 2010; Saxe et al., 2001; Stoddard, Jr. et al., 2009). Furthermore, they extend these previous findings in an adult injured trauma population (Bryant et al., 2009) by showing that opiates may reduce the risk for PTSD even after controlling for concurrent pharmacotherapy, even up to 1 year post-trauma. Animal studies suggest that opiates inhibit the locus coeruleus, a main noradrenergic center in the brain, and attenuate fear acquisition and block stress-induced signals to the amygdala producing hypoalgesic response (Christie, 1991; Good & Westbrook, 1995; Westbrook, Greeley, Nabke, & Swinbourne, 1991). Pre-clinical studies also showed that morphine attenuates norepinephrine after stress exposure and causes amnesia for fear conditioning (Kohno, Tanaka, Hoaki, Ida, & Nagasaki, 1983; Tanaka et al., 1983; Tanaka et al., 1991). On a psychological level, cognitive models posit that the individual appraisal of the event may catalyze intrusive memories leading to PTSD symptoms (Ehlers & Clark, 2000; Olff et al., 2005). Morphine may, by decreasing threat appraisal, therefore, prevent subsequent posttraumatic stress reactions. Another possible explanation for a protective effect of opiates on the development of PTSD, may be the dampening of pain responses. Studies showed that pain may contribute to the development and maintenance of PTSD symptoms (Bryant et al., 2009; Norman et al., 2008; Zatzick & Galea, 2007). The administration of opiate analgesics to injury patients at our trauma center is mainly guided by the level of reported or expected pain by a patient or the medical staff. Since we did not assess acute pain in the current study, it is unclear whether pain reduction mediated the relation between opiates and PTSD symptoms in our study.
Due to the low prescription of beta-blockers, corticosteroids and benzodiazepines within our naturalistic sample of injury patients, their role in the development of PTSD symptoms was not examined further. Of note, a previous epidemiological study also found that these medications were rarely prescribed in a population of adult or adolescent injury patients at a level 1 trauma center (Zatzick & Roy-Byrne, 2006).

A major limitation of an observational design is that patients who receive specific medications are, by definition, different from those that did not. Therefore, we adjusted for various potential relevant factors to gain insight in the relationship between opiates and PTSD. However, there is always the risk of residual confounding still being present. Ideally, the prescription of medication should be randomized to avoid this issue, but this is of course not ethical. An important limitation of our data was that the prescription of pharmacotherapy was only available in a dichotomous (yes/ no) format. Since we do not know what dosages were prescribed, the dosages may have been too low to generate an effect. Finally, we did not control for acute pain, which may mediate the effect of a pharmacological agent on PTSD's development.

Based on our findings it is premature to suggest any clinical implications for the early use of opiates in the prevention of PTSD after injury. Further research is needed to test the effectiveness of early in-hospital opiate administration compared to placebo in preventing PTSD in recent trauma survivors. In addition, future studies may elucidate the mechanisms through which opiates may reduce the risk of PTSD. Future research into the role of beta-blockers, corticosteroids and benzodiazepines, administered early after trauma, in injured trauma populations may better profit from controlled examination of the effectiveness of these medications on subsequent PTSD, to replicate any previous findings.

In conclusion, this study suggests a possible beneficial influence of opiate administration within 48 hrs posttrauma on the development of PTSD symptoms. Future studies may evaluate the effectiveness of in-hospital opiate analgesics compared to placebo in preventing PTSD and may focus on the mechanisms underlying the effect of opiates in preventing PTSD.
CHAPTER 8: Discussion
8.1 OVERVIEW OF THE THESIS

The findings presented in this thesis centred on the prediction and prevention of psychological symptoms, especially PTSD symptoms, as a consequence of traumatic injury. The aims of the studies were: (1) to investigate the predictive role of acute post-injury cortisol and DHEAS for acute and chronic PTSD (Chapter 2); (2) to examine the diagnostic accuracy of three early screening instruments for 6-month PTSD (Chapter 3); (3) to develop and test the effectiveness of a web-based early psychological intervention to prevent PTSD in injured trauma survivors (Chapters 4, 5, and 6); and (4) to investigate the association between early pharmacotherapy within the initial 48 hours of injury and PTSD at 6 weeks and within the first year after trauma (Chapter 7). In this general discussion, I will summarize the main findings of our research, discuss methodological considerations, and provide practical and clinical implications for the results of the studies.

8.2 CONCLUSIONS

8.2.1 Cortisol and DHEAS as predictors for PTSD (Chapter 2)

To examine whether acute plasma cortisol and DHEAS levels predict later PTSD, data from 397 adult injury patients from the AMC’s and VUmc’s Trauma Units were collected. The results showed that patients with lower acute cortisol levels to trauma were more likely to develop acute and chronic PTSD symptoms. These results were independent from known confounding factors, such as age, gender, time of blood sampling, injury severity, trauma history, and ICU admission. Higher acute DHEAS levels and a smaller cortisol-to-DHEAS ratio were found to contribute to 6-week PTSD symptoms, but not after controlling for the same confounding factors, and not at 6 months. Diagnoses of acute or chronic PTSD were not predicted by cortisol, DHEAS or cortisol-to-DHEAS ratio. Lastly, acute DHEAS did not contribute significantly to PTSD symptom change between 6 weeks and 6 months.

Our findings confirm the hypothesis that insufficient activation of the HPA-axis in response to stress may lead to the development of PTSD (Yehuda, 2002). More specifically, our results of low levels of circulating cortisol marking a vulnerability factor for developing PTSD symptoms are in line with several previous studies (Aardal-Eriksson et al., 2001; Delahanty et al., 2000; Ehring et al., 2008; McFarlane et al., 2011), but not with studies who found no association between cortisol and PTSD (Bonne et al., 2003; Resnick et al., 1997; Shalev et al., 2008). Our results also indicate that cortisol is not only a predictor for acute PTSD symptoms, but continues to predict chronic PTSD symptoms at 6 months, even when controlling for relevant trauma and injury characteristics. Regarding acute DHEAS, our study was the first prospective investigation of its role in the prediction of PTSD. It was concluded that
DHEAS responses differ between trauma-exposed individuals compared to non-exposed individuals, as suggested from mixed results from previous cross-sectional and longitudinal studies on DHEA(S) and PTSD (Gill et al., 2008; Jogems-Kosterman et al., 2007; Yehuda et al., 2006). Possibly, the assessment of DHEA instead of DHEAS levels may have shown greater predictive value, as DHEA responds more pronounced to situations of acute stress as opposed to DHEAS (Lennartsson et al., 2012).

8.2.2
Diagnostic accuracy of early PTSD risk screening (Chapter 3)

To test the diagnostic accuracy of the SPAN, TSQ and IES-R in predicting a diagnosis of PTSD at 6 months, we aimed for a fixed, high sensitivity of 80%. As previous studies in injury victims have shown sensitivities of early PTSD risk screening instruments varying between 80% to 90% (for a review, see O’Donnell et al., 2008), it may be argued that 80% sensitivity is acceptable for an early PTSD risk screener. Data of 311 of the 852 included injury patients of the AMC and VUmc hospitals were analysed who completed the instruments and clinical assessments. Eighteen patients (5.8%) of the final sample were diagnosed with PTSD at 6 months, significantly less than in excluded patients from the total sample (*n* = 74, 13.7%). The results showed good and similar AUCs for all instruments (0.82-0.83), indicating adequacy in distinguishing between individuals with and without PTSD at 6 months. The specificities were modest for all instruments (SPAN: 64%, TSQ: 59%, IES-R: 72%), implying poor quality in identifying non-cases. Thus, the instruments could well be used as a first selection step of possible cases, but a second, more comprehensive, diagnostic examination is needed to identify individuals in need of treatment. Importantly, the specificities did not significantly differ between tests, suggesting that the briefer instruments, SPAN and TSQ, are as accurate as the longer, IES-R.

8.2.3
The effectiveness of an internet-based early intervention to prevent PTSD (Chapters 4, 5, 6)

The main purpose of the Trauma TIPS intervention, a self-guided internet-based early psychological intervention, was to decrease acute hyperarousal and anxiety and to prevent the onset of PTSD. Learning from the experiences with psychological debriefing (Rose et al., 2003; Sijbrandij et al., 2006), the program was designed to incorporate free choice using optional features and targeted at successful recovery instead of conferring symptom information. Elements of CBT were presented in 6 consecutive steps and included information/psychoeducation, modeling, stimulating seeking social support, stress management, and in vivo exposure exercises. Pilot study results of 5 consecutive traumatic injury patients and 5 matched healthy
controls showed that the intervention was feasible and acceptable and had no immediate adverse psychological reactions for the patients or the control subjects.

To test the effectiveness of the Trauma TIPS program in preventing PTSD after injury, 300 consecutive adult injury patients from the Trauma Units of the AMC and VUmc hospitals were randomized into an intervention condition \( n = 151 \) and a control condition without intervention \( n = 149 \). PTSD symptoms decreased significantly but equally over time in both groups. In addition, there were no group differences in prevalence of PTSD and MDD diagnoses, or in severity of depression and anxiety at 12 months. Adherence to the program was low: one in five patients in the intervention group never logged into the intervention. This lack of adherence may have been the result of the freedom we allowed patients in accessing the intervention and in choosing the elements -based on the lessons learned from the debriefing studies- although similar online self-help programs suffered from comparable adherence problems (Christensen et al., 2009). Features, such as a more interactive social platform or therapist feedback, have been found to enhance participant motivation (Brouwer et al., 2011; Crutzen et al., 2011; Donkin et al., 2011), and may have increased exposure to the working elements of the program, which is needed to obtain health effects from an intervention (Crutzen et al., 2011). Another possibility is that a computerized program did not match the acute needs of the injury victims, resulting in some of them not using it. Besides limited usage of the intervention, our sample’s overall low PTSD symptom level left little room for symptom improvement for the whole group and may have led to the absence of significant group differences. Results from post hoc subgroup analyses suggested that the Trauma TIPS intervention was effective in reducing PTSD symptoms in individuals with high initial symptom levels. Based on these results, we conclude that there are currently no indications that offering a voluntary, information-based prevention program via the Internet to unselected injury victims is useful in preventing PTSD symptoms.

8.2.4 Influence of acute pharmacotherapy on PTSD development (Chapter 7)

All in-hospital administration of beta-blockers, benzodiazepines, corticosteroids and opiate analgesics within the initial 48 hrs post-injury were documented for 629 consecutive injury patients from the AMC’s Trauma Unit. Opiate administration within 48 hrs was negatively associated with 6-week PTSD symptoms, controlling for background and injury-related characteristics. Explorative univariate analyses showed that, compared to patients without any of the specified pharmacotherapy categories, fewer patients with opiate analgesics within 48 hrs post-injury were diagnosed with PTSD at 6 weeks and within the whole first year after trauma. Because beta-blockers (3.8%), corticosteroids (2.2%) and benzodiazepines (7.8%) were rarely prescribed, their role in the development of PTSD was not examined further.
In line with previous studies (Bryant et al., 2009; Holbrook et al., 2010; Nixon et al., 2010; Saxe et al., 2001; Stoddard, Jr. et al., 2009), our results points to a possible preventive effect of early opiate administration on subsequent PTSD symptom development. Our results also extend previous findings by showing that opiates may reduce the risk for PTSD, even after controlling for concurrent pharmacotherapy, and even up to 1 year post-trauma. It is possible that opiate administration early after trauma interfered with the acquisition or consolidation of fear memories, thus inhibiting the formation of intrusions of the traumatic experiences, and subsequently PTSD symptoms. Alternatively, opiates may have protected against the development of PTSD by dampening pain responses. Beta-blockers, corticosteroids and benzodiazepines were prescribed too little to examine in relation to the development of PTSD. A previous epidemiological study of adult and adolescent injury patients at a level 1 trauma center also found that these medications were rarely prescribed (Zatzick & Roy-Byrne, 2006). From our results, we conclude that our study added to the evidence of a possible beneficial effect on PTSD development of acute opiate administration after injury. However, the mechanisms that drive this effect need more clarification. Moreover, the effectiveness of in-hospital opiate analgesics compared to placebo in preventing PTSD may be tested in a randomized clinical trial in recent trauma survivors.

8.3 METHODOLOGICAL CONSIDERATIONS

8.3.1 Strengths

A particular strength of the Trauma TIPS trial is the inclusion of a large heterogeneous sample of consecutive injury patients, reflecting the broad range of injury victims presenting at a level-1 trauma centre. As opposed to studies in which participants are referred from various sources or respond to advertisements, consecutive inclusion reduces selection bias based on certain motivation from referring parties or participants themselves. We were able to include patients from two centres, which may be beneficial to the generalisability of our results. Perhaps the greatest strength of our trial were the face-to-face clinical interviews at multiple follow-up time points, allowing us to have clinical diagnoses of psychopathology besides our self-report instruments, which have been found to overestimate the prevalence of psychopathology (Fokkema, Smits, Kelderman, & Cuijpers, 2013). Another strong point is the integration of the acute biological assessment into the standard procedures of the Trauma Units, which enabled the assessment of the acute stress hormone response from blood taken at the Trauma Units within minutes to hours of the traumatic event.
8.3.2
Limitations in recruitment, attrition and participation

Compared to other trauma-affected populations, such as victims of domestic violence, rape or disasters, traumatic injury patients can be identified and monitored in the immediate phase after trauma. That makes them the object of frequent investigation when it comes to the aetiology and course of post-trauma psychopathology (Koren, Arnon, & Klein, 1999; Michaels et al., 1998; O’Donnell et al., 2004; Shalev et al., 1998). However, injury survivors are not necessarily easy to motivate for (long term) research participation. Despite our repeated efforts, either in-hospital, via telephone or via postal mail, we were unable to contact one fifth \( (n = 664) \) of the total adult population of the two trauma centres for participation in the trial for unknown reasons. They simply did not respond to any of our efforts. Compared to patients assessed for eligibility \( (n = 1,729) \), non-responders were significantly younger \( (p < .001) \) and spent less days in hospital after injury \( (p < .001) \). Therefore, we cannot rule out possible selection bias of participants in the trial.

Another important consideration with regard to our patient sample is the attrition at the 6 and 12 month follow-up assessments. Patients that dropped out after 6 or 12 months were more often unmarried \( (p < .05) \), younger \( (p < .05) \), less severely injured \( (p < .01) \), had a higher GCS score \( (p < .05) \) and scored higher on baseline self-reported anxiety and depressive symptoms (HADS; \( p < .01 \)) than those that remained in the study. This indicates that specific subgroups of patients might not be evenly well represented in the later assessments. Lastly, as described in Chapter 3, 330 patients of the total sample of 852 patients did not complete the screening instruments at the baseline assessment. Six month PTSD was more than twice as prevalent in patients who did not complete the screeners (14%) compared to those who did (6%), which indicates a certain reluctance for screening or research participation among patients at risk of later PTSD.

8.3.3
Statistical power

Based on previous research in comparable populations (Conlon et al., 1999), we estimated to find 19% PTSD incidence. This turned out to be 12% at 4-6 weeks post-trauma in our total sample (see Table 1.1 in the Introduction), with lower rates in subsamples, such as the RCT (Chapter 7). It may be that the psychological impact of the traumatic events leading to the injury in our study was less severe. In general, rates of psychopathology after unintentional trauma, i.e., accidents or natural disasters, are substantially lower than after intentional trauma, i.e., acts of violence, rape or war (Santiago et al., 2013). In our study this led to several
limitations. First, it may have caused lack of power to detect stronger or significant associations with acute stress hormones (Chapter 2) and acute pharmacotherapy (Chapter 7). Second, it hindered the exact determination of cut-off values for screening for a future diagnosis of PTSD, due to the limited number of participants with 6-month PTSD who completed all screening instruments (Chapter 4). Third, it may also have left little room for symptom improvement on the whole in comparing the web-based intervention and the control group (Chapter 7). In addition, it may have led participants to experience little personal incentive to access and use the intervention. Our post hoc subgroup analyses, in which we found that individuals with high initial symptom levels possibly benefited from the intervention, underscore this, although caution is necessary due to the limited size of the subgroups.

8.3.4 Generalisability

The fact that we included consecutive patients from multiple locations with heterogeneous injuries and injury mechanisms adds to the generalisability of our results to other injury populations. However, as mentioned above, one in five consecutive patients did not respond to our recruitment endeavours and thus we are uncertain whether our results are valid for this particular group. Certain patients were also excluded from participation due to restrictions in language, residency, cognitive abilities, pre-existing psychiatric morbidity or physical fitness. Therefore, caution must be met when generalizing our results to the broader population of injury patients presenting at the ER or Trauma Unit. Further, in our RCT, participants also needed to be able to log in within the first month after injury, as this was part of our design to examine the preventive effectiveness of the intervention. This inhibited us to include patients who were physically or cognitively unable to perform the intervention within our time restrictions. Lastly, translating our results to trauma-affected populations with higher conditional PTSD prevalence rates, such as survivors of violence or rape, should also be met with caution.

8.4 IMPLICATIONS FOR PRACTICE

The acute phase after traumatic injury is hectic. Perhaps before realizing the event even occurred, the survivor may be confronted with being injured, being in pain, being transported by ambulance to a hospital, undergoing extensive medical examination, and -often- being hospitalised. Not all injury patients may undergo this sequence consciously during the acute phase, but in the days and weeks that follow, they may face the impact of the event and its consequences in multiple domains of life. The injury victim may have to deal with the fear of permanent disability, with financial insecurities, with the loss of family members or even children. Unmistakably, the family of the injured victim is affected too, firstly by the shock of the incident and the injury, secondly by the effects for daily life, possibly accompanied by
personal grief. As a consequence, dealing with psychological issues may be of later importance. As our and previous studies have shown, most patients are resilient and show a natural psychological recovery within the first year. A proportion of trauma patients, however, develop persistent psychological symptoms, and those are the patients worth targeting early on.

The results from our RCT suggest that patients with high initial PTSD symptoms may benefit from an early psychological internet intervention, such as the Trauma TIPS program. Due to power issues we do not know whether the intervention may have also worked for patients with lower levels of acute distress. However, the Trauma TIPS program showed potential in preventing PTSD, as one of the few universal self-help psychological interventions targeting a recently traumatized sample. Important aspects in the clinical implication for trauma patients are its voluntary nature, allowing patients to match elements of the program to their needs in their own timeframe, and the low burden on existing personnel resources. Certain modifications to the program may increase its effectiveness. Using mobile application software increases flexibility for usage of the program, especially for bedridden patients with limited access to computers or laptops. In addition, mobile applications can be linked to alert messages, social platforms and information services that may also positively affect adherence to the program, as previous studies have shown (Kelders, Kok, Ossebaard, & Van Gemert-Pijnen, 2012). Another modification is allowing the possibility for guided self-help. A recent RCT showed that offering imaginal and in vivo exposure as early as 24 hrs after injury, and followed up at one and two weeks later, may prevent the development of PTSD symptoms (Rothbaum et al., 2012). Besides offering information on in vivo self-exposure exercises, as currently in the program, a module may be added that allows patients to design their personal in vivo exposure hierarchy in consultation with a therapist. A similar guided self-help protocol has shown promise in the treatment of PTSD patients (Rothbaum et al., 2012). This may also include follow-up monitoring and feedback, and could involve the patient’s social network, both for support to the patient and for the wellbeing of the family members themselves.

Within a stepped care approach for trauma survivors, this program may fit as an intermediate step before offering curative treatment for PTSD, such as CBT or EMDR. Ideally, the program is offered to survivors with high initial distress. This implies that injury patients are screened systematically to select those with the worst prognosis for psychological recovery. Screening for early PTSD symptom levels in the days following injury has shown predictive for chronic PTSD. Therefore, one possibility to implement early screening after injury is to register email addresses or mobile telephone numbers at the ER or Trauma Unit to contact patients in the subsequent days or weeks for voluntary screening and monitoring of symptoms. This may also be done via email or mobile applications alerts, and may be linked to information services for follow-up contact with a personal GP or trauma specialist. The screening questionnaire may consist of the SPAN, TSQ, or IES-R, as these showed comparable results in prognostic accuracy for 6 month PTSD. In practice,
when patients score high on acute distress, they may be offered the Trauma TIPS program as a next step together with monitoring of the symptom course. If symptoms persist, patients are to be followed up with more elaborate diagnostic examination and treatment if necessary.

Although acute cortisol levels contributed significantly to the development of PTSD, its use as an individual biological screener for PTSD, especially considering the low explained variance found in our sample, still has to be proven. Our results confirmed the assumption that HPA-axis dysregulations may impair the possibility for recovery after trauma (Yehuda, 2002). Consequently, this solidifies the basis for interventions on the acute glucocorticoid response, congruent with results from recent studies (Delahanty et al., 2013; Schelling et al., 1999; Schelling et al., 2001; Schelling et al., 2004; Schelling et al., 2006; Zohar, Yahalom et al., 2011).

Our observed association between early opiate administration and fewer PTSD symptoms at 6 weeks may indicate that morphine benefits psychological recovery after injury. However, the nature of the study precludes inferences about causality and effectiveness. An additional consequence of early morphine administration may also be impairment of declarative memory. Besides impairment of fear conditioning (Szczytkowski-Thomson et al., 2013) and of newly retrieved memory under conditions of intense stress (Schneider et al., 2013), morphine may also impair the consolidation of details of the event that may be useful to recollect for other purposes, such as in criminal law cases. Therefore, more knowledge into opiate’s effects on memory is needed.

8.5 FUTURE RESEARCH

Based on the results from our study, we propose several suggestions for future research. First, the Trauma TIPS intervention may be modified to mobile applications with more adherence increasing features, as described above, possibly adding therapist guidance in performing in vivo exposure exercises, and subsequently tested for feasibility before implementing in injury populations. This may include user-based evaluations of the elements in the program, to ensure that the program elements are functional, but also easy to understand and perform (Kassam-Adams, 2014). Additionally, the effectiveness of the Trauma TIPS intervention in individuals with high levels of distress needs to be replicated in a randomized controlled trial.

As mentioned in the previous paragraph, the sensitivity and specificity of acute cortisol for predicting future PTSD needs to be examined to make inferences on its usefulness as an early PTSD risk screener. Acute cortisol levels have shown an interesting biomarker for augmenting the acute stress response (Zohar, Yahalom et al., 2011; Zohar, Juven-Wetzler et al., 2011). As an addition to current studies, it would be interesting to examine whether administering hydrocortisone to acutely injured trauma patients may increase the effects of preventive exposure exercises, as previous studies have shown that hydrocortisone increases extinction learning (de Quervain et al., 2011).
Another suggestion for future research is to investigate the effectiveness of early opiate analgesics on preventing PTSD after injury in a RCT, as the current findings of our and previous studies have been limited to observed associations in injury samples (Bryant et al., 2009; Holbrook et al., 2010; Nixon et al., 2010; Saxe et al., 2001; Stoddard, Jr. et al., 2009).

In terms of a stepped care approach for PTSD after injury, future research may examine the effectiveness of early screening, monitoring, offering of a (guided) self-help program and curative treatment compared to care as usual. At this instance, care as usual implies that patients have intensive medical contact during their time in the ER and hospital stay, but are out of sight when they leave the hospital. Some may have a follow-up appointment at the trauma specialist or GP for their injuries, but generally no check-up of psychological wellbeing at any stage during this time. Early referral to psychological services of patients with high initial distress is incidental and dependent on the mindfulness of the trauma staff member or GP. To date, no comprehensive study of the effectiveness of stepped care for PTSD after injury has been performed.
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Summary
Summary

Research focus

The findings presented in this thesis originated from the Trauma TIPS-project. Trauma TIPS, which stands for “The Incidence of Post-trauma psychopathology Study”, was a prospective longitudinal study into the psychological recovery of injured trauma patients from the level-1 trauma centres of the Academic Medical Centre (AMC) and the VU university medical centre (VUmc). A total of 852 adult trauma patients participated in the study. The study focused on the prediction and prevention of post-trauma psychopathology in the acute phase following traumatic injury. The aims of the studies were:

1. to investigate the predictive role of acute post-injury cortisol and DHEAS for acute and chronic PTSD (Chapter 2);
2. to examine the diagnostic accuracy of three early screening instruments for 6-month PTSD (Chapter 3);
3. to develop and test the effectiveness of a web-based early psychological intervention to prevent PTSD in injured trauma survivors (Chapters 4, 5, and 6);
4. to investigate the association between early pharmacotherapy within the initial 48 hours of injury and PTSD at 6 weeks and within the first year after trauma (Chapter 7).

Conclusions

Cortisol and DHEAS as predictors for PTSD (Chapter 2)

To examine whether acute plasma cortisol and DHEAS levels predict later PTSD, data from 397 adult injury patients from the AMC’s and VUmc’s Trauma Units were collected. The results showed that patients with lower acute cortisol levels to trauma were more likely to develop acute and chronic PTSD symptoms. These results were independent from known confounding factors, such as age, gender, time of blood sampling, injury severity, trauma history, and ICU admission. Higher acute DHEAS levels and a smaller cortisol-to-DHEAS ratio were found to contribute to 6-week PTSD symptoms, but not after controlling for the same confounding factors, and not at 6 months. Diagnoses of acute or chronic PTSD were not predicted by cortisol, DHEAS or cortisol-to-DHEAS ratio. Lastly, acute DHEAS did not contribute significantly to PTSD symptom change between 6 weeks and 6 months. Our findings confirm the hypothesis that insufficient activation of the HPA-axis in response to stress may lead to the development of PTSD.
Three self-report instruments for PTSD symptoms, the SPAN (4 items), TSQ (10 items) and IES-R (22 items), were evaluated and compared on the accuracy for predicting a diagnosis of PTSD at 6 months. To minimise the chance for false positives, we aimed for a fixed, high sensitivity of 80%. Data of 311 of the 852 included injury patients of the AMC and VUmc hospitals were analysed who completed the instruments and clinical assessments. Eighteen patients (5.8%) of the final sample were diagnosed with PTSD at 6 months, significantly less than in excluded patients from the total sample (n = 74, 13.7%). The results showed good and similar AUCs for all instruments (0.82-0.83), indicating adequacy in distinguishing between individuals with and without PTSD at 6 months. The specificities were modest for all instruments (SPAN: 64%, TSQ: 59%, IES-R: 72%), implying poor quality in identifying non-cases. Thus, the instruments could well be used as a first selection step of possible cases, but a second, more comprehensive, diagnostic examination is needed to identify individuals in need of treatment. Importantly, the specificities did not significantly differ between tests, suggesting that the briefer instruments, SPAN and TSQ, are as accurate as the longer, IES-R.

The main purpose of the Trauma TIPS intervention, a self-guided internet-based early psychological intervention, was to decrease acute hyperarousal and anxiety and to prevent the onset of PTSD. The program was designed to incorporate free choice using optional features, and targeted at successful recovery instead of conferring symptom information. Elements of CBT were presented in 6 consecutive steps and included information/psychoeducation, modeling, stimulating seeking social support, stress management, and in vivo exposure exercises. Pilot study results of 5 consecutive traumatic injury patients and 5 matched healthy controls showed that the intervention was feasible and acceptable and had no immediate adverse psychological reactions for the patients or the control subjects. Adjustments to the programme concerned changing the online instrument for anxiety assessment, using an alternative voice for the relaxation exercises and eliminating technical difficulties (Chapter 4).

In Chapters 5 and 6, the design and results of a randomized controlled trial was described, in which 300 traumatic injury patients of the AMC and VUmc hospitals were randomized into an intervention condition (n = 151) and a control condition without intervention (n = 149). PTSD symptoms decreased significantly but equally over time in both groups. In addition, there were no group differences in prevalence of PTSD and MDD diagnoses, or in severity of depression and anxiety at 12 months. Another important finding was the low adherence to the program: one in five patients in the intervention group never logged into the intervention. The
freedom patients had in accessing the intervention and choosing the elements, may have contributed to this lack of adherence, although adherence is generally low in online self-help programs. Features, such as a more interactive social platform or therapist feedback, may have enhanced participant motivation and, consequently, the health benefits by increased exposure to the working elements. Another possibility is that a computerized program did not match the acute needs of the injury victims, resulting in some of them not using it. Besides limited usage of the intervention, our sample’s overall low PTSD symptom level left little room for symptom improvement for the whole group and may have led to the absence of significant group differences. Results from post hoc subgroup analyses suggested that the Trauma TIPS intervention was effective in reducing PTSD symptoms in individuals with high initial symptom levels. Based on these results, we conclude that there are currently no indications that offering a voluntary, information-based prevention program via the Internet to unselected injury victims is useful in preventing PTSD symptoms.

Influence of acute pharmacotherapy on PTSD development (Chapter 7)

All in-hospital administration of beta-blockers, benzodiazepines, corticosteroids and opiate analgesics within the initial 48 hrs post-injury were documented for 629 consecutive injury patients from the AMC’s Trauma Unit. Opiate administration within 48 hrs was negatively associated with 6-week PTSD symptoms, controlling for background and injury-related characteristics. Explorative univariate analyses showed that, compared to patients without any of the specified pharmacotherapy categories, fewer patients with opiate analgesics within 48 hrs post-injury were diagnosed with PTSD at 6 weeks and within the whole first year after trauma. Because beta-blockers (3.8%), corticosteroids (2.2%) and benzodiazepines (7.8%) were rarely prescribed, their role in the development of PTSD was not examined further. Our results point to a possible preventive effect of early opiate administration on subsequent PTSD symptom development. Our results also extend previous findings by showing that opiates may reduce the risk for PTSD, even after controlling for concurrent pharmacotherapy, and even up to 1 year post-trauma. However, the mechanisms that drive this effect need more clarification. Moreover, the effectiveness of in-hospital opiate analgesics compared to placebo in preventing PTSD may be tested in a randomized clinical trial in recent trauma survivors.

Implications for practice

The acute phase after traumatic injury is hectic. Perhaps before realizing the event even occurred, the survivor may be confronted with being injured, being in pain, being transported by ambulance to a hospital, undergoing extensive medical examination, and -often- being hospitalised. Not all injury patients may undergo this
sequence consciously during the acute phase, but in the days and weeks that follow, they may face the impact of the event and its consequences in multiple domains of life. The injury victim may have to deal with the fear of permanent disability, with financial insecurities, with the loss of family members or even children. Unmistakably, the family of the injured victim is affected too, firstly by the shock of the incident and the injury, secondly by the effects for daily life, possibly accompanied by personal grief. As a consequence, dealing with psychological issues may be of later importance. As our and previous studies have shown, most patients are resilient and show a natural psychological recovery within the first year. A proportion of trauma patients, however, develop persistent psychological symptoms, and those are the patients worth targeting early on.

The results from our RCT suggest that patients with high initial PTSD symptoms may benefit from an early psychological internet intervention, such as the Trauma TIPS program. Important aspects in the clinical implication for trauma patients are its voluntary nature, allowing patients to match elements of the program to their needs in their own timeframe, and the low burden on existing personnel resources, such as emergency department staff or GP's. Certain modifications to the program may increase its effectiveness. Using mobile application software increases flexibility for usage of the program, especially for bedridden patients with limited access to computers or laptops. Another modification is allowing the possibility for guided self-help. This may also include follow-up monitoring and feedback, and could involve the patient’s social network, both for support to the patient and for the wellbeing of the family members themselves.

Within a stepped care approach for trauma survivors, this program may fit as an intermediate step before offering curative treatment for PTSD, such as CBT or EMDR (Eye Movement Desensitization and Reprocessing). Ideally, the program is offered to survivors with high initial distress. This implies that injury patients are screened systematically to select those with the worst prognosis for psychological recovery. Screening for early PTSD symptom levels in the days following injury has shown predictive for chronic PTSD. Therefore, one possibility to implement early screening after injury is to register email addresses or mobile telephone numbers at the emergency department or Trauma Unit to contact patients in the subsequent days or weeks for voluntary screening and monitoring of symptoms. This may also be done via email or mobile applications alerts, and may be linked to information services for follow-up contact with a personal GP or trauma specialist. The screening questionnaire may consist of the SPAN, TSQ, or IES-R, as these showed comparable results in prognostic accuracy for 6 month PTSD. In practice, when patients score high on acute distress, they may be offered the Trauma TIPS program as a next step together with monitoring of the symptom course. If symptoms persist, patients are to be followed up with more elaborate diagnostic examination and treatment if necessary.
Nederlandse samenvatting (Dutch Summary)
Nederlandse samenvatting (Dutch Summary)

Focus van het onderzoek

De onderzoeksgesprens van de studies beschreven in dit proefschrift zijn afkomstig uit het Trauma TIPS-project. Trauma TIPS staat voor “The Incidence of Post-trauma psychopathology Study” en betreft een prospectieve, longitudinale studie waarin patiënten van de Trauma Units van het Academisch Medisch Centrum (AMC) en het Vrije Universiteit medisch centrum (VUmc) een jaar lang werden gevolgd op het gebied van hun geestelijke gezondheid. In totaal namen 852 volwassen letselpatiënten deel. De studies in dit proefschrift waren gericht op het voorspellen en voorkomen van posttraumatische stress stoornis (PTSS) in de acute fase na traumatisch letsel en hadden de volgende doelstellingen:

(1) het onderzoeken van de rol van acute cortisol en DHEAS bloedwaarden in de voorspelling van PTSS na traumatisch letsel (Hoofdstuk 2);
(2) het onderzoeken en vergelijken van de accuratesse van drie veelgebruikte screeningsinstrumenten afgenomen in de acute fase na trauma om patiënten met verhoogd risico op PTSS 6 maanden na het trauma te identificeren (Hoofdstuk 3);
(3) het ontwikkelen en testen van de effectiviteit van een vroege, psychologische internet-interventie ter preventie van PTSS na traumatisch letsel (Hoofdstukken 4, 5, 6);
(4) het onderzoeken van het verband tussen vroege farmacotherapie na letsel en PTSS na 6 weken en binnen het eerste jaar na trauma (Hoofdstuk 7).

Conclusies

Cortisol en DHEAS als voorspellers van PTSS (Hoofdstuk 2)

Uit bloedafname tijdens het initiële medische onderzoek op de Trauma Unit werden de niveaus van cortisol en DHEAS bepaald van 397 letselpatiënten. Patiënten met lagere acute cortisolwaarden hadden een grotere kans op het ontwikkelen van PTSS-symptomen 6 weken en 6 maanden na trauma. Deze resultaten waren onafhankelijk van invloedsgroepen, zoals leeftijd, geslacht, timing van bloedafname, letselernst, eerdere traumatische ervaringen en intensive care opname. Hogere acute DHEAS-waarden en een kleinere ratio tussen cortisol en DHEAS waren alleen significant geassocieerd met PTSS-symptomen na 6 weken, maar niet na controle voor de eerder genoemde invloedsgroepen, en niet na 6 maanden. Diagnoses van acute en chronische PTSS werden niet voorspeld door de stresshormonen. Tevens vertoonden acute DHEAS en de ratio tussen cortisol en DHEAS geen significante relatie met verandering in PTSS-symptomen tussen 6 weken en 6 maanden. Deze
resultaten bevestigen de hypothese dat een verstoorde activatie van de HPA-as in reactie op stress kan leiden tot de ontwikkeling van PTSS, waarbij een lage cortisolrespons een kwetsbaarheid kan vormen voor acute en chronische PTSS.

**Accuratesse van vroege risicoscreeners voor PTSS (Hoofdstuk 3)**

Drie zelfrapportagevragenlijsten voor PTSS-symptomen, de SPAN (4 vragen), de TSQ (10 vragen) en de IES-R (22 vragen), werden geëvalueerd en vergeleken in hun vermogen om een diagnose PTSS 6 maanden na letsel te voorspellen. Om de kans op vals positieven te beperken werd daarbij uitgegaan van een sensitiviteit van 80%. Van de 852 deelnemers werden 311 patiënten onderzocht die de vragenlijsten en de klinische meting van PTSS hadden volbracht. De drie instrumenten waren even goed in het onderscheiden van individuen met en zonder PTSS op 6 maanden na trauma (Areas Under the Curve=0.82-0.83). Bij de vastgestelde sensitiviteit van 80% waren de gevonden specificiteitswaarden bescheiden (SPAN: 64%, TSQ: 59%, IES-R: 72%). Hieruit blijkt dat hoewel de instrumenten patiënten met toekomstige PTSS adequaat kunnen identificeren, ze minder goed zijn in het uitsluiten van patiënten zonder diagnose PTSS. Uit deze gegevens concluderen wij dat deze instrumenten gebruikt kunnen worden voor een eerste, bredere selectie van risicopatiënten voor PTSS, gevolgd door meer uitgebreid diagnostisch onderzoek om personen te selecteren die baat hebben bij verdere behandeling. Qua specificiteit verschillen de kortere lijsten SPAN en TSQ niet significant van de langere lijst IES-R, wat erop duidt dat kortere screeners even accuraat zijn als langere in het selecteren van patiënten met verhoogd risico op PTSS na letsel.

**Het ontwikkelen en testen van de effectiviteit van een vroege, psychologische internet-interventie ter preventie van PTSS na traumatisch letsel (Hoofdstukken 4, 5, 6)**

Als onderdeel van dit project werd de Trauma TIPS internet interventie ontwikkeld. Het doel van deze interventie was om symptomen van acute spanning en angst te verminderen en daarmee de ontwikkeling van PTSS-symptomen tegen te gaan. In zes stappen werden de volgende elementen uit de cognitieve gedragstherapie gebruikt: informatie/psychoeducatie, modeling, stimuleren van het zoeken van sociale steun, stressmanagement en in vivo exposure oefeningen. Pilotstudieresultaten onder vijf consecutieve letselpatiënten en vijf gematchte, niet-getraumatiserde, gezonde controles lieten zien dat de interventie toepasbaar en veilig was voor vervolgonderzoek. Enkele aanpassingen aan de interventie waren onder andere het wijzigen van de online angstmeting, het wijzigen van de stem van de ontspanningsoefeningen en het elimineren van technische knelpunten (Hoofdstuk 4). In hoofdstukken 5 en 6 kwamen de opzet en de resultaten van vergelijkend effectiviteitsonderzoek van de Trauma TIPS-interventie aan de orde. Drie honderd opeenvolgende volwassen letselpatiënten van de Trauma Units van het AMC
en VUmc werden gerandomiseerd over een interventieconditie \((n = 151)\) en een controleconditie zonder interventie \((n = 149)\). In beide groepen namen de PTSS-symptomen significant af in tijd, zonder verschil tussen de groepen. De groepen waren ook gelijk in prevalentie van PTSS en depressie en in de ernst van depressieve en angstsymptomen 12 maanden na trauma. Een belangrijke andere uitkomst was dat één op de vijf deelnemers in de interventiegroep niet in de interventie had ingelogd. Hoewel dit een bekend probleem is bij online zelfhulpprogramma’s, kan dit te maken hebben met de vrijheid die patiënten hadden in het uitvoeren van de interventie. Specifieke elementen zoals een geavanceerder sociaal platform of begeleiding bij de zelfhulpoefeningen hadden de motivatie voor het uitvoeren van het programma of de toewijding eraan mogelijk vergroot. Het zou ook kunnen dat een gecomputeriseerde interventie in de acute fase na het trauma niet aansluit bij de behoeften die letselpatiënten op dat moment hebben. Naast beperkingen in het gebruik van de interventie hadden de deelnemers over het algemeen lage niveaus van psychopathologie, waardoor weinig ruimte overbleef voor symptoomverbetering op groepsniveau. Daarnaast is het mogelijk dat sommige deelnemers weinig persoonlijk voordeel zagen in het uitvoeren van de interventie, omdat ze weinig psychopathologie ervoeren. Dit werd ondersteund door de resultaten van onze post-hoc analyses, waaruit bleek dat bij patiënten met meer vroege PTSS-klachten de Trauma TIPS-interventie effectief was in het verminderen van PTSS-symptomen in het jaar na letsel. Hieruit concluderen we dat het aanbieden van een vrijwillige, preventieve internetinterventie aan ongeselecteerde letselpatiënten niet effectief is in het voorkomen van PTSS-symptomen, maar dat aanwijzingen bestaan dat letselpatiënten met vroege PTSS-klachten er mogelijk wel baat bij hebben.

**De invloed van acute farmacotherapie op de ontwikkeling van PTSS (Hoofdstuk 7)**

Van 629 letselpatiënten van de Trauma Unit van het AMC werd alle medicatie in de categorieën beta-blockers, benzodiazepines, corticosteroïden en opioides pijnstilling gedocumenteerd die was toegediend in de eerste 48 uur na het letsel. Het krijgen van opioides pijnstilling binnen 48 uur na trauma was geassocieerd met minder PTSS-symptomen 6 weken na het letsel, waarbij gecontroleerd werd voor geslacht, leeftijd, hartslagfrequentie op de eerste hulp, letselernst, GCS, type trauma en gelijktijdige farmacotherapie (d.w.z., beta-blockers, benzodiazepines, corticosteroïden). Uit verkennende analyses bleek bovendien dat, vergeleken met patiënten zonder medicatie in de eerder genoemde categorieën, minder patiënten met opioides pijnstilling binnen 48 uur na trauma een diagnose van PTSS hadden na 6 weken en binnen het eerste jaar na het letsel. Beta-blockers, corticosteroïden en benzodiazepines werden slechts incidenteel voorgeschreven en daardoor niet verder onderzocht in verband met PTSS. In navolging van eerdere observationele studies in letselpopulaties duiden onze bevindingen op een mogelijk gunstig effect van opioides pijnstilling op de ontwikkeling van PTSS na letsel. Nader onderzoek kan uitwijzen welk mechanisme aan dit effect ten grondslag ligt. Ook zou een
gerandomiseerde effectstudie (RCT) moeten worden uitgevoerd naar de effectiviteit van opioïde pijnstilling ter preventie van PTSS.

Praktische implicaties

De acute fase na traumatisch letsel is hectisch. Van het ene op het andere moment heeft het slachtoffer mogelijk te maken met de schok van de gebeurtenis, pijn, ambulancevervoer, medische onderzoeken en -meestal- ziekenhuisopname. Al ondergaat niet iedere patiënt dit allemaal bewust, wat volgt is de confrontatie met de gevolgen ervan: angst voor blijvende invaliditeit, zorgen over de financiële toekomst, soms ook zorgen over gewonde familieleden of zelfs rouw om het verlies daarvan. Onmiskenbaar wordt de familie van de patiënt ook getroffen en moet omgaan met de schok van het gebeurde, bezorgdheid over de dierbare en de gevolgen voor het dagelijks leven, mogelijk naast het eigen verdriet. Aandacht voor de psychologische gevolgen van alles komt hierdoor voor sommigen pas later aan de orde. Zoals deze en eerdere studies lieten zien, herstellen de meeste mensen vanzelf van hun psychische klachten in het eerste jaar na trauma. Bij ongeveer één op de vijf patiënten verbetert dit niet, en zij kunnen mogelijk gebaat zijn bij de uitkomsten van dit onderzoek.

De uitkomsten van de interventiestudie suggereren dat personen met veel vroege PTSS-klachten baat kunnen hebben bij het uitvoeren van een vroege psychologische internet-interventie, zoals Trauma TIPS. Belangrijke aspecten van het programma zijn de vrijheid in het kiezen van de programma-elementen en het uitvoeren in een persoonlijk tijdsbestek, zodat het beter past bij de wensen en behoeften van de patiënt, en dat het nauwelijks een beroep doet op bestaande personele bezettingen, zoals SEH-verpleegkundigen of huisartsen. Het programma kan baat hebben bij bepaalde aanpassingen, zoals mobiele applicatie software voor het verhogen van de flexibiliteit en motivatie voor het uitvoeren van het programma. Ook zou zelfhulpbegeleiding kunnen worden toegevoegd zodat patiënten met professioneel advies en eventueel monitoring hun dagelijkse routine kunnen proberen terug te vinden. Hierbij zou ook het sociale netwerk van de patiënt kunnen worden betrokken, voor steun richting de patiënt en tegelijkertijd voor het welzijn van de familieleden.

Idealiter vormt een dergelijk programma een tussenstap tussen het vaststellen van vroege stressklachten en het aanbieden van behandeling, zoals cognitieve gedragstherapie of EMDR (Eye Movement Desensitization and Reprocessing). Dit betekent dat letselpatiënten systematisch gescreeën worden op een verhoogd risico voor langdurige psychische klachten. Een manier om dit te implementeren is om e-mailadressen of mobiele telefoonnummers te registreren bij binnenkomst op de SEH of Trauma Unit. Vervolgens kan in de dagen of weken erna contact worden gelegd met de patiënt voor vrijwillige screening en monitoring. Hierbij zijn alertberichten via e-mail of mobiele telefoon en directe links naar informatie of
contactgegevens van huisarts of vervolghulpverlening mogelijk. Zoals gevonden in dit onderzoek, zouden de instrumenten SPAN, TSQ of IES-R goed gebruikt kunnen worden voor het voorspellen van PTSS na 6 maanden. In de praktijk zou dit alles betekenen dat patiënten die hoog scoren op vroege PTSS-klachten, het programma aangeboden kunnen krijgen naast het monitoren van hun klachten. Als de klachten aanhouden, wordt een uitgebreider diagnostisch onderzoek verricht met mogelijk behandeling.
Dankwoord
Dankwoord

Opa’s verhalen over Indië, ik slurpte ze op. Die exotische voorbije wereld, onze familiegeschiedenis, ik kon er geen genoeg van krijgen. Mijn allereerste onderzoek, voor geschiedenisles in vijf-gymnasium, ging dan ook over de repatriëring uit Nederlands-Indië, en ik wist bij wie ik kon aankloppen voor eerstehands informatie. In retrospect de voedingsbodem voor mijn interesse in de psychotrauma: een eerste inkijk in sommige langdurige emotionele effecten van schokkende gebeurtenissen.

Bij het Veteraneninstituut in Doorn kon ik deze interesse professioneel maken en me verder verdiepen in hoe ervaringen jaren later en duizenden kilometers verder nog dagelijks een stempel drukken op het leven. De mogelijkheid om aansluitend te kijken naar hoe traumatisatie ontstaat, voorspeld en mogelijk zelfs voorkomen kan worden, als promovenda bij het Topzorgprogramma Psychotrauma, AMC Psychiatrie, maakte voor mij de cirkel rond. Het project Trauma TIPS werd snel daarna geboren.

‘It takes a village to raise a child’ bleek zeer toepasselijk voor het TIPS-kind. Het project werd een jarenlang begrip, een afdeling binnen de afdeling, een geoliede machine die afhankelijk was van de directe en indirecte betrokkenheid van zovelen. Het voelt goed om op deze plaats mijn dank daarvoor uit te spreken.

Traumatisch letsel, het overkomt bijna 800.000 personen per jaar in Nederland. Dit onderzoek draait om hen en de tijd en energie die de deelnemers tijdens een kwetsbare periode aan de studie hebben gegeven vervult me nog steeds met bewondering en dankbaarheid.

Mijn dank gaat uit naar mijn promotoren Miranda Olff en Berthold Gersons en copromotor Marit Sijbrandij, bedenkers en initiators van Trauma TIPS en mijn begeleiders. Miranda, onder jouw leiding heb ik het gevoel gehad dat the sky the limit was, er was niets te gek, en jouw motto “nooit geschoten, altijd mis” leidde meermaals tot (academische en geografische) uitstapjes die mijn blik verbredden en ervaringen vergrootten. Dank voor je vertrouwen en vrijheid. Berthold, je bent een grootheid in de wereld van de psychotrauma en ik voel me vereerd dat je tot aan het eind van dit traject mijn promotor bent gebleven. Jouw kracht in het project is geweest om niet te vergeten om wie het draaide, de patiënten. Dank voor alle klinische inspiratie. Marit, where to begin? Had iedere promovendus maar zijn eigen Marit. Als postdoc en later copromotor kende je betrokkenheid geen grenzen, vanaf mijn allereerste werkdag op de Tafelbergweg tot de allerlaatste versie van dit proefschrift. Dank voor je steun, je begeleiding en alles dat je me hebt geleerd. Een grote kracht van het Trauma TIPS-project was de verwevenheid met de
traumatologie, het samenspel tussen geest en lichaam. Carel Goslings en Jan Luitse, van top tot teen, van design tot uitvoer, van patiëntenvragen tot feedback op manuscripten, waren jullie er voor Trauma TIPS. Samenwerken met jullie maakte dit traject zo waardevol. Hans Reitsma, ik prijs me gelukkig dat je ons epidemiologisch geweten was. Ik pluk nog steeds de vruchten van jouw geduldige privécolleges over imputatie en mixed models. Rens van de Schoot, door je aanstekelijke enthousiasme over Bayesiaanse statistiek en motiverende peptalks verlaat ik altijd blij en geïnspireerd de Uithof. Op naar mooie nieuwe artikelen!

Aansluitend wil ik de afdelingen spoedeisende hulp, de trauma units en alle betrokken verpleegafdelingen in het AMC en VUmc danken voor de prettige samenwerking. In het bijzonder dank aan Arjen Budding, Fred Bakker, Bart Veenings en Joost van Galen voor het praktische meedenken. Dank ook aan mijn collega’s bij AMC chirurgie met wie ik kon sparen bij logistieke of instrumentele knelpunten: Mark, Ping, Teun Peter, Pieter, Jorgos en de overige leden van de REACT-projectgroep.

De studie was niet mogelijk geweest zonder de financiële steun van het ZonMW Doelmatigheidsprogramma en Stichting Achmea Slachtoffer en Samenleving. Mijn dank gaat tevens uit naar de leden van de begeleidingscommissie, Iris Bakker, Patrick Bindels, Hans te Brake, Mariët van Gelder, Carel Goslings, Jannie van den Hul-Omta, Sonja Leferink, Jan Luitse en Jos Weerts, en de werkgroepen Gevolgen van letsels (georganiseerd door de voormalige Stichting Consument en Veiligheid) en Trauma en neurobiologie voor alle nuttige commentaar en adviezen tijdens de loop van het onderzoek.

Op deze plaats spreek ik graag mijn dank uit aan Judith Sluiter, Margreeth Vroom, Henk van Weert, Pim Cuijpers, Bernet Elzinga en Ed van Beeck voor de bereidheid zitting te nemen in de promotiecommissie.

Het grootste deel van ‘the village’ dat nodig was om Trauma TIPS te doen opgroeien, betreft het team van onderzoeksassistenten, stagiaires en scriptiestudenten. Susanne van Buschbach, Nina van der Togt en Hendrieke Bolding, mijn trouwe werkvloer managers, jullie waren de drijvende kracht achter het project. Een nieuw registratiesysteem, extra stagiaires, last minute data-invoer vanwege een congres? Niets was jullie te gek of te veel. Dank voor jullie oneindige inzet, flexibiliteit en creativiteit om de machine draaiende te houden. De Trauma TIPS-koektrommel wordt nog steeds in ere gehouden. Aan alle studenten die door de jaren heen meewerkten aan de dataverzameling en -invoer, Linda, Sabina, Rutger, Lena, Rosalie, Kees-Jan, Annet, Michelle, Xiomara, Sanderina, Heleen, Lana, Melanie, Marina, Yak Mee, Elise, Maud, Kimberley, Annemieke, Saskia, Loes, Mara, Serge, Margina, Djahill, Maaike, Caroline en Carlijn, dank voor jullie inzet en samenwerking.
Collega's van het psychotraumateam en daarbuiten, Rogier Visser, Mirjam Nijdam, Giel-Jan de Vries, Mariel Meewisse, Gré Westerveld, Renée Hutter, Adrienne Frewie, Noor de Bruij, Sirry Thomar, Anke Witteveen, Sujuan Zhang, Frenny Wiersema, Kitty Schimmel (in herinnering), Ineke Vrijlandt, Rosaura Polak, Mirjam van Zuiden, Jessie Frijling, Laura Nawijn, Saskia Koch, Anja Lok, Charlotte Molenaar, Ellen Klaassens, Iva Bicanic, Els van Meijel, Pim Scholte, Femke Verduin, wat een voorrecht om met zoveel lieve en gezellige mensen samen te werken en mooie plekken te bezoeken. Wellbeing in Venetië, fietsen door Central Park, zwemmen in Kroatië, zoveel dierbare herinneringen en lang niet genoeg pagina's over om ze recht aan te doen. Ik zeg, het is wel weer tijd voor een reünie. Voetjes van de vloer!

Aan mijn nieuwe, Leidse collega's: dank voor jullie steun bij deze laatste loodjes. Ondanks ieders drukke agenda vond ik altijd wel een luisterend oor, praktische adviezen of zelfs personal coaching.

Annemieke en Marieke, allerliefste vriendinnen, natuurlijk zijn jullie mijn paranimfen. We vielen als puzzelstukjes in elkaar vanaf de allereerste werkgroep in ons allereerste studiejaar psychologie. Ik kan me niet meer gesteund voelen dan met jullie aan mijn zijde. JAM rules, 4-ever!

Aan mijn eigen steunnetwerk, lieve pap, mam, Dewi, Vicky, Mike, Stephen, (schoon-) familie, vrienden en vriendinnen, nu kan ik jullie laten zien waar ik al die tijd mee bezig was. Ongemerkt hebben jullie me de energie gegeven om hiermee door te gaan. Dank voor alle eetdates, saunabezoekjes, kinderspeeldates, oppasavondjes en ladies (later: mommies) nights out. Mam, aan jouw keukentafel vond ik de broodnodige laatste concentratie die nodig was om dit af te maken. Achteraf heel logisch: jij gaf me het vertrouwen dat ik het zelf kon doen, vanaf mijn allereerste spreekbeurt tot dit proefschrift. Dank dat je er altijd bent.

Lieve Ryan, mijn gestress, gesjees, getobber en gerace weten jou nooit omver te blazen. Hoewel ik het soms niet direct op waarde schat, ben ik stiekem jaloers op je eeuwige relaxedheid en je vermogen om overal de lol van in te zien. Je zei het laatst nog, het doel is een leuk leven te leiden. Jij maakt het leuk. Mijn schatjes, mijn apies, Jade en Liv. Ik hoef maar aan jullie te denken en ik weet waar het leven om draait. Ik hoop dat jullie altijd dansend door het leven zullen gaan (met papa en mama erbij). Happiness is the truth!
Curriculum Vitae, List of publications and Portfolio
Curriculum vitae

Joanne Mouthaan was born on August 29, 1979, in Sittard, The Netherlands. After a brief stopover in H.I. Ambacht, she moved to Papendrecht at age seven. After her pre-university education at Johan de Witt-gymnasium, Dordrecht, she started her studies in psychology at Utrecht University in 1997. In 2001, she graduated in the specializations Work, Health and Organisational Psychology and Clinical and Health Psychology. Her internship and Master’s thesis at the Veterans Institute (Doorn, The Netherlands) was focused on the needs and wishes of peacekeeping veterans. Next, as a scientific employee at the Centre for Knowledge and Expertise at the Veterans Institute, she studied the health and wellbeing of UNIFIL veterans (United Interim Force in Lebanon, 1979-1985). At the end of 2004, Joanne started on her PhD project at the Centre for Psychological Trauma of the Academic Medical Centre in Amsterdam, The Netherlands. In this project, she focused on the incidence, prediction and prevention of post-trauma psychopathology, aka ‘Trauma TIPS’, the results of which are described in this thesis. During her PhD work, Joanne also ventured in research projects into, among others, PTSD risk screening in police officers and disaster victims and stepped psychosocial care at the emergency department (Care Innovation Impulse), and regularly gave seminars and lectures to medical students and hospital staff. Joanne currently works as a lecturer in Clinical Psychology at Leiden University.
List of publications

Peer reviewed articles:


Books, book chapters and research reports:


### Portfolio

**Name PhD student:** Joanne Mouthaan  
**PhD period:** November 2004 - Februari 2013  
**Name PhD supervisor:** Prof. dr. M. Olff, Prof. dr. B.P.R. Gersons

## 1. PhD Training

### GENERAL COURSES

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### Conferences

- 4 Oral Presentations at the European Conference on Traumatic Stress Studies
- 3 Oral Presentations at Annual Meetings of the International Society of Traumatic Stress Studies
- Oral Presentation at the First International E-Mental Health Summit
- 2 Oral Presentations at Symposia for Dutch Association Anaesthetists
- Poster Presented at the Annual Meeting of the Dutch Speaking Society for Psychotrauma
- Oral Presentation at the Annual Spring Conference of the Dutch Society for Psychiatry
- 4 Poster Presentations at Annual Meetings of the International Society of Traumatic Stress Studies

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<td>4 Courses of Psychosocial Care After Trauma, Dept. of Medicine, Police Acute Care Teams</td>
<td>2006 - 2010</td>
<td>0.6</td>
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<td>2 Courses of Research Skills, Faculty of Medicine</td>
<td>2006 - 2007</td>
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<tr>
<td>10 Lectures on Psychological Trauma, Psychology and Medical Students and Faculty</td>
<td>2005 - 2012</td>
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<tr>
<td>4 Training Courses on Administration of the CAPS to Psychology and Medical Students and Faculty</td>
<td>2005 - 2009</td>
<td>0.6</td>
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### Supervising

- Supervising 2 Junior Researchers                                     | 2011 - 2012 | 2.0             |
- Supervising 10 MSC Students Writing Their Master's Thesis (6 Months) | 2005 - 2010 | 10.0            |
- Supervising 24 MSC Students During Their Clinical Internships (9 Months) | 2005 - 2010 | 20.0            |

### 2. Teaching
3. Parameters of Esteem

<table>
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<tr>
<th>GRANTS</th>
<th>Year</th>
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</thead>
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<tr>
<td>ORGANISATION FOR HEALTH RESEARCH AND DEVELOPMENT (ZONMW), GRANT NO. 62300038</td>
<td>2007-2011</td>
</tr>
<tr>
<td>STICHTING ACHMEA SLACHTOFFER EN SAMENLEVING (SASS), AID TO VICTIMS</td>
<td>2005-2011</td>
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<tr>
<td>CARE INNOVATION IMPULSE, AGIS ZORGVERZEKERINGEN</td>
<td>2008</td>
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Injured body, Injured soul?

Predicting and preventing posttraumatic stress disorder after injury

Joanne Mouthaan

Traumatic injury is common and may have a major impact on the survivor’s life. In the Netherlands alone, over 7 million injuries are registered yearly, caused by accidents in traffic, at home, at work, or by interpersonal violence. Besides physical recovery, survivors often deal with the psychological impact. Although most are resilient and show a natural psychological recovery within the first year, a proportion develops persistent psychological symptoms, among which posttraumatic stress disorder (PTSD). The studies in this thesis focused on how to predict and how to prevent the development of PTSD in the acute phase after traumatic injury.

Joanne Mouthaan (1979) received her Master’s degree in Psychology at Utrecht University in 2001, after which she worked as a behavioural scientist at the Veterans Institute in Doorn. In 2004, she started her PhD research on the Trauma TIPS project, the results of which are described in this thesis, at the Center for Psychological Trauma, Department of Psychiatry of the Academic Medical Center, Amsterdam, under the supervision of prof. dr. Miranda Olff, prof. dr. Berthold Gersons and dr. Marit Sijbrandij. She currently works as a lecturer in Clinical Psychology at Leiden University.