

POSTTRAUMATIC STRESS DISORDER AND CHRONIC
MUSCULOSKELETAL PAIN: HOW ARE THEY RELATED?

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ABSTRACT

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POSTTRAUMATIC STRESS DISORDER AND CHRONIC MUSCULOSKELETAL PAIN: HOW ARE THEY RELATED?

Symptoms of post-traumatic stress disorder (PTSD) are a common comorbidity in veterans seeking treatment of chronic musculoskeletal pain (CMP). However, little is known regarding the mutual influence of PTSD and CMP in this population. Using cross-sectional and longitudinal data from a randomized clinical trial evaluating a stepped care intervention for CMP in Iraq/Afghanistan veterans (ESCAPE), this dissertation examined the relationships between PTSD and CMP along with other factors including depression, anxiety, catastrophizing and health-related quality of life. The Classification and Regression Tree (CART) analysis was conducted to identify key factors associated with baseline PTSD besides CMP severity. A series of statistical analyses including logistical regression analysis, mixed model repeated measure analysis, confirmatory factor analysis and cross-lagged panel analysis via structural equation modeling were conducted to test five competing models of PTSD symptom clusters, and to examine the mutual influences of PTSD symptom clusters and CMP outcomes. Results showed baseline pain intensity and pain disability predicted PTSD at 9 months. And baseline PTSD predicted improvement of pain disability at 9 months. Moreover, direct relationships were found between PTSD and the disability component of CMP, and indirect relationships were found between PTSD, CMP and CMP components (intensity

and disability) mediated by depression, anxiety and pain catastrophizing. Finally, the coexistence of PTSD and more severe pain was associated with worse SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores. Together these findings provided empirical support for the mutual maintenance theory.

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Chapter I: Introduction

Overview

Posttraumatic stress disorder (PTSD) and chronic pain often co-occur and patients with chronic pain often report more severe PTSD symptoms (T. Moeller-Bertrama April 2009). The high rate of comorbidity suggests that the two disorders are related (Otis, Keane et al. 2003). To explore the nature of this relationship between PTSD and chronic pain, a number of theories have been proposed. For example, the Mutual Maintenance model (Sharp and Harvey 2001), one of the most influential theories, posits PTSD and chronic pain exacerbate and maintain each other through seven intermediate factors: (1) attentional and reasoning biases, (2) anxiety sensitivity, (3) reminders of the trauma, (4) avoidance of activities and sensations associated with pain and trauma, (5) depression and reduced activity levels, (6) anxiety and pain perception, (7) cognitive demand from symptoms that interfere with use of adaptive strategies. Another theory, the Shared Vulnerability Model (Asmundson, Coons et al. 2002) considers anxiety sensitivity as a predisposing risk factor for both PTSD and chronic pain. And the Perpetual Avoidance theory (Liedl and Knaevelsrud 2008) hypothesizes a PTSD and pain cycle in which each condition influences each other through avoidance/inactivity and hyperarousal; two of the primary symptoms shared by both PTSD and pain.

This chapter and related study discusses several conceptual models related to PTSD and chronic pain and aims to examine these models empirically using data from a clinical trial evaluating a stepped care intervention for chronic

musculoskeletal pain in Iraq/Afghanistan veterans (ESCAPE). In particular, this study aims to analyze the relationship and mutual influence between PTSD symptoms, chronic musculoskeletal pain, and other intermediate factors and outcomes such as depression, anxiety sensitivity, disability and quality of life. To complete the study aims, factor analysis, structural equation modeling and other statistical methods will be used.

This dissertation contains several chapters. First, Chapter 1 gives an overall introduction to the study objectives, rationale and methods. Next the chapter describes the study background including the diagnosis, prevalence, assessment instruments and conceptual models of posttraumatic stress disorder and chronic pain, as well as the empirical findings and theories about their comorbidity. Finally, several key components of the study are highlighted, including the statement of the problem, study objectives, study methodologies, study rationale and significance, study assumptions, and a brief summary of this chapter. Chapter 2 reviews the literature on PTSD and chronic pain comorbidity and several studies examining their relationship. Chapter 3 details the study design, hypotheses, and analytical methods.

Posttraumatic Stress Disorder

According to the *Diagnostic and Statistical Manual of Mental Disorders Fourth Edition* (DSM-IV)(American Psychiatric Association. 2000), posttraumatic stress disorder (PTSD) is one of several anxiety disorders, and is characterized by “the re-experiencing of an extremely traumatic event, symptoms of increased

arousal and avoidance of stimuli associated with the trauma.” To meet the diagnostic criteria for PTSD, an individual must have been exposed to a traumatic event as a victim or witness, and must have 1) at least one re-experiencing symptom; 2) at least three avoidance symptoms; 3) at least two arousal symptoms; and 4) those symptoms persisting for at least one month and causing significant distress to the patient (see Appendix A for detail of PTSD diagnostic criteria).

According to the National Comorbidity Survey Replication (NCS-R), the lifetime prevalence of PTSD was 6.8% among the U.S. adult population (Kessler, Berglund et al. 2005). Current past year PTSD prevalence was estimated at 3.5% (Kessler, Chiu et al. 2005). Both lifetime and 12-month prevalence rates were nearly three times as high among women as they were among men (Survey. 2005). Understandably studies of at-risk individuals (e.g., combat veterans, victims of vehicle accidents or criminal violence) have yielded higher prevalence rates. Depending on ascertainment methods and the population sampled, the prevalence rates reported by individual studies vary considerably. For example, a study reported 8.6% of patients seen in primary care clinics had PTSD (Kroenke, Spitzer et al. 2007). Of Iraq/Afghanistan War veterans,, approximately 13.8% have PTSD (Tanielian 2008), more than double the rate in the general population. In addition, PTSD is associated with other physical health problems including cardiovascular and respiratory diseases, chronic pain conditions, gastrointestinal illnesses, and cancer, as well as suicide attempts, poor quality of life, and short- and long-term disability (Sareen, Cox et al. 2007).

Psychological theories

A number of psychological theories have been proposed to explain the causes of PTSD.

- Behavior theory (OH 1960; Keane TM 1985): this theory proposes PTSD is caused by learned fear and avoidance behaviors that minimize the contact time with the conditioned cues to an extreme stressor such as a traumatic event. The avoidance behaviors thus prevent extinction of the learned fear.
- Fear network theory (cognitive and information-processing models): According to this theory, a fear network is formed following a traumatic event storing information about what is threatening and what should be escaped or avoided (Foa 1989). Anxiety disorders develop when the fear network contains faulty connections such as distorted evaluations of external threats that do not truly represent the state of the world (Foa 1989). When compared to other anxiety disorders, the size of the fear network in PTSD is larger, the networks are more easily activated, and the affective and physiological response elements of the network are more intense (Foa and Kozak 1986).
- Social-cognitive theory: this theory emphasizes the meaning of the trauma and the content of cognitions, assuming trauma survivors have a “completion tendency” that involves cycling between intrusive images and nightmares about the meaning of the trauma and defense processes, such as numbing and denial (Horowitz 1986). The experience of trauma

shatters the individual's assumptions about (1) personal invulnerability, (2) the world being meaningful, and (3) the self as positive or worthy (Janoff-Bulman 1992).

Biologically, PTSD is thought to be associated with a series of physiologic changes within the brain (including prefrontal cortex, amygdala and hippocampus), the autonomic nervous system, and the endocrine system (Kulich, Mencher et al. 2000). For example, PTSD has been associated with low levels of urinary cortisol and high levels of catecholamines, with a norepinephrine/cortisol ratio consequently higher than comparable individuals without PTSD.

Assessment instruments

Several screening tools and diagnostic instruments are available to assist clinicians in making a PTSD diagnosis, documenting a traumatic event, and assessing symptom severity. These include structured or semi-structured diagnostic interviews, such as the Clinician-Administered PTSD Scale (CAPS), the Structured Clinical Interview for DSM-IV (SCID), the Diagnostic Interview Schedule for DSM-IV (DIS-IV), and the Composite International Diagnostic Interview (CIDI), all of which might be used prior to or as a complement to the clinical interview; and non-diagnostic assessment and screening instruments such as the PTSD Checklist (PCL), the Posttraumatic Diagnostic Scale, the Davidson Trauma Scale, and the Keane PTSD Scale of the Minnesota

Multiphasic Personality Inventory (MMPI-PK), which assess *DSM-IV* symptoms of PTSD and symptom severity as well as associated features of PTSD.

The ESCAPE study includes the PCL as one of the psychological distress outcome assessment tools. The PCL is a 17-item self-report measure of the 17 *DSM-IV* symptoms of PTSD. Three validated versions (PCL-M for military, PCL-C for civilian, and PCL-S for specific stressful experience) of the PCL are available and can be used to screen individuals for PTSD, diagnose PTSD, or monitor symptom change during and after treatment.

The PCL is scored in the following ways (VA National Center for PTSD June 2010):

- A total symptom severity score (range = 17-85) can be obtained by summing the scores from each of the 17 items. Evidence suggests that a 5-10 point change represents reliable change (i.e., change not due to chance) and a 10-20 point change represents clinically significant change.
- A PTSD diagnosis can be made by:
 1. Determining whether an individual meets *DSM-IV* symptom criteria, i.e., at least 1 B item (symptoms of re-experiencing, see Appendix A), 3 C items (symptoms of avoidance, see Appendix A), and at least 2 D items (symptoms of arousal, see Appendix A). Symptoms rated as "Moderately" or above (responses 3 through 5) are counted as present.
 2. Determining whether the total severity score exceeds a given cut point. Some studies consider a score of 50 as a conservative PCL-

17 cut point (Forbes, Creamer et al. 2001; Gerrity, Corson et al. 2007). Other studies use a score of 44 as a cut point for PTSD diagnosis (Chossegros, Hours et al. 2011), or consider 41 as a valid cut point (Sherman, Carlson et al. 2005).

3. Combining methods (1) and (2) to ensure that an individual has sufficient severity as well as the necessary pattern of symptoms required by the DSM.

All three methods above are acceptable for research purposes, although method #1 and #3 tend to be more consistent with formal clinical diagnosis made by clinicians using structured or semi-structured diagnostic interviews.

Chronic pain

Unlike chronic pain syndrome, which is one type of somatoform disorder classified by DSM-IV, chronic pain is not a formal diagnosis. Any type of pain that persists for 6 months or longer is typically referred to as “chronic” pain (Merskey H). According to an internet-based survey, about 30% of US adults suffer from chronic pain (Johannes, Le et al. 2010). Chronic pain costs the U.S. up to \$635 billion each year in medical treatment and lost productivity (Institute of Medicine Report from the Committee on Advancing Pain Research 2011).

Chronic pain can be categorized by its origin, such as cancer pain, musculoskeletal pain (including arthritis, back problems, repetitive stress injuries, and fibromyalgia), headache and migraine, and neuropathic pain (e.g., pain related to herpes zoster or diabetes). According to the 1999-2002 National

Health and Nutrition Examination Survey (NHANES), chronic pain condition prevalence estimates were 10.1% for back pain, 7.1% for pain in the legs/feet, 4.1% for pain in the arms/hands, and 3.5% for headache (Hardt, Jacobsen et al. 2008). The three most common types of chronic pain are back pain, headache, and joint pain, two of which are categorized as musculoskeletal pain. The prevalence of musculoskeletal pain ranges between 38% and 47% among Persian Gulf War and Operation Iraqi Freedom/Operation Enduring Freedom veterans (Girona, Clark et al. 2006) (The Iowa Persian Gulf Study Group 1997). Musculoskeletal pain is the most common, disabling, and costly of all pain conditions (Badley, Rasooly et al. 1994; Elliott, Smith et al. 1999).

Chronic pain is frequently comorbid with psychiatric disorders, the most common ones being affective disorders (depression and anxiety), substance-related disorders, and personality disorders (Fishbain, Cutler et al. 1998). The following psychological theories have been proposed to explain the development and maintenance of chronic pain.

Psychological theories

- Behavior theory (operant theory): this theory focuses exclusively on “pain behaviors” and contingencies of reinforcement. According to this theory, pain behaviors, if negatively reinforced by, e.g. overprotection from work or household chores, could persist beyond the normal healing time expected for an injury (Fordyce 1996).

- Cognitive behavioral theory: this theory assumes unhelpful cognitive and behavioral reactions to pain such as catastrophizing, avoidance of pain-elicited activities or hypervigilance to bodily sensations and can lead to prolonged duration of pain, and higher levels of distress, dysfunction and disability.

Assessment instruments

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommended six core outcome domains for the assessment of pain: 1) pain severity/intensity, 2) physical functioning, 3) emotional functioning, 4) patient ratings of improvement and satisfaction with treatment, 5) associated symptoms, and 6) adverse effects. The IMMPACT group also recommended several outcome measures and instruments for these six domains including the Brief Pain Inventory, the Massachusetts General Hospital Pain Center's Pain Assessment Form, and the Beck Depression Inventory, for example.

The ESCAPE study measures pain-related disability and pain severity using the following instruments:

- The Roland Disability Scale is a 23-item pain-specific measure of physical disability originally validated in patients with back pain and subsequently validated in patients with non-malignant pain problems. Scoring is simple and ranges from 0 (no disability) to 23 (severe disability).

- The Graded Chronic Pain Scale (GCPS) is a brief 7-item scale that rates global severity of chronic pain in two domains: intensity and disability. Rich normative data exists for the GCPS.
- The SF-36 Bodily Pain scale contains two items which assess pain severity and interference. A large body of normative data available for this scale.
- The BPI Interference scale has 7 items that rates the interference of pain with mood, physical activity, work, social activity, relations with others, sleep, and enjoyment of life.

PTSD and chronic pain comorbidity

A review of PTSD and chronic pain studies indicated that pain symptoms and chronic pain are prevalent in patients with PTSD. The converse is also true, PTSD symptoms are common in patients with chronic pain, particularly in those with more severe pain, greater interference with activities of daily living, and more negative affect (Asmundson, Coons et al. 2002).

In particular, compared with the general population, the prevalence of PTSD has been found in a number of studies to be elevated among individuals with the following nine types of chronic pain: fibromyalgia, headache, migraine, orofacial pain syndromes, accident related pain, back pain, pelvic pain, mastalgia, and complex regional pain syndrome (Tobias Moeller-Bertram 2011). Another study found, however, patients with migraine did not experience PTSD symptoms more than the general population (Ifergane, Buskila et al. 2009). Evidence also shows that PTSD is most prevalent in patients with chronic

musculoskeletal pain who are classified as dysfunctional (i.e. those displaying higher pain severity, pain interference, elevated affective distress and fear, and lower activity), compared with those classified as interpersonally distressed (i.e. those displaying lower perceived social support) or adaptive copers (i.e. those displaying lower pain severity, pain interference, and affective distress) (Asmundson, Bonin et al. 2000). (Ifergane, Buskila et al. 2009)

Furthermore, PTSD and PTSD symptoms are strongly associated with current pain, overall pain ratings, and pain-related disability (Beckham, Crawford et al. 1997). McGhee et al. found that PTSD severity and chronic pain severity are positively correlated (McGhee, Slater et al. 2011). Other studies have shown that patients experiencing both PTSD and chronic pain report greater disability and poorer quality of life, and are less likely to receive effective treatment than those experiencing only one of the two conditions (Ifergane, Buskila et al. 2009). PTSD may also mediate the relationship between pain severity and depression, functional adjustment, and satisfaction with life (Bryant, Marosszeky et al. 1999).

The high comorbidity of PTSD and chronic pain suggests these two disorders are likely related. A number of theoretical models have been proposed to explain this relationship, which will be discussed in detail in the next chapter.

Statement of the Problem

The frequent co-occurrence of PTSD and chronic pain has been reported by many epidemiological studies. A limited number of studies have examined the relationship between PTSD and chronic musculoskeletal pain, resulting in

several testable conceptual models. Although these models seem to be supported by certain study results, there is still no consensus on the exact nature of the relationship between PTSD and chronic musculoskeletal pain due to its complexity. In particular, evidence is still lacking to answer the following questions:

- 1) How strong is the relationship between PTSD and chronic musculoskeletal pain?
- 2) Which factors mediate the relationship between PTSD and chronic musculoskeletal pain?
- 3) Do different clusters of PTSD symptoms (e.g. re-experiencing vs. avoidance vs. arousal) affect chronic musculoskeletal pain outcomes differently?

This study aims to answer the above questions using data from a longitudinal trial evaluating the effect of a stepped care intervention for Iraq/Afghanistan veterans with musculoskeletal pain. Various statistical methods will be used to explore and test the direct, indirect and possibly bi-directional relationships between PTSD symptoms, chronic musculoskeletal pain outcomes and other factors that may mediate or moderate the PTSD and chronic musculoskeletal pain relationship. The strength of these relationships will also be examined.

Study Objectives

In summary, this study's objectives include:

1. Examine the cross-sectional relationships between PTSD, depression, anxiety, chronic musculoskeletal pain severity, pain disability and quality of life.
2. Examine the relationships between different PTSD symptom domains, pain outcomes (pain intensity and pain disability) and pain beliefs (pain-related catastrophizing).
3. Examine the longitudinal relationships between PTSD and chronic musculoskeletal pain.

This study will test a number of hypotheses that may be implicated by various theories. It is not, however, intended to test or validate any specific conceptual model or theory.

Study Methodology

This study uses data from the ESCAPE trial. To evaluate the effectiveness of the stepped care intervention, the ESCAPE trial measured a comprehensive set of relevant outcomes and key variables at baseline as well as 3-, 6-, and 9-months after baseline. For our study, we are most interested in those variables related to 1) pain severity; 2) pain disability; 3) PTSD symptoms; 4) pain beliefs (pain-related catastrophizing), each of which may play a role in helping us better understand the relationship between PTSD and pain and the underlying mechanisms that explain this relationship.

Various statistical methods, including factor analysis, structural equation modeling and multivariate regression models will be used to examine the relationships and mechanisms hypothesized by various conceptual models.

Study Rationale and Significance

PTSD and chronic musculoskeletal pain are very common among veterans and cost billions of dollars each year in medical treatment and lost productivity. PTSD and chronic musculoskeletal pain frequently co-occur among veterans seeking treatment of either condition alone. Patients with both PTSD and chronic musculoskeletal pain are often more difficult to treat, utilize more health services, and suffer more distress and lower quality of life.

Despite the high comorbidity and negative impact of these two conditions, there have been relatively few studies investigating their longitudinal relationships. Several studies have attempted to examine the Mutual Maintenance model empirically. So far the results are incomplete and inconclusive due to 1) limited pain conditions studied: oral/facial pain e.g., no musculoskeletal pain; 2) limited trauma type: car accident, intimate partner violence, no combat injuries; 3) few longitudinal studies; 4) lack of control for confounding variables in most studies such as sleep quality, anxiety sensitivity, and attentional biases; 5) use of a single-factor rather than multi-factor model for PTSD symptoms ; 6) various competing and plausible models such as Shared Vulnerability model and Perpetual Avoidance model making it hard to determine which one represents the true relationships based on existing evidence.

This study will help improve our understanding of the relationship of PTSD and chronic pain, especially musculoskeletal pain, by analyzing a comprehensive set of data collected as part of a randomized controlled clinical trial. A better understanding of this relationship may help us develop a more effective assessments and treatment protocols when the two disorders co-occur. Clinically, a failure to appreciate the intricacies of co-occurring PTSD and chronic pain may result in reduced treatment efficacy and continuing negative outcomes (Asmundson, Coons et al. 2002).

Study Assumptions

This study is based on the assumption that PTSD symptoms are significantly associated with chronic musculoskeletal pain symptoms, including pain severity and life interference due to pain, and other psychiatric symptoms. The pain severity, interference, pain related disabilities, cognitive, physical and social functions and quality of life are worse among patients with comorbid chronic musculoskeletal pain and PTSD than among patients with chronic musculoskeletal pain only. The pain severity and other related outcomes are positively correlated with the severity of PTSD symptoms. After 9 months of treatment, the baseline PTSD symptoms and other factors can predict pain severity.

This study also assumes PTSD and chronic musculoskeletal pain may have a mutual maintenance relationship through various mechanisms. For example, the pain perception and catastrophic cognitions may be exacerbated by

PTSD symptoms such as hyperarousal or re-experiencing symptoms. Meanwhile, the sensation of pain may be a reminder of trauma experience for PTSD patients, resulting in increased PTSD symptoms. In addition, PTSD symptoms may exert their influence on chronic musculoskeletal pain severity through generalized anxiety or depression.

Summary

PTSD and chronic musculoskeletal pain frequently co-occur and may be related in some way. Several theories and models have been published to explain this relationship. This study aims to test a number of hypotheses empirically that may be implied by these models using data collected from a longitudinal study. A better understanding of the relationship between PTSD and chronic musculoskeletal pain may help us develop more effective assessments and treatment protocols when the two disorders co-occur.

Chapter II: Review of the Literature

Overview

According to the National Comorbidity Survey Replication (NCS-R) conducted between 2001 and 2003, PTSD is the 5th most common psychiatric disease in the United States with a lifetime prevalence of 6.8% among adults (Kessler, Berglund et al. 2005). In primary care clinics, prevalence of “current” PTSD is 8.6% (CI, 6.9% to 10.6%) (Kroenke, Spitzer et al. 2007). Of Iraq/Afghanistan War veterans, approximately 13.8% have PTSD (Tanielian 2008), more than double the rate in the general adult population. In addition, PTSD is significantly associated with other physical health problems including chronic pain conditions, as well as suicide attempts, poor quality of life, and short- and long-term disability (Sareen, Cox et al. 2007).

Chronic pain and PTSD frequently co-occur partly because several of the more common causes of chronic pain involve traumatic events such as motor vehicle accidents and work-related incidents (Sharp 2004). Besides, chronic pain especially musculoskeletal pain, and PTSD often share common symptoms, comorbidity, and risk factors (Asmundson, Coons et al. 2002). In fact, high comorbidity has been found among low back pain, fibromyalgia, and PTSD, which seems to suggest a common etiology (Schur, Afari et al. 2007).

Several narrative reviews (Asmundson, Coons et al. 2002; Otis, Keane et al. 2003; Sharp 2004; Sharp and Keefe 2006; Asmundson and Katz 2009) and one systematic review (Tobias Moeller-Berrtram 2011) have discussed the comorbidity of PTSD and chronic pain. These reviews support the following

general findings: 1) PTSD and chronic pain frequently co-occur (Asmundson, Coons et al. 2002; Otis, Keane et al. 2003; Asmundson and Katz 2009; Tobias Moeller-Berrtram 2011); 2) The prevalence of PTSD in the chronic pain population is higher than the general population (Asmundson, Coons et al. 2002; Otis, Keane et al. 2003; Sharp 2004; Sharp and Keefe 2006; Asmundson and Katz 2009; Tobias Moeller-Berrtram 2011); 3) The prevalence of chronic pain in the PTSD population, especially among veterans, is higher than the general population (Otis, Keane et al. 2003; Asmundson and Katz 2009; Tobias Moeller-Berrtram 2011); 4) The comorbidity of PTSD and chronic pain often increase the symptom severity of either condition (Otis, Keane et al. 2003).

The high comorbidity suggests PTSD and chronic pain are likely related. A number of theories have been proposed to explain this relationship, including the Mutual Maintenance Model (Sharp and Harvey 2001), the Shared Vulnerability Model (Asmundson, Coons et al. 2002), and the Perpetual Avoidance Model (Liedl and Knaevelsrud 2008), to name just a few. Meanwhile, a small but growing number of studies have examined the relationships of PTSD and chronic pain, and validated the above theoretical models.

This chapter will review the following topics: 1) prevalence of chronic pain in PTSD cohorts and vice versa; 2) influence of PTSD on chronic pain and vice versa; 3) conceptual models explaining the relationship between PTSD and chronic pain; 4) treatment of patients with both PTSD and chronic pain. Previous reviews will serve as the foundation of this dissertation research, which aims to

further examine the relationship between PTSD and chronic pain using empirical data collected from a randomized controlled clinical trial in a primary care setting.

Prevalence of Chronic Pain in PTSD

Pain is among the most commonly reported physical symptom in individuals with PTSD, especially among U.S. veterans (Tobias Moeller-Bertram 2011). Beckham et al. found the prevalence of chronic pain to be as high as 80% among 129 consecutive out-patient combat veterans with PTSD (Beckham, Crawford et al. 1997). Shipherd et al. reported that two-thirds (66%) of the Veteran Affairs (VA) patients with PTSD had a chronic pain diagnoses prior to mental health treatment for their PTSD (Shipherd, Keyes et al. 2007). In a sample of Croatian war veterans, headache was experienced by 63.8% of the subjects with PTSD, facial pain by 12.8%, and pain in the region of the jaw by 10.6%, suggesting that PTSD patients are at increased risk for the development of temporomandibular disorder symptoms (Uzac, Kovac et al. 2006). White et al found that over a four-year period for 543 veteran inpatients treated for PTSD, 25% developed some type of musculoskeletal problem frequently accompanied by pain (White and Faustman 1989).

Compared to patients without PTSD, patients with PTSD have significantly higher odds of pain (Odds ratio (OR) ranging from 2.1 to 9.7) (Lowe, Kroenke et al. 2011), psychiatric comorbidity such as depression, anxiety, panic disorder and substance abuse, as well as several physical health problems including cardiovascular, respiratory, musculoskeletal, neurological,

gastrointestinal symptoms and cancer (McFarlane, Atchison et al. 1994; McWilliams, Cox et al. 2003; Arguelles, Afari et al. 2006; Sareen, Cox et al. 2007; Sareen, Cox et al. 2007; Afari, Harder et al. 2009). One case-control study conducted among adolescent girls with a PTSD diagnosis showed that musculoskeletal disorders were significantly associated with both “simple” (no associated psychiatric disorders, OR=2.3) and “complex” (complicated by a dissociative disorder or borderline personality disorder, OR=5.6) PTSD, while fibromyalgia was only significantly associated with complex PTSD (OR=8.0). (Seng, Graham-Bermann et al. 2005).

In addition, Arguelles et al. found PTSD symptoms were significantly linked to wide spread pain among a community-based sample of twins (OR=3.5). In a sample of care-seeking Gulf War veterans, patients with PTSD had the highest comorbid symptom count independent of demographic characteristics, veteran-reported environmental exposures, and comorbid medical conditions (Engel, Liu et al. 2000).

The combination of pain with PTSD is often present in persons exposed to multiple war traumatic experiences and more psychosocial problems (Avdibegovic, Delic et al. 2010). Several studies suggest that depression, anxiety or substance abuse may either moderate or mediate the effect on the PTSD-chronic pain relationship (Roy-Byrne, Smith et al. 2004; Jakupcak, Osborne et al. 2006).

Prevalence of PTSD in Chronic Pain

Over the last 25 years multiple studies have reported the high prevalence of PTSD in patients with chronic pain. Most data on PTSD and chronic pain co-occurrence come from studies examining the prevalence of psychiatric disorders in samples that report chronic pain, e.g. community dwellers with chronic arthritic pain and low back pain. The prevalence of anxiety disorders including PTSD is higher than that of all types of mood disorders in the chronic pain population sampled (Sharp and Keefe 2006).

Table 2.1 (Appendix B) lists 17 studies of patients with various types of chronic pain in various care settings. The prevalence rates for PTSD varied considerably depending on the sample studied and the nature of the pain complaint, ranging from 6.5% among patients with migraine to 64% among patients with general headache. Five studies examined patients with fibromyalgia, with a 28.6% average prevalence of PTSD.

Table 2.2 (Appendix C) lists 5 studies that compared the prevalence of PTSD among patients with and without chronic pain. Three studies reported an odds ratio greater than 3. The other two studies found the prevalence of PTSD was significantly greater among patients with chronic pain than without. In particular, individuals with fibromyalgia were 5 times more likely to have PTSD than persons without fibromyalgia. Additional data from the National Comorbidity Study indicated that patients with musculoskeletal pain were 4 times more likely to develop PTSD than are those without musculoskeletal pain (Asmundson, Coons et al. 2002).

Relationship between pain and PTSD symptom severity

Table 2.3 (Appendix D) lists several studies that examined the relationship between pain and PTSD symptom severity. These relationships can be summarized into the following findings.

Higher pain severity correlates positively with higher PTSD symptom severity: Higher levels of pain severity are associated with higher levels of PTSD symptoms in cross-sectional studies (Humphreys, Cooper et al. 2010). Pain severity also predicts PTSD symptoms severity in longitudinal studies (Glynn, Shetty et al. 2007; Whitehead, Perkins-Porras et al. 2006; Sullivan, Thibault et al. 2009).

Pain persistence and relationship to PTSD severity: At least two prospective cohort studies concluded that chronic or persistent pain may predict more severe PTSD symptoms (Bonin, Norton et al. 2000; Chossegros, Hours et al. 2011).

Pain related cognitions are associated with increased PTSD severity and persistence: pain catastrophizing and pain related anxiety are associated with more severe PTSD symptoms, and pain catastrophizing predicted the persistence of PTSD (Van Loey, Maas et al. 2003; Sullivan, Thibault et al. 2009).

Greater pain and more severe PTSD symptoms are related to more disability: A study using structural equation modeling analytics examined the relationship between PTSD symptoms, pain severity, and perceived life control among people with motor vehicle accident caused pain. The investigators found more severe PTSD symptoms and greater pain complaints were related to

psychosocial impairment. However, only pain, but not PTSD was significantly related to impairment in physical functioning (Palyo and Beck 2005). Another study found pain and PTSD symptoms were frequent and disabling factors after orthopedic trauma (Ponsford, Hill et al. 2008). Patients with fibromyalgia syndrome and PTSD reported greater pain, lower quality of life, higher functional impairment and suffered more psychological distress than patients with PTSD without fibromyalgia syndrome (Amir, Kaplan et al. 1997).

Relationship between PTSD, pain severity, interference with activities, and disability

Several studies have identified PTSD as a risk factor for chronic pain (Miro, Nieto et al. 2008; Jenewein, Moergeli et al. 2009), for the transition from acute to chronic pain (Kongsted, Bendix et al. 2008; Shaw, Means-Christensen et al. 2010), and for the subsequent development of chronic widespread pain (Ang, Peloso et al. 2006).

PTSD is associated with increased pain severity (De Leeuw, Bertoli et al. 2005; Williams, Newman et al. 2009) and pain disability (Katz, Asmundson et al. 2009; Peterlin, Tietjen et al. 2009)(Burriss, Cyders et al. 2009)(Corry, Klick et al. 2010). Furthermore, PTSD increases the likelihood of transitioning from sub-acute to chronic back pain (Shaw, Means-Christensen et al. 2010). Meanwhile, peritraumatic pain was found to increase the risk of PTSD (Norman, Stein et al. 2008).

PTSD symptom severity mediates the relationships between chronic pain severity and the severity of both child abuse and assaultive intimate partner violence (Wuest, Ford-Gilboe et al. 2009). PTSD also mediates the relationship between chronic pain severity and depression, functional adjustment, and satisfaction with life (Bryant, Marosszeky et al. 1999).

Several studies report that PTSD symptoms exert their influence on pain severity through other factors such as depression, anxiety, substance abuse and sleep quality (Burriss, Cyders et al. 2009) (Roy-Byrne, Smith et al. 2004); Jakupcak, Osborne et al. 2006).

Conceptual models

Despite a large body of research documenting elevated rates of PTSD in patients with chronic pain, elevated rates of chronic pain in patients with PTSD, and the frequent comorbidity of chronic pain and PTSD across different populations, it remains unclear whether there is a causal relationship between PTSD and chronic pain. As Asmundson et al noted (Asmundson, Coons et al. 2002), for any 2 variables (or conditions), possible relations are as follows: 1) they co-occur but are unrelated, 2) one causes the other (that is, PTSD causes pain, or vice versa), 3) each influences the other in some way (for example, chronic pain exacerbates symptoms of PTSD, or vice versa), or 4) some third factor (for example, a genetic predisposition) causes both. Fishbain et al. (Fishbain, Cutler et al. 1997) discussed five major hypotheses concerning the relationship of depression and chronic pain, some of which may be applied to the

relationship of PTSD and chronic pain as well. These categories include 1) antecedent hypothesis—depression precedes the development of chronic pain (i.e. depression causes pain); 2) consequence hypothesis—depression is a consequence and follows the development of pain (i.e. pain causes depression); 3) scar hypothesis—episodes of depression occurring before the onset of pain predispose an individual to a depressive episode after pain onset (i.e. pain and pre-pain depression causes post-pain depression); 4) cognitive behavioral mediation hypothesis—cognitions mediate the relationship between chronic pain and the development of depression (i.e. pain and depression co-occur but are not directly-related); and 5) common pathogenetic mechanisms hypothesis (i.e. some third factor causes both pain and depression).

Various hypothesis and conceptual models have also been proposed to explain the relationships between chronic pain and PTSD. These models can generally be classified into three classes: 1) mutual maintenance class (i.e. PTSD and chronic pain have a mutual maintenance relationship); 2) shared vulnerability class (i.e. PTSD and chronic pain share the same pre-existing risk factors); and 3) shared pathway class (i.e. PTSD and chronic pain share the same after-trauma pathway). Table 2.4 (Appendix F) lists the major points of seven of these models, along with their classifications and brief comments from the dissertation author.

In general, most of these models follow the cognitive behavioral mediation hypothesis (e.g. mutual maintenance model and fear-avoidance model), or common pathogenetic mechanisms hypothesis (e.g. shared vulnerability model

and triple vulnerability model). Some of these models were originally developed to explain the cause of chronic pain and were subsequently applied to explain the relationship between PTSD and chronic pain (e.g. fear-avoidance model and Diathesis-stress model).

The Fear Avoidance Model assumes activity or cognitive avoidance due to fear of pain or fear of traumatic experience is the common cause of prolonged PTSD and chronic pain. Two other models, the Shared Vulnerability and the Triple Vulnerability model, also focus on the common causes of PTSD and chronic pain, and assume there are pre-existing factors (e.g. the single anxiety sensitivity factor as stated in the Shared Vulnerability model, or multiple biological, generalized psychological and specific psychological factors as stated in the Triple Vulnerability model) that contribute to the development of both disorders. The pre-disposing vulnerability hypothesis is also an important part of the stress system dysregulation model and the diathesis-stress model.

The Mutual Maintenance Model and the Perpetual Avoidance Model both focus on the interaction of PTSD symptoms and chronic pain symptoms, and hypothesize that PTSD and chronic pain have a mutual maintaining relationship either through seven identifiable psychological, cognitive and behavioral mechanisms as stated in the Mutual Maintenance Model (Figure 2.1), or through the interaction of the so-called PTSD (symptom) circle and chronic pain (symptom) circle as stated in the Perpetual Avoidance Model (Figure 2.2). The Mutual Maintenance Model is more comprehensive than the Perpetual Avoidance Model, as it involves not only the interaction of shared symptoms

between PTSD and chronic pain, but also the influence of possible depression and anxiety, two of the most common psychological disorders among PTSD and chronic pain patients, as well as the distress and disability factors, through which the seven mechanisms exert additional influence on both PTSD and chronic pain. As a result, the Mutual Maintenance Model has received significant attention and has been (partially) validated in several studies.

Figure 2.1: The Mutual Maintenance Model (Sharp and Harvey 2001)

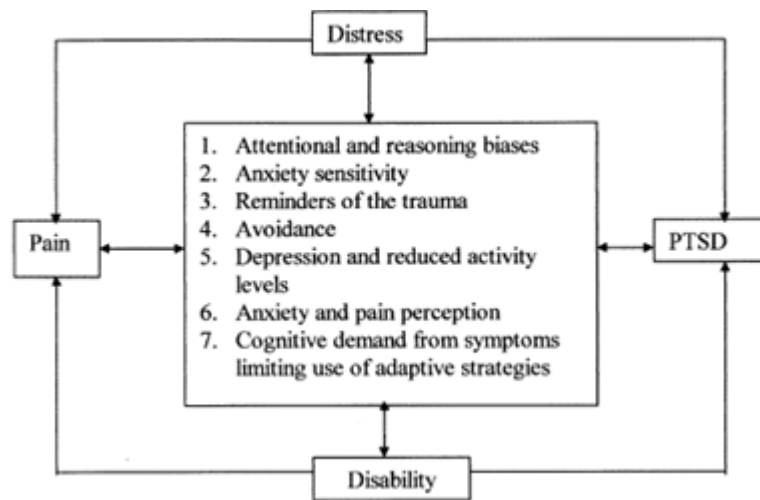
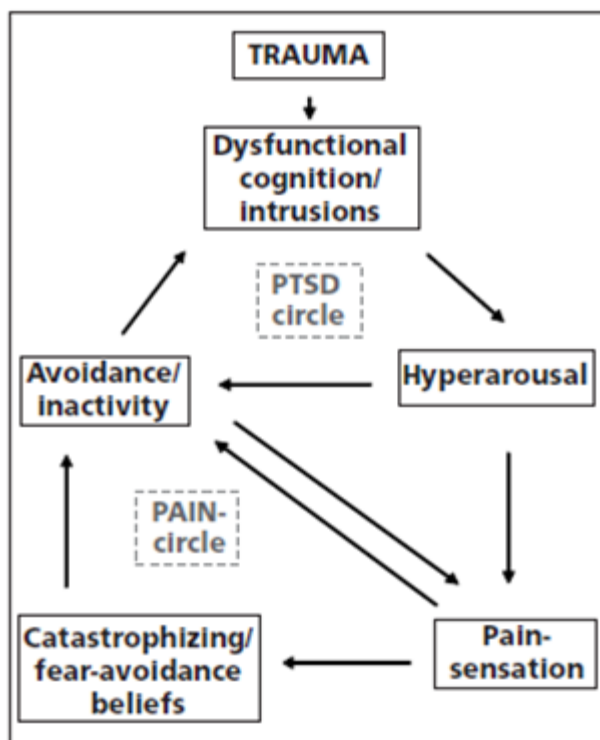
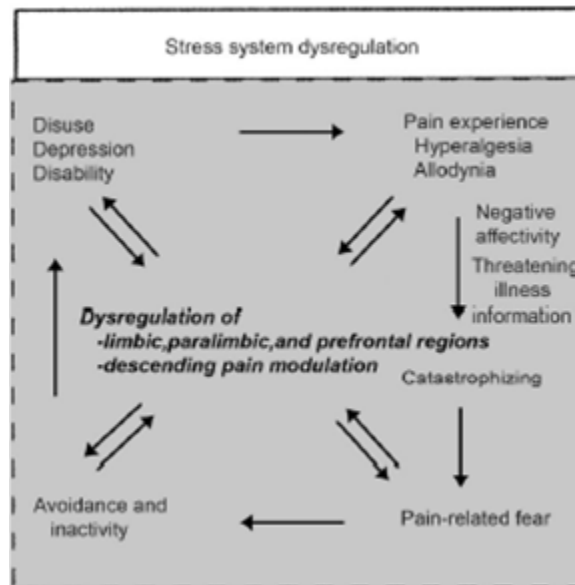


Figure 2.2: The Perpetual Avoidance Model (Liedl and Knaevelsrud 2008)



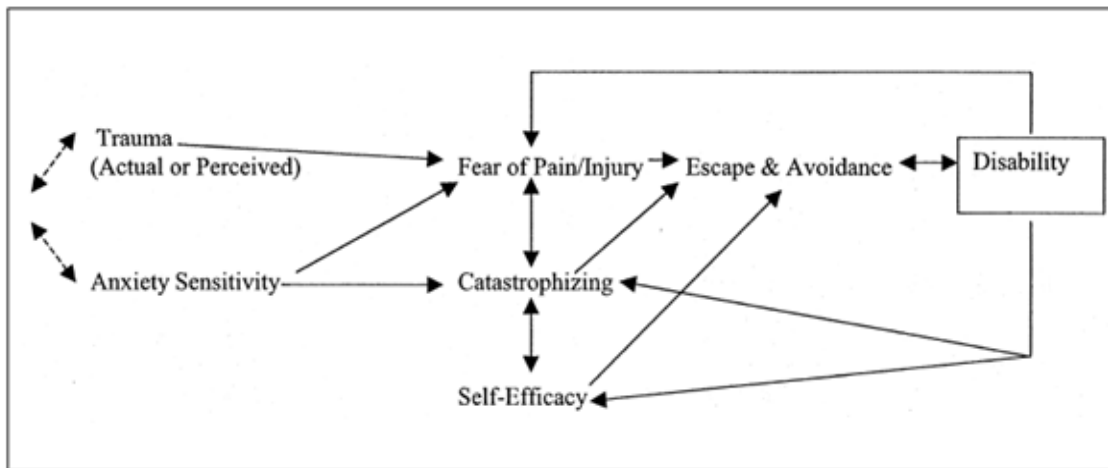
The Stress System Dysregulation Model emphasizes the key role of a vulnerable human stress response system, a biological mechanism, to the development of both PTSD and chronic pain (Figure 2.3), and hypothesizes there is a causal relationship between abnormal stress response system and psychological and cognitive factors that exacerbate PTSD and chronic pain symptoms. Multiple mechanisms have been proposed by which abnormal stress system function during or after a stressor might increase the risk of both PTSD and chronic pain development by disrupting the neurobiological processes which orchestrate an adaptive stress response (McLean, Clauw et al. 2005).

Figure 2.3: The Stress System Dysregulation Model (McLean, Clauw et al. 2005)



The Diathesis-Stress Model emphasizes the interaction of pre- and post-traumatic cognitive behavioral factors and the exposure to a trauma (Figure 2.4). In particular, the following factors are included within the original model: anxiety sensitivity, anticipation of pain, catastrophizing, attributions about the causes of the symptoms, worries about the future, self-efficacy, fear-avoidance beliefs and operant conditioning (e.g. inactivity due to pain may be positively reinforced by attention from a spouse or health care provider). Martin A, Halket E, et al further extended this model by including posttraumatic stress symptoms (PTSS) within it and found pain intensity accounted for 15% of the variance in PTSS and PTSS had a large effect on pain disability, accounting for 45% of the variance.

Figure 2.4: The Diathesis-Stress Model (Turk 2002)



It is worth noting that disability is included in three of these models: mutual maintenance model, stress system dysregulation model and diathesis-stress model. In the mutual maintenance model, disability, together with distress and other cognitive behavioral factors, mediates the interaction between PTSD and chronic pain. In the stress system dysregulation model, disability lies within the circle of pain experience, pain catastrophizing, pain-related fear, behavioral and psychological avoidance, and disuse/depression/disability, and influences (and is influenced by) the stress response system, whose dysregulation may be the cause of both chronic pain and PTSD. In the (extended) diathesis-stress model, there is a feedback loop between disability and fear of pain, through which PTSD symptoms may have an influence on chronic pain.

All of the above models are supported from empirical studies. Some of these studies are cross-sectional and thus cannot provide information on the relative timing of pain and PTSD symptoms onset. Some are longitudinal, which

are better designed to explore the causal relationships among PTSD, chronic pain and other cognitive behavioral factors. All of the above models have found support from empirical studies. For example, there are longitudinal studies that confirmed a mutual maintaining relationship between pain and PTSD (Ramchand, Marshall et al. 2008; Zatzick, Jurkovich et al. 2008; Jenewein, Wittmann et al. 2009; Liedl, O'Donnell et al. 2010), or a unidirectional impact of PTSD on pain (Tsao, Dobalian et al. 2004; Jenewein, Wittmann et al. 2009; Katz, Asmundson et al. 2009), or vice versa (McGhee, Slater et al. 2011). A recent study by Sterling et al. (Sterling, Kenardy et al. 2003) found that PTSD symptoms after a motor vehicle collision (MVC) predicted whiplash severity at 6 months. Another study found vulnerability to develop PTSD after MVC may also predict the development of fibromyalgia (McLean, Clauw et al. 2005).

Several studies used structural equation modeling or cross panel analysis to investigate the longitudinal relationships (Schell, Marshall et al. 2004; Marshall, Schell et al. 2006; Ramchand, Marshall et al. 2008; Jenewein, Wittmann et al. 2009). One notable example is a recent study that found two four-factor models of PTSD symptom clusters that fitted the data reasonably well, and different PTSD symptom clusters predicted different components of pain (Cyders, Burris et al. 2010). One of the four-factor models contained the re-experiencing, avoidance, numbing and hyperarousal factors. The other model contained the re-experiencing, avoidance, dysphoria and hyperarousal factors with different factor loadings in the third and fourth factors. Hierarchical regression models have also been used to examine the relationship between

PTSD symptom clusters and pain (Clapp, Beck et al. 2008). Yet no randomized controlled studies have been found to test the causal relationship of PTSD and chronic pain.

In summary, available evidence tends to support that pain and PTSD are closely associated, PTSD contributes to increased pain severity, and increased pain severity contributes to increased PTSD prevalence or PTSD symptom (e.g. arousal and/or re-experiencing) severity.

Several studies demonstrate that pain impacts PTSD through increased arousal and re-experiencing symptoms, rather than avoidance. Meanwhile, hyperarousal is a potent predictor of subsequent re-experiencing, avoidance and hyperarousal (Schell, Marshall et al. 2004; Marshall, Schell et al. 2006). On the other hand, avoidance is not correlated with pain (Sterling, Kenardy et al. 2003). This seems to contradict major conceptual models such as the Mutual Maintenance Model, Perpetual Vulnerability Model, and Fear Avoidance Model, where avoidance plays an important role in the development and maintenance of both PTSD and pain.

In addition, Asmundson et al (Asmundson, Bonin et al. 2000) using the multi-axial assessment of pain, found chronic pain patients differ substantially in their propensity to become fearful and in their likelihood to develop PTSD. A substantial proportion of patients classified as dysfunctional (i.e. those displaying higher pain severity, pain interference, elevated affective distress and fear, and lower activity) and interpersonally distressed (i.e. those displaying lower perceived social support) meet diagnostic criteria for PTSD, much more than

patients who are classified as minimizers/adaptive copers (i.e. those displaying lower pain severity, pain interference, and affective distress).

Biological Models

Some of the conceptual models discussed in previous section are based on biological models/assumptions on the causes of PTSD and chronic pain. For example, both the Triple Vulnerability Model and the Diathesis-Stress model are based on the assumption that biological vulnerability to develop certain psychopathological disorder exists. And the Stress Dysregulation Model is based on the biological theory that abnormal stress system function during or after a stressor might increase the risk of PTSD development by disrupting the neurobiological processes which orchestrate an adaptive stress response through multiple mechanisms.

Although multiple biological models have been proposed to explain how a traumatic event may cause PTSD (van der Kolk, Greenberg et al. 1985) or a combination of both PTSD and chronic pain (McLean, Clauw et al. 2005), no such model (biological pathway) has been developed to explain how PTSD and chronic pain may exacerbate each other in a similar way as the Mutual Maintenance and other conceptual models have suggested. On the contrary, a number of studies have confirmed the theory of stress-induced analgesia (SIA) among PTSD patients (Pitman, van der Kolk et al. 1990; Mickleborough, Daniels et al. 2011). In these studies, reduced experimental pain response was observed among patients with PTSD compared to patients without. The SIA

theory and related evidence seem to contradict with the Mutual Maintenance and other conceptual models that implicate an increased pain response among PTSD patients.

A recent systematic review (Tobias Moeller-Bertram 2011) identified six studies that used an experimental pain assessment approach to find out how PTSD affects pain sensation and pain processing. The evidence presented in the review is inconclusive as conflicting results were reported regarding whether PTSD reduced or increased pain sensitivity, pain rating, and pain threshold. The review also presented an exploratory meta-analysis of four studies that used functional magnetic resonance imaging to examine the effect of PTSD on the sensation of experimental pain. The study found PTSD was associated with reduced pain sensitivity through altered neural activation patterns (Geuze, Westenberg et al. 2007). Specifically, there was increased activation of right middle insula and right dorsolateral prefrontal cortex during initial painful simulation (Strigo, Simmons et al. 2010).

Although biological models may help us better understand the nature of the relationships between PTSD and chronic pain, they are not going to be further examined in our present study.

Treatment of Patients with Both PTSD and Chronic Pain

Muse reported pain treatment had little impact on PTSD symptoms improvement (Muse 1986). In contrast, Hickling noted (Hickling EJ 1992) treating

PTSD improved pain symptoms. Yet a growing number of studies have tested an integrated approach to treat patients with both PTSD and chronic pain.

For example, an integrated approach designed for veterans with comorbid chronic pain and PTSD using components of cognitive processing therapy (CPT) and cognitive behavioral therapy (CBT) proved to be feasible and demonstrated clinical benefit (Otis, Keane et al. 2009). The innovative Integrative Health Clinic and Program (IHCP) designed by the Veterans Affairs Health Care System is another successful example of using integrated, non-pharmacologic biopsychosocial approaches to treat chronic non-malignant pain, stress-related depression, anxiety and symptoms of PTSD simultaneously (Smeeding, Bradshaw et al. 2010). Preliminary data were presented recently on the pattern of treatment response of combining interoceptive exposure (IE) with trauma-related exposure therapy (TRE) in five female patients with posttraumatic stress disorder (PTSD) and comorbid chronic musculoskeletal pain originating from motor vehicle accidents (Wald, Taylor et al. 2010).

Biofeedback supported cognitive behavioral therapy was also used to address both pain and PTSD among victims of war and torture in a pilot study (Knaevelsrud, Wagner et al. 2007). A randomized controlled study was published recently demonstrating the effectiveness of the above therapy (Liedl, Muller et al. 2011). Another study indicated that pain rehabilitation programs which provide directed interventions for PTSD symptoms among chronic pain patients with accident-related pain improved pain treatment outcomes (Roth, Geisser et al. 2008).

Kulich et al reviewed treatment outcomes with comorbid pain and PTSD and noted that tailored cognitive or pharmacologic interventions based on individual differences in their symptoms and deficit areas were critical. It is often difficult to make decisions in terms of pharmacologic choices due to complications of concurrent psychotherapeutic interventions, and the possibility of other comorbid diagnoses such as concurrent substance abuse and chronic pain (Kulich, Mencher et al. 2000).

Challenges and strategies for treating polytrauma pain and associated comorbid conditions such as PTSD were outlined in another publication (Girona, Clark et al. 2009). One of the most important components in treating traumatized patients with chronic pain should be education about the relationship between chronic pain and PTSD (Liedl and Knaevelsrud 2008). In addition, PTSD symptoms may be an important determinant of selecting a treatment modality for patients experiencing pain subsequent to traumatic injury (Clapp, Masci et al. 2010). Additional treatment research is needed that will eventually lead to guidelines for patients with co-morbid pain and PTSD (Liedl, Muller et al. 2011).

Summary

Our review of epidemiologic studies found consistent evidence that the prevalence of chronic pain among patients with PTSD is significantly higher than that among general population. Likewise, the prevalence of PTSD is increased among patients with chronic pain. Moreover, higher pain severity correlates with

higher PTSD symptom severity, and the combination of pain and PTSD is associated with greater disability and complicates treatment (therefore an integrated treatment is needed). The high comorbidity and positive correlation of chronic pain and PTSD suggest that PTSD and chronic pain are related in some way, and a number of conceptual models have been proposed to explain this relationship. More studies are needed to exam the nature of this relationship empirically, and to validate existing conceptual models and corresponding hypothesis of causal relationships between PTSD, chronic pain and other biopsychosocial mediating factors.

Chapter III: Methodology

Introduction

As stated in Chapter I, the current study aims to answer the following research questions using data collected in the ESCAPE study: 1) How strong is the relationship between PTSD and chronic musculoskeletal pain? 2) Which factors mediate the relationship between PTSD and chronic musculoskeletal pain? 3) Do different clusters of PTSD symptoms affect chronic musculoskeletal pain outcomes differently? In Chapter II, we have reviewed existing theories and previously published studies that helped generate our hypotheses for these questions. In addition, our review of the literature in Chapter II summarized a growing number of studies that used the Structural Equation Modeling technique to confirm the factor structure of PTSD, and to examine the differential relationships of PTSD symptom domains with chronic pain outcomes (Burriss, Cyders et al. 2009; Jenewein, Wittmann et al. 2009; Cyders, Burriss et al. 2010; Liedl, O'Donnell et al. 2010). To our knowledge, no studies have used the Decision Tree technique to examine the relationship between PTSD and chronic pain, although this technique has drawn increasing interest over the last twenty years in clinical research studies.

Structural Equation Modeling

Structural equation modeling (SEM) is a methodology for representing, estimating, and testing a theoretical network of (mostly) linear relations between observed (measured) and unobserved (latent) variables (Rigdon 1998). SEM

enables researchers to readily develop, estimate, and test complex multivariable models, as well as to study both direct and indirect effects of variables involved in a given model (Raykov and Marcoulides 2000). SEM differs from classical linear modeling techniques such as regression analysis, analysis of variance, analysis of covariance, and a large part of multivariate statistical methods in different aspects. For example, SEM includes measured variables (manifest variables) as well as implied variables (latent variables), allowing for a simpler and better fitting. In addition, SEM handles measurement errors explicitly through measurement model, without the assumption of no measurement error as required by classical statistical modeling. Finally SEM allows for simultaneous evaluation of complex model construct relationships, making it an ideal tool for researchers to test various theoretical models in social and life sciences.

Confirmatory factor analysis and path analysis are two of the most common SEM techniques used for cross-sectional data analysis, and have been used to examine the relationship between PTSD and chronic pain in several studies. For example, Cyder et al. used confirmatory factor analysis to compare five PTSD symptom domain models and concluded the two four-factor models fit their data best (Cyders, Burris et al. 2010). This result is consistent with a similar analysis by Asmundson et al (Asmundson, Coons et al. 2002). Asmundson et al found a 4-factor inter-correlated PTSD domain model fit the data significantly better than the hierarchical 2- or 3-factor model. Furthermore the factor loadings differed between groups of patients with and without chronic pain. Following the confirmatory analysis, a path analysis was conducted to examine the differential

relationships of those domains with chronic pain outcomes (Cyders, Burris et al. 2010). The influence of PTSD symptoms on pain-related disability (Multidimensional Pain Inventory pain interference subscale), partially mediated through depression and general activity levels (MPI general activity level subscale), was found to be uniquely a function of avoidance, numbing, and dysphoria, not re-experiencing or hyperarousal symptoms. In particular, it was found avoidance influenced pain-related disability directly, and indirectly through the mediation of general activity levels, and numbing and dysphoria influenced disability indirectly only through the mediation of depression. Alternatively, the influence of PTSD symptoms on pain severity (MPI pain severity subscale), mediated through sleep quality, was found to be a function of only hyperarousal, not numbing, avoidance, dysphoria, or re-experiencing symptoms.

Cross-lagged panel analysis is one of the most popular SEM techniques for longitudinal data analysis, and has been used in several studies to examine the causal relationship between chronic pain and PTSD (Schell, Marshall et al. 2004; Marshall, Schell et al. 2006; Ramchand, Marshall et al. 2008; Jenewein, Wittmann et al. 2009). Analysis of panel data has been recognized for its advantages in testing for causal effects because it can provide evidence regarding all three conditions of causality: covariation of the 2 variables, time precedence of the causal variable, and nonspuriousness (i.e., the association of the 2 variables must not be produced by a joint association with a third variable or set of variables) (Finkel 1995). It is worth noting that the cross-lagged approach investigates causality in the absence of a randomized experimental

design. Instead of addressing the traditional causal question of whether X causes Y ", the cross-lagged analysis examines which is the predominant cause-effect direction. As such, it should be viewed as an indicator of temporal precedence, and not as proof of causation.(Anderson 1982). The minimal cross-lagged panel design involves two variables measured at two separate times. Multiple regression analyses in which the time two measures are regressed on the time one measures can also be used to analyze data. However, SEM is better suited for simultaneous evaluation of causality among model constructs without imposing the strict assumptions (e.g. no measurement error) required by traditional regression analysis.

Generally, the maximum likelihood estimation will be used in Structural equation modeling (SEM). The overall fit of a model will be assessed by various indices. These indices can be categorized into three categories 1) absolute fit indices (a measure of how well the model fits in comparison to no model at all), including Chi-Squared test (χ^2), root mean square error of approximation (RMSEA), goodness-of-fit statistic (GFI), adjusted goodness-of-fit statistic (AGFI), root mean square residual (RMR) and standardized root mean square residual (SRMR); 2) Incremental fit indices (a measure of how well the model fits in comparison with a baseline model where the null hypothesis is that all variables are uncorrelated), including normed-fit index (NFI) and comparative fit index (CFI); and 3) Parsimony fit indices (a measure of how much a model differs from a saturated, complex model that is tied to sample data only), including the parsimony goodness-of-fit index (PGFI) and the parsimonious normed fit index

(PNFI). The most commonly applied fit indices to date are NNFI and CFI (>0.90 indicates good fit), RMSEA (<0.08 indicates acceptable fit), and relative χ^2 statistic ($\chi^2 / \text{d.f.}$ ratio of 3 or less), which tend to meet the following criteria proposed by Marsh, Balla and McDonald (Marsh 1988): relative independence of sample size, accuracy and consistency to assess different models, and ease of interpretation aided by a well defined pre-set range.

CART Analysis

One of the most widely used nonparametric decision tree techniques is the classification and regression tree (CART) analysis. In CART analysis, a set of rules is developed for dividing a large heterogeneous population into smaller, more homogeneous groups with respect to a particular target variable. It is ideally suited to generate clinical decision rules, and also provides an effective way to reveal important data relationships that may remain hidden using traditional analytical tools. For example, CART analysis has been used in tailored therapy studies to identify subgroups of patients who may react more favorably to certain treatments (Foster, Taylor et al. 2011; Ruberg, Chen et al. 2011). It has also been identified as a promising research tool to identify at-risk populations in public health research and outreach (Lemon, Roy et al. 2003; Louie, Tektonidou et al. 2011). Although CART analysis has not been used in studies on PTSD, it has been used in studies on chronic pain. For example, CART analysis was used to determine what level of early pain improvement best predicted later response to duloxetine treatment for fibromyalgia pain. (Fulton-Kehoe, Stover et al. 2008;

Wang, Ruberg et al. 2011). Using CART analysis, another study found pain interference and radiating leg pain comprised the best predictive model of work disability status 1 year after claim submission (Fulton-Kehoe, Stover et al. 2008).

Design of the ESCAPE Study

The study population consists of 242 OEF/OIF (Operation Enduring Freedom/Operation Iraqi Freedom) veterans with moderate musculoskeletal pain of the spine and extremities. Participants were enrolled from the Roudebush Veterans Administration Medical Center (RVAMC) outpatient clinics. Willing patients underwent an eligibility interview and those who met entry criteria and provided informed consent were enrolled.

Potential participants were identified by querying CPRS to create a master list of OEF/OIF veterans who had at least moderate pain intensity (pain score ≥ 4) according to the pain scale (“0” no pain to “10” worst pain imaginable) routinely measured in VA outpatient clinics within the preceding 6 months. Potential participants were then contacted by phone to assess eligibility and determine their interest in participating. If the veteran was eligible, verbal consent were obtained from those who desired to participate. An informed consent statement and HIPPA authorization were mailed to the patient with a pre-addressed, postage paid return envelope (with phone reminders if not returned). Additional patients were consented in person prior to the baseline interview.

Participants were randomized to stepped care or usual care (N= 121 each group). The stepped care intervention consisted of optimizing analgesic and

adjuvant treatment coupled with a 12 week pain self-management program (PSMP) for step 1. Step 2 consisted of 12 weeks of brief cognitive behavioral therapy (CBT). Interviewers blinded to the study hypotheses and treatment assignments conducted outcome assessments at baseline, 3, 6, and 9 months.

Sample Selection

OIF/OEF veterans were eligible if they met all of the following criteria summarized in Table 3.1.

Table 3.1: Eligibility criteria

<u>Inclusion</u>	<u>Exclusion*</u>
<ul style="list-style-type: none"> • Musculoskeletal pain of low back, cervical spine, or extremities (hip, knee, or shoulder) • Pain for 3 months or longer • Moderate functional impairment defined as Roland Disability Score \geq 7 • Access to working telephone† • Willing to travel at least once to study sites 	<ul style="list-style-type: none"> • Severe medical conditions that would limit participation (e.g. Class III or IV heart failure) • Active psychosis • Incompetent for interview (per patient's physician or research assistant) • Severe impairment of hearing or speech • Active suicidal ideation • Diagnosis of schizophrenia • Prior back surgery or surgery pending • Current alcohol (substance) dependence • Pregnant or trying to become pregnant

* Access to a telephone is required because both the intervention and outcome assessments will be conducted via phone

* Exclusion criteria are designed to eliminate potential participants for whom the proposed interventions are inappropriate and/or for whom there may be disincentives for improvement. Most data to apply these

Data Collection

A comprehensive set of relevant outcomes and key variables were measured and timing of assessment is listed in Table 3.2. The baseline interview lasted approximately one hour; the 3 month interviews about 30 minutes, and the 6 and 9 month interviews about 45 minutes. Baseline patient characteristics included sociodemographics, work status, comorbid medical and psychiatric disorders, and prior treatments for pain. All study participants included received PTSD screening at baseline. Those who screened positive for PTSD were further assessed by the PCL-17 to evaluate PTSD severity at baseline and 9 months. Pain severity was evaluated at baseline, 1, 3, 6 and 9 months. A PCL-C total score of 41 is considered a valid clinical cutoff for defining whether a patient's symptoms are consistent with a DSM-IV diagnosis of PTSD (Sherman, Carlson et al. 2005).

Table 3.2: ESCAPE outcome assessment protocol: measures and administration timing

Domain	No	Measure	Items	Schedule (month)			
				BL	3	6	9
Demographics	1	age, race, sex, education, marital, job status, income	7	X			
Military	2	Duty, branch, deployment	3	X			
Medical comorbidity	3	9 diseases	9	X			
Pain related disability	4	Roland Disability Scale	24	X	X	X	X
	5	Brief Pain Inventory	7	X	X	X	X
Pain severity	6	GCPS	8	X	X	X	X
	7	Pain treatment and relief	2	X			
	8	Bodily Pain scale of SF-36	†	X	X		X
Work function	9	Work effectiveness item	1	X			

	10	Work productivity scale	7	X			
Generic health-related quality of life (HRQL)	11	SF-36v2	36	X	X		X
	12	EQ-5D	5	X			
Pain Beliefs	13	Pain Catastrophizing scale	13	X			
	14	Arthritis self-efficacy scale	6	X	X		X
	15	Pain Centrality Scale	12	X			
Depression	16	PHQ-9	9	X			
Anxiety	17	GAD-7 (7), Social Anx (3) Panic (1→ 5) PTSD (1)	13	X	X		X
PTSD	18	PTSD screener	4	X			
	19	PCL-Checklist	17	X			
Alcohol use	20	Audit 10	10	X			
Somatization	21	PHQ-somatic (12 items)	12	X	X		X
Stressors	22	PHQ stressor scale	9	X	X		X
Cognitive function	23	Sickness Illness Profile	7	X			
Social function and integration	24	Social Provisions Scale	8	X			
Deployment exposure	25	Deployment Stress Questionnaire	33	X			
Physical activity	26	IPAC	7	X			
Occupational	27	COPM	18	X			X

PTSD diagnosis and severity are measured by PCL-17. Pain severity and pain-related disability are measured by GCPS. Other psychological symptoms measured include depression (PHQ-9), anxiety (GAD-7), stressors (PHQ stressor score), and pain beliefs (Pain Catastrophizing scale, Pain Centrality Scale, and Arthritis self-efficacy scale). These instruments will be used in our current analysis and will be discussed further in the next section.

Instrumentation

PCL-17

The PCL-17 is derived from DSM III-R criteria for PTSD, and is used for diagnosis and as a severity measure. The PCL-17 has demonstrated adequate test–retest reliability ($r=.96$), internal consistency (coefficient alpha: $r=.92$), (Blanchard, Jones-Alexander et al. 1996) and sensitivity and specificity > 70%. (Stamm 1996) The PCL-17 is a 17-item, clinician-rated instrument of PTSD symptoms (each item scored from 0 = not at all to 4 = extremely, total score ranging from 0 to 68). A PCL-17 total score of ≥ 41 is considered a valid cutoff for determining whether patient symptoms are consistent with a clinical diagnosis of PTSD. (Sherman, Carlson et al. 2005). We assume patients who screened negative for PTSD had a PCL-17 total score < 41 even though their PCL-17 total scores were not measured in ESCAPE trial.

GCPS

The Graded Chronic Pain Scale (GCPS) is a brief 7-item scale that rates global severity of chronic pain in two domains: intensity and disability (Von Korff, Dworkin et al. 1990). Rich normative data exists for the GCPS. Based on the combination of pain intensity, disability score and disability days, pain severity can be classified into 5 categories (table 3.3). (Von Korff, Ormel et al. 1992; Von Korff, Deyo et al. 1993; Smith, Penny et al. 1997)

Table 3.3: Summary of pain grade categories

Grade	Findings	Type	Outcome
0	no pain problems for the prior 6 months	pain free	Good
I	characteristic pain intensity < 50 disability points < 3	low disability low intensity	Good
II	characteristic pain intensity >= 50 disability points < 3	low disability high intensity	Fair
III	disability points 3 or 4	high disability moderately limiting	Poor
IV	disability points 5 or 6	high disability severely limiting	Poor

PHQ-9

The Patient Health Questionnaire (PHQ-9)(Kroenke, Spitzer et al. 2001) is a brief (9-item) measure of depression severity becoming widely used in clinical and research settings.

A PHQ-9 score > or =10 was found to have a sensitivity of 88% and a specificity of 88% for major depression (Kroenke, Spitzer et al. 2001). The cut point of 10 or greater will therefore be used to classify patients with and without depression in our relationship modeling involving depression measurement.

GAD-7

Anxiety severity will be assessed with 7 items from the GAD-7 anxiety scale (0=not at all; 3=nearly every day).(Spitzer, Kroenke et al. 1999).

A GAD-7 score > or = 10 was found to have a sensitivity of 89% and a specificity of 82% for generalized anxiety disorder (GAD) (Spitzer, Kroenke et al. 2006). The cut point of 10 or greater will therefore be used to classify patients with and without GAD in our relationship modeling involving GAD.

Pain Catastrophizing Scale

Catastrophizing will be assessed with the Pain Catastrophizing Scale a 13-item scale with three dimensions: rumination; magnification, and helplessness.(Osman, Barrios et al. 1997)

Hypotheses

Based on our literature review of previously published theories (primarily the Mutual Maintenance model)(Sharp and Harvey 2001) and studies, we posit the following hypotheses related to each pre-stated research objective. For clarity purpose, we have listed in Appendix G (table 3.5) examples of published studies that are found to support some of these hypotheses.

OBJECTIVE 1: Examine the cross-sectional relationships between PTSD, depression, anxiety, chronic musculoskeletal pain severity, pain disability and quality of life using multiple regression, structural equation modeling, and decision tree techniques.

The following hypotheses will be tested for this objective:

- 1) Higher PTSD symptoms will be associated significantly with poorer pain-related and psychosocial outcomes. While many studies have found higher PTSD symptoms are associated with increased pain severity and pain disability as shown in Appendix G (table 3.5) (Geisser, Roth et al. 1996; Beckham, Crawford et al. 1997; Jenewein, Wittmann et al. 2009; Zatzick, Jurkovich et al. 2008), few studies have shown higher PTSD symptoms are also related to higher pain catastrophizing scores or poorer quality of life among patients with chronic pain.
- 2) Higher pain severity will be associated with more severe PTSD and psychosocial outcomes. Only one study is found to support this hypothesis among formerly-abused women population (Humphreys, Cooper et al. 2010). Little is known about whether this association still exists among war veterans with no gender restriction.
- 3) Besides pain severity, there are other key factors that are associated with PTSD. PTSD tends to be associated with multiple factors. For example, the Shared Vulnerability model considers anxiety sensitivity as a major risk factor shared by both PTSD and chronic pain (Asmundson, Coons et al. 2002), while the Triple Vulnerability Model considers other generalized biological and psychological risk factors (Otis, Keane et al. 2003). Several studies found other risk factors of PTSD such as higher functional disability, higher average pain intensity, a previously diagnosed substance use disorder, or post-traumatic amnesia

(Magruder and Yeager 2008; Mak, Chu et al. 2010; Chossegras, Hours et al. 2011). In this dissertation, we are most interested in the relationship between PTSD and chronic pain, and hypothesize a clinical PTSD diagnosis is associated with patients whose pain severity exceeds a certain level (cut point). We also hypothesize clinical PTSD is more likely to develop in patients with comorbid depression or generalized anxiety.

- 4) The relationship between PTSD severity and chronic musculoskeletal pain severity will be mediated through depression, anxiety, or pain catastrophizing. Moreover, PTSD and pain severity will adversely affect quality of life (SF-36, MCS/PCS components) independently; and patients with high chronic musculoskeletal pain (GCPS severity grade ≥ 3) and PTSD will have worse quality of life than patients with only one or neither of these conditions (i.e., high chronic musculoskeletal pain or PTSD). This hypothesis is implied by both the Mutual Maintenance model and the Diathesis-Stress model.

OBJECTIVE 2: Examine the relationships between different PTSD symptom domains, pain outcomes (pain intensity and pain disability) and pain beliefs (pain-related catastrophizing) using confirmatory factor analysis and structural equation modeling techniques.

The following hypothesis will be tested:

- 5) Different PTSD symptom domains will have differential relationships with chronic musculoskeletal pain outcomes, either directly, or through

mediating factors such as depression or general anxiety disorder. This hypothesis was supported by a cross-sectional study among female patients with orofacial pain (Cyders 2010). It is worthwhile to test this hypothesis in both cross-sectional and longitudinal analyses among a different population.

OBJECTIVE 3: Examine the longitudinal relationships between PTSD and chronic musculoskeletal pain using mixed models repeated measures and cross-lagged panel analysis techniques.

The following hypothesis will be tested:

- 6) Baseline PTSD domains will predict chronic musculoskeletal pain severity grade at 9 months, and baseline chronic musculoskeletal pain severity grade will predict PTSD domains at 9 months. This hypothesis is implied by the Mutual Maintenance model (Sharp and Harvey 2001), and was supported by several longitudinal studies (Whitehead, Perkins-Porras et al. 2006; Glynn, Shetty et al. 2007; Jenewein, Wittmann et al. 2009); (Ramchand, Marshall et al. 2008; Zatzick, Jurkovich et al. 2008). However most of these studies were conducted among civilians with accident related injuries in non-primary care setting. It is therefore valuable to test this hypothesis with ESCAPE trial data among veterans in primary care setting.
- 7) The longitudinal change in pain severity will be predicted by PTSD at baseline. The PTSD at 9 months will be predicted by pain intensity and disability at baseline. This hypothesis is also implicated by the Mutual

Maintenance model but is supported by a couple of longitudinal study (Norman, Stein et al. 2008; Van Loey, Maas et al. 2003) in non-primary care setting.

In sum, although most of the above hypotheses are supported or partially supported by one or more other clinical trials, none of those trials were conducted within a primary care setting, or designed for war veterans suffering from musculoskeletal pain. Besides, to our best knowledge, our present study is the only one to take the combination of pain intensity and pain disability (five pain grades) into model construction, the only one to use decision tree technique to explore the relationship between PTSD and chronic pain, and the only one to include the quality of life measures in the complex model of PTSD and chronic pain relationship that may be mediated or moderated through various psychological factors. Finally, this study is also the only one to apply various statistical methods to test a comprehensive list of hypotheses implicated by existing conceptual models and theories. A combination of all these tests and corresponding findings will give us a better overall picture of the direction and strength of the relationship between PTSD, chronic pain and other variables.

These hypotheses will be tested by various statistical methods including Multiple Regression, Structural Equation Modeling, Classification and Regression Tree (CART) and multiple regression analysis, which will be discussed further in the next section.

Analysis

The following analyses are proposed to test our hypotheses above.

Baseline Data Analysis

1) Hypothesis 1 (Higher PTSD symptoms will be associated significantly with poorer pain-related and psychosocial outcomes): To test this hypothesis, the following 3 analyses will be conducted:

- Univariate analysis: Evaluate patients' demographic and clinical outcome differences among patients with (PCL-C total score \geq 41) vs. without clinical PTSD symptoms (PTSD screening negative or PCL-C total score $<$ 41). T-tests (for continuous variables) and chi-square tests (for categorical variables) will be utilized to assess differences.
- Pearson correlation: To explore the relationships among multiple measures, Pearson correlation coefficients will be calculated.
- Logistic regression: Demographic and clinical predictors of PTSD (PCL-17 total score \geq 41) will be determined through multiple logistic regression (MLR). This analysis will help us determine parameters included in our relationship modeling.

2) Hypothesis 2 (Higher pain severity will be associated with more severe PTSD and psychosocial outcomes.): To test this hypothesis, the following 3 analyses will be conducted:

- Univariate analysis: Evaluate patients' demographic and clinical outcome difference among patients with GCPS pain severity in (1,

2) and GCPS pain severity in (3, 4).

- Pearson correlation: To explore the relationships among multiple measures, Pearson correlation coefficients will be calculated.
- Logistic regression: Demographic and clinical predictors of GCPS pain severity will be determined through multiple logistic regression (MLR).

- 3) Hypothesis 3 (Besides pain severity, there are other key factors that are associated with PTSD): The classification and regression tree (CART) analysis will be employed using SAS Enterprise Miner 6.1 to identify significant factors associated with PTSD. CART analysis, a tree building technique, is able to select many possible 'predictors', deal with complex interactions between predictors, and non-normal and non-linear distributed clinical variables. In this analysis, the target is clinical PTSD (PCL-17 total score ≥ 41). The binary recursive partitioning is accomplished by searching all potential predictors to best classify patients into clinically significant PTSD or non-clinically significant PTSD groups. The possible 'predictors' include pain (severity and disability), pain beliefs, and psychological symptoms.
- 4) Hypothesis 4 (The relationship between PTSD severity and chronic musculoskeletal pain severity will be mediated through depression, anxiety, or pain catastrophizing. Moreover PTSD and pain severity will adversely affect quality of life independently; and patients with high chronic musculoskeletal pain and PTSD will have worse quality of life than

patients with only one or neither of these conditions): The following analyses will be conducted:

- ANCOVA analysis will be used to test the hypothesis that patients with GCPS pain severity ≥ 3 and PCL-17 total score ≥ 41 were associated with worse SF-36.
- Structural equation modeling analysis will be conducted to test the hypothesis of mediating factors between PTSD (PCL-17 ≥ 41 or not) and chronic pain severity implicated by the Mutual Maintenance Model. Specifically, we will test two models. In Model #1, PTSD will have a direct effect on anxiety (GAD-7 total score ≥ 10), and an indirect effect on pain severity through depression (PHQ-9 total score ≥ 10); and pain severity will have an indirect effect on PTSD through pain catastrophizing (figure 3.1). Pain severity is classified into five categories based on the combination of pain intensity and pain disability (table 3.3). In Model #2, PTSD will have an indirect effect on pain severity through pain catastrophizing and comorbid anxiety and depression (figure 3.2). In both models, the physical health component score of the quality of life measure (SF-36 PCS) will be affected by the severity of pain, and the mental health component score (SF-36 MCS) will be affected by the severity of PTSD.

Figure 3.1: SEM path analysis diagram for model #1

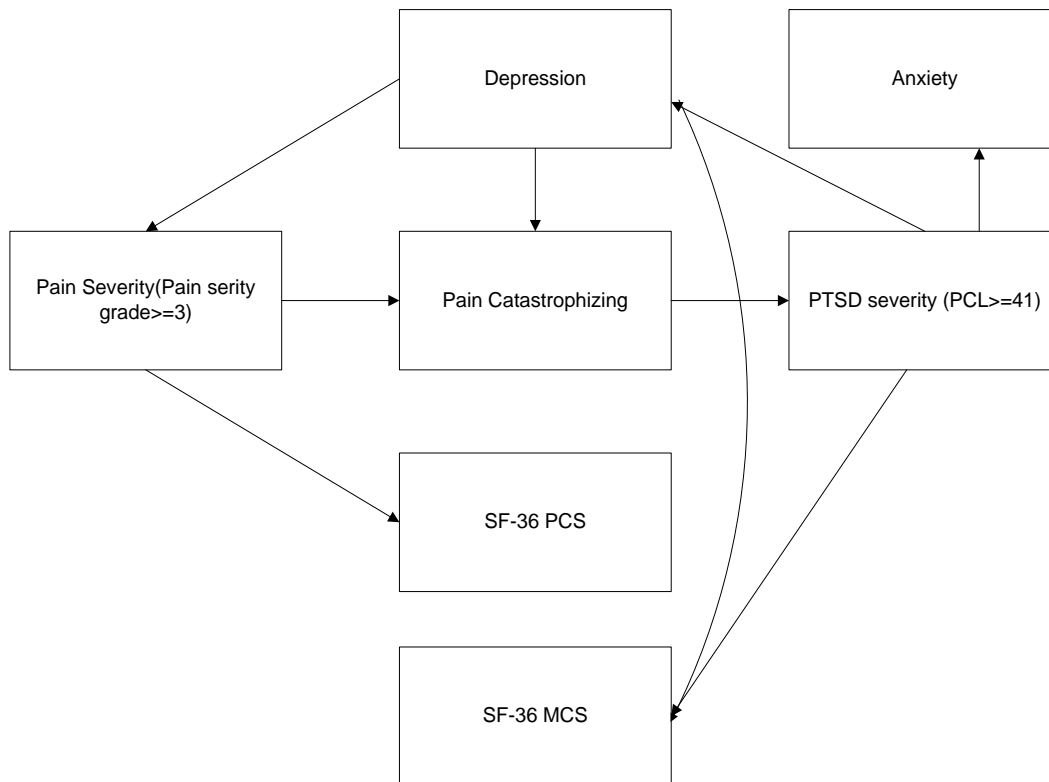
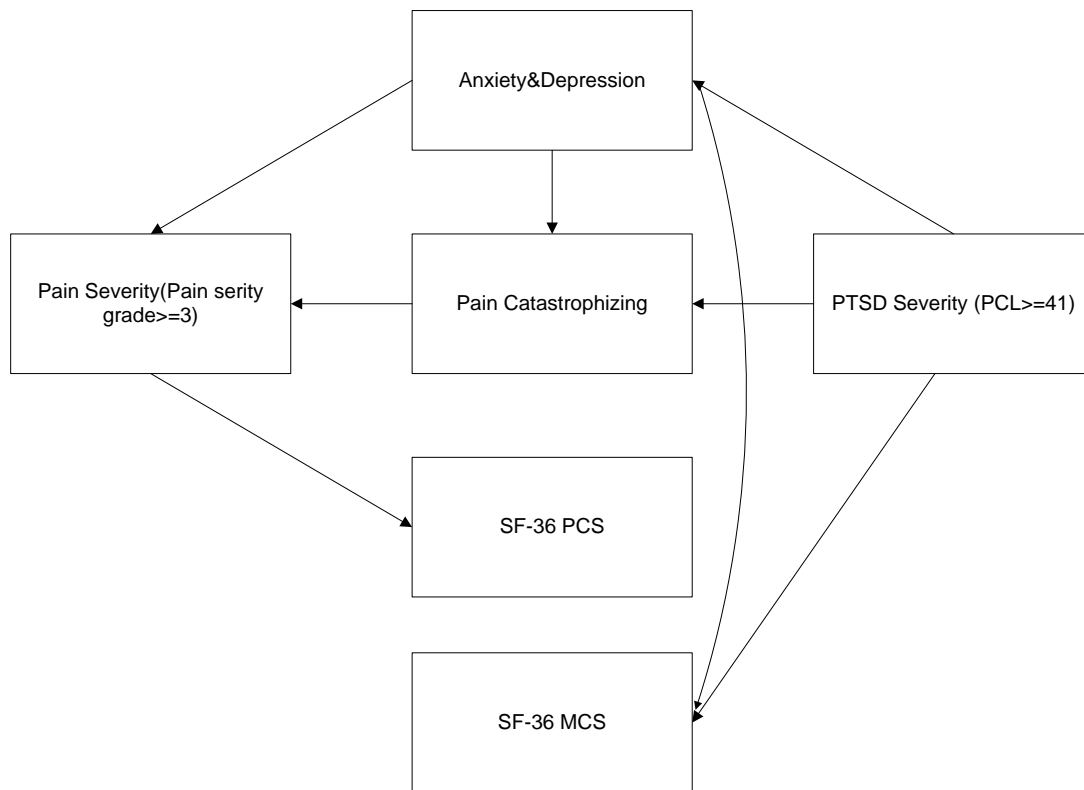


Figure 3.2: SEM path analysis diagram for model #2



- Structural equation modeling analysis will be conducted to test the hypothesis of mediating factors between PTSD (PCL-17 \geq 41 or not), pain intensity and pain disability derived from the Mutual Maintenance Model. Specifically, we will test the following models (Model #3 and #4). In model #3, PTSD will have a direct effect on pain intensity, and an indirect effect on pain disability through pain catastrophizing and comorbid anxiety and depression (figure 3.3). Meanwhile, pain disability will have a direct effect on PTSD and pain intensity. In model #4, pain intensity effects pain disability directly, and pain disability effects pain intensity indirectly through pain catastrophizing.

Comorbid anxiety and depression mediates the relationship between PTSD and pain catastrophizing, pain intensity and pain disability (figure 3.4). Similar to model #1 and #2, in both model #3 and #4, the physical health component score of the quality of life measure (SF-36 PCS) will be affected by the severity of pain directly, and the mental health component score (SF-36 MCS) will be affected by the severity of PTSD directly.

Figure 3.3: SEM path analysis diagram for model #3

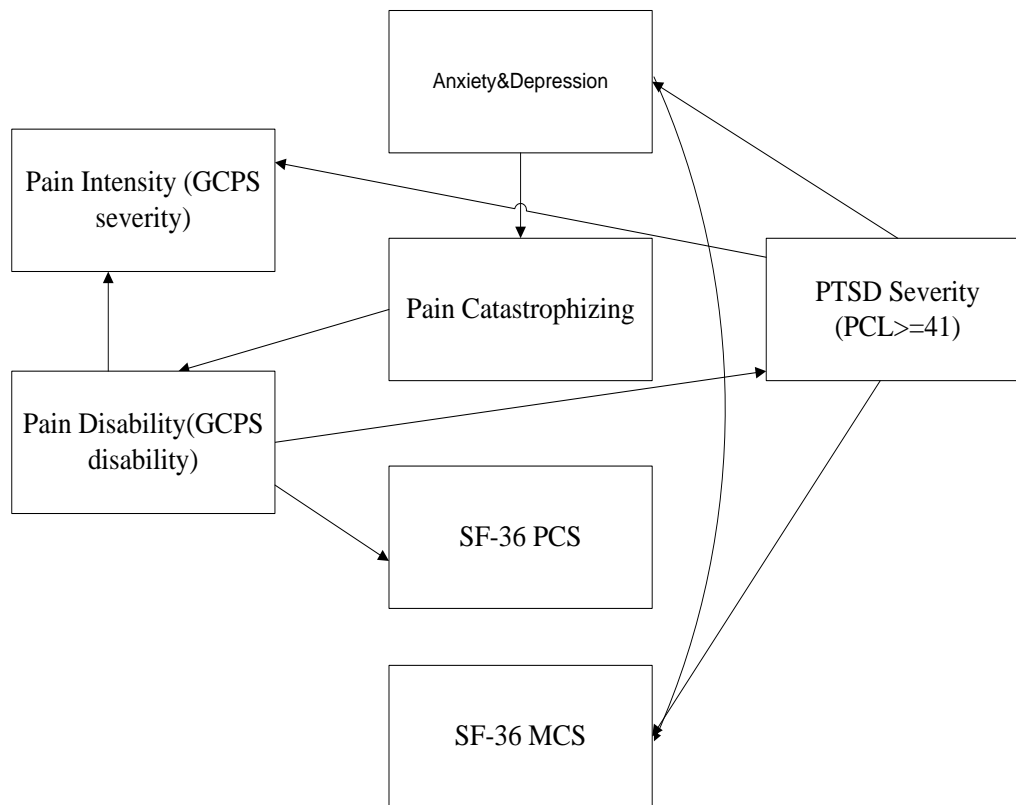
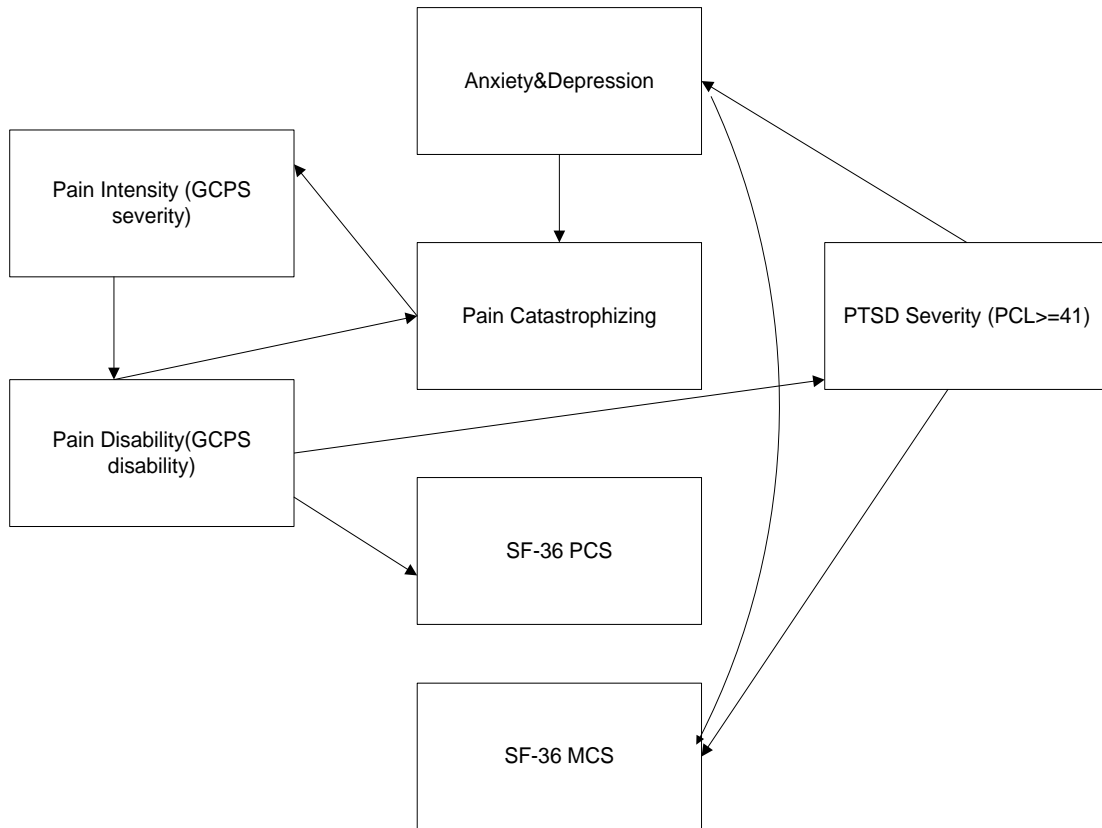


Figure 3.4: SEM path analysis diagram for model #4



- To test the sensitivity of above models, structural equation modeling analysis will also be conducted to test the four simplified models with the two quality of life measures (SF-36 PCS and MCS) removed from model #1, #2, #3, and #4, respectively.

5) Hypothesis 5 (Different PTSD symptom domains will have differential relationships with chronic musculoskeletal pain outcomes, either directly, or through mediating factors such as depression or general anxiety disorder): To test this hypothesis, the following 2 analyses will be conducted for the patients with both PCL17 and GCPS evaluations:

Analysis 1: Confirmatory factor analyses will be conducted to determine PTSD domains using baseline information of patients who screened positive for PTSD. The following five models will be tested, based on a similar analysis conducted by Cyders et al (Cyders, Burris et al. 2010). The model summaries are presented in table 3.4.

- Model A is a one-factor model where all PCL-17 items load onto a single PTSD factor.
- Model B is an intercorrelated two-factor model, with one factor representing re-experiencing/avoidance symptoms and a second factor representing numbing/hyperarousal symptoms.
- Model C is an intercorrelated three-factor model, with a re-experiencing, an avoidance, and a hyperarousal model (the DSM-IV separation of PTSD symptoms).
- Model D is comprised of four intercorrelated factors: re-experiencing, avoidance, numbing, and hyperarousal factors.
- Model E is comprised of four different intercorrelated factors: reexperiencing, avoidance, dysphoria, and hyperarousal factors.

Table 3.4: Model summary of PCL-17 domains structure

Model	Factors	PCL-C items
A	PTSD	All 17 items
B	Re-experience/avoidance	1-7
	Numbing/hyperarousal	8-17
C	Re-experiencing	1-5
	Avoidance	6-12
	Hyperarousal	13-17
D	Re-experiencing	1-5
	Avoidance	6-7
	Numbing	8-12
	Hyperarousal	13-17
E	Re-experiencing	1-5
	Avoidance	6-7
	Dysphoria	8-15
	Hyperarousal	16-17

The confirmatory factory analysis (CFA) is used to assess how well the hypothesized factor models (Model A-E) of PCL-17 fit our data. Cyders et al found the two four-factor models, model D (figure 3.5) and E (figure 3.6), provided better model fit indices based on a cross-sectional study on female patients with oral facial pain (Cyders, Burris et al. 2010). These findings will be validated in our study using ESCAPE trial data.

Figure 3.5: Confirmatory factor analysis of model D

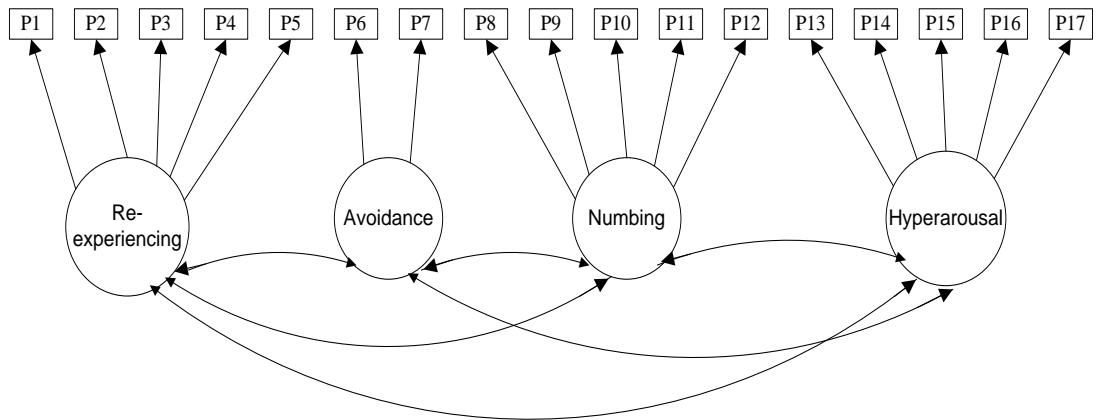
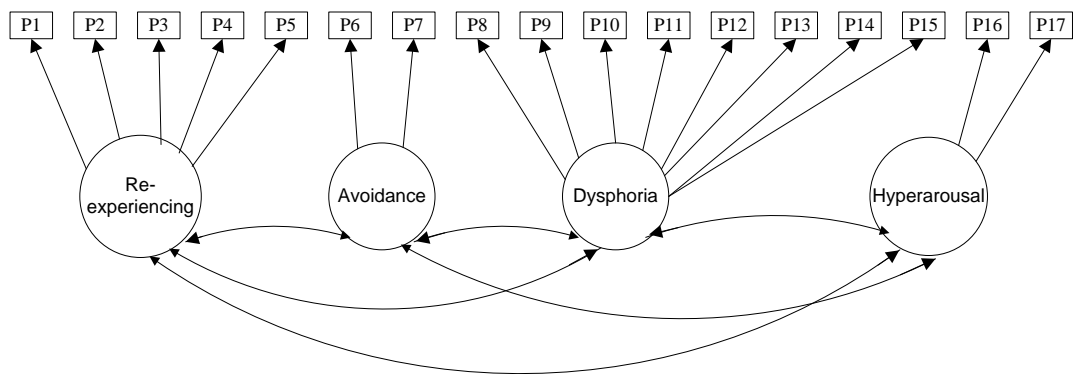


Figure 3.6: Confirmatory factor analysis of model E



Following the determination of the best factor structure of PTSD symptoms (Analysis 1) and a series of descriptive and correlation analyses, we will conduct additional SEM in the following analysis (Analysis 2) to explore and test our hypothesis about the differential relationships of different PTSD symptom domains (Hypothesis 5). The PTSD symptom factors will be defined as latent variables. Pain severity and disability, and other mediated factors (mentioned above) will be defined as measured variables in SEM tests.

Analysis 2: Structural equation modeling will be used to test the following sub-hypotheses:

- Hyperarousal and re-experiencing symptom clusters will predict pain severity;
- Avoidance and numbing/dysphoria symptom clusters will predict pain-related disability
- The above relationships will be mediated by the following factors:
 - Depression
 - Any mental disorder (depression, GAD)
 - Catastrophizing

Specifically, we're going to test the following two structural equation models. In the first model (figure 3.7), we hypothesize the numbing factor will have an indirect effect on pain disability through depression. In the second model (figure 3.8), the dysphoria factor will have a similar indirect effect on pain disability through depression. In both models, hyperarousal factor will have a direct effect on pain intensity, and avoidance will have a direct effect on pain disability. In addition, the relationship between reexperiencing and pain disability will be mediated by pain catastrophizing. And quality of life (SF-36 PCS and MCS) will be affected directly by numbing/dysphoria and pain disability.

Figure 3.7: Structural equation modeling based on a four-factor model (model D) of PTSD symptom clusters

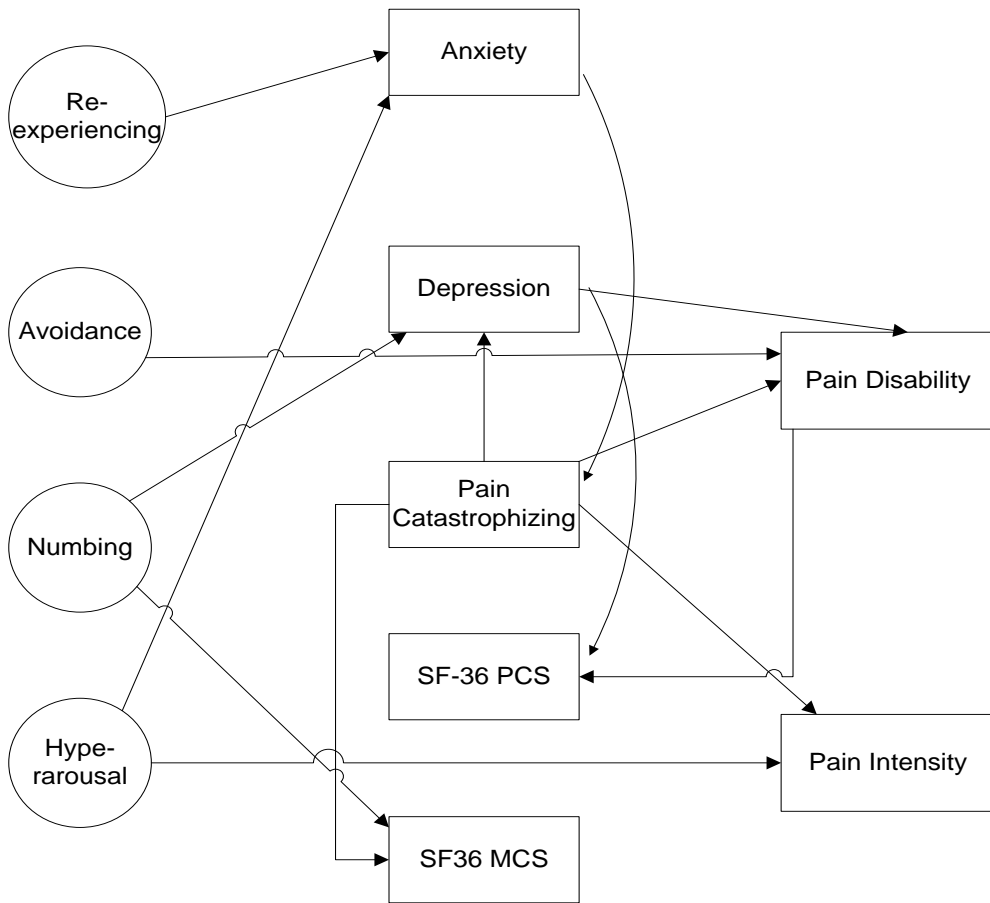
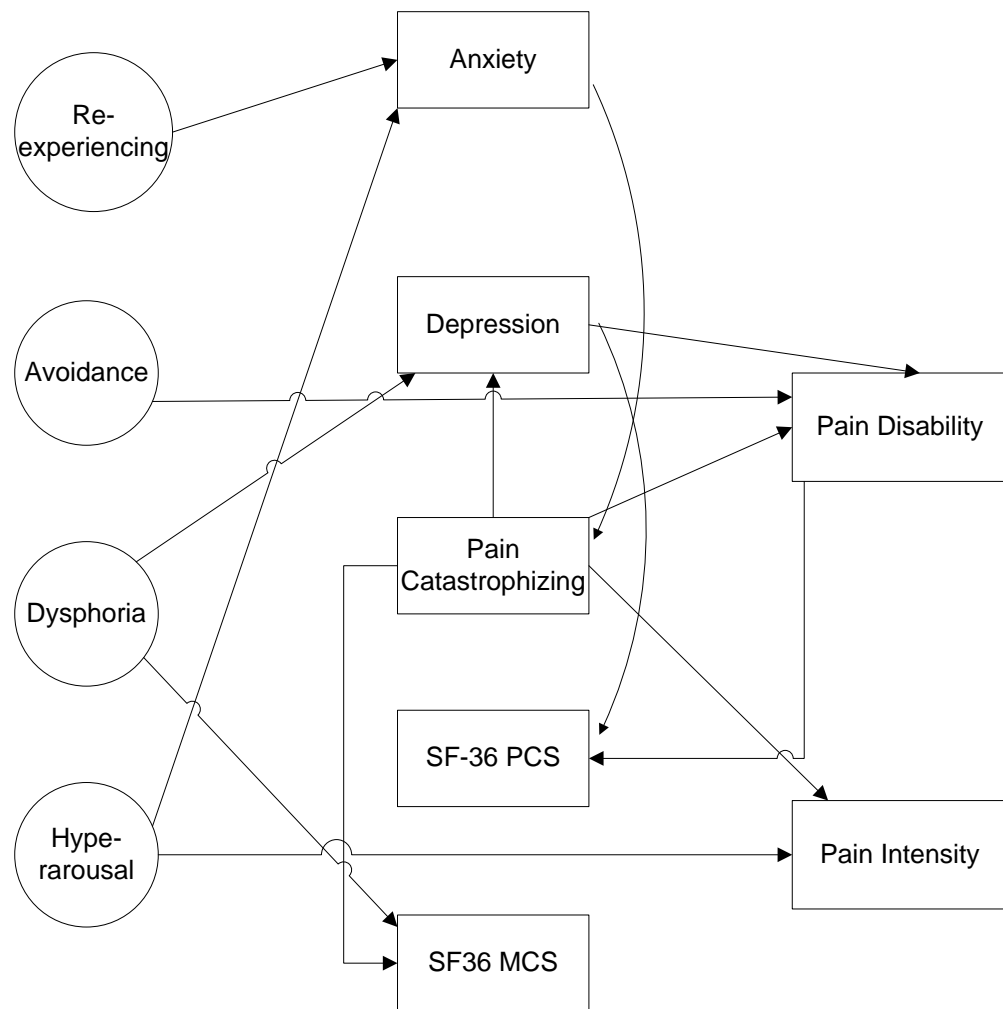


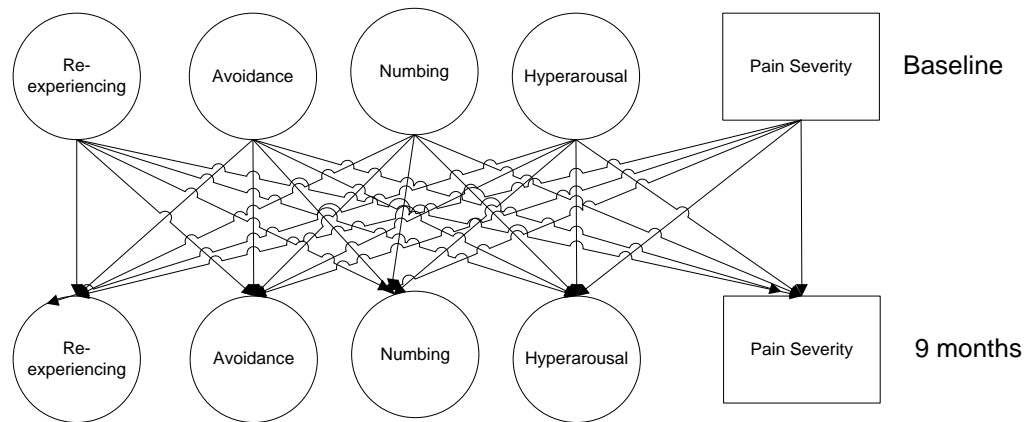
Figure 3.8: Structural equation modeling based on a four-factor model (model E) of PTSD symptom clusters



Longitudinal Data Analysis

- 6) Hypothesis 6 (Baseline PTSD will predict chronic musculoskeletal pain severity grades at 9 months, and baseline chronic musculoskeletal pain severity grades would predict PTSD at 9 months): To test this hypothesis, we'll conduct a cross-lagged panel analysis using SEM (figure 3.9).

Figure 3.9: Cross-lagged panel model of the relationship of pain severity and PTSD symptom clusters based on a four-factor model (model D)



- 7) Hypothesis 7 (The longitudinal change in pain severity will be predicted by PTSD at baseline. The PTSD at 9 months will be predicted by pain intensity and disability at baseline.): A repeated measures model analysis and logistic regression analysis will be used to examine this hypothesis.

Chapter IV: Results

Introduction

We used SAS Enterprise 6.1 for CART analysis, Mplus 5.1 for Confirmatory Factor Analysis and Structural Equation Modeling (SEM) analysis, and SAS 9.2 for other statistical analyses such as regression and correlation analyses. In our analyses, PTSD diagnosis and severity are measured by the PCL-17. Pain intensity and pain-related disability are measured by the GCPS. Pain severity is defined by five grades (ranges 0 to 4) based on the combination of pain intensity and pain-related disability measured by the GCPS (see chapter 3).

We first conducted a series of descriptive, correlational and logistic regression analyses with baseline data to explore how chronic musculoskeletal pain outcomes are associated with PTSD outcomes after adjusting for demographic, social, economic, and psychological factors. These analyses were used to test our hypothesis 1 (Higher PTSD symptoms will be significantly associated with poorer pain-related and psychosocial outcomes) and hypothesis 2 (Higher pain severity will be associated with more severe PTSD and poorer psychosocial outcomes). We then conducted a CART analysis to identify the strongest predictors of PTSD and pain outcomes (hypothesis 3: Besides pain severity, there are other key factors that are associated with PTSD), followed by a confirmatory factor analysis and a series of SEM analyses with baseline data to examine the direct/indirect relationships between different PTSD symptom clusters, chronic musculoskeletal pain outcomes and other variables of interests.

These latter analyses were used to test our hypothesis 4 (The relationship between PTSD and chronic musculoskeletal pain severity will be mediated through depression, anxiety, or pain catastrophizing. Moreover PTSD and pain severity will adversely affect quality of life independently. And patients with high chronic musculoskeletal pain and PTSD will have worse quality of life than patients with only one or neither of these conditions) and hypothesis 5 (Different PTSD symptom domains will have differential relationships with chronic musculoskeletal pain outcomes, either directly, or through mediating factors such as depression or general anxiety symptoms). Finally we conducted longitudinal analyses using both mixed model repeated analysis and cross-lagged panel analysis to examine if there are predictable relationships 1) between baseline PTSD symptoms and chronic musculoskeletal pain symptoms at 9 months, and 2) between baseline chronic musculoskeletal pain symptoms and PTSD symptoms at 9 months (hypothesis 6 and 7).

For each SEM analysis, we report both absolute fit indices including Chi-Squared test, Relative Chi Square, Root Mean Square Error of Approximation (RMSEA); and relative fit indices including Comparative Fit Index (CFI) and Non-Normed Fit Index (NNFI). Interpretation and acceptable thresholds (“rules of thumb”) for these fit indices are listed in Appendix E.

In subsequent sections, we first define a subsample of patients who had their PTSD symptoms assessed and compare it with the full sample in terms of patient demographics and baseline characteristics. This subsample was used in some of our analyses because more measurement data (e.g. PTSD symptom

assessment) was available on this sample. Next we report results from individual analyses in the order of associated hypotheses as outlined in Chapter 3. Lastly, we end with a brief summary.

Baseline Characteristics of All ESCAPE participants vs. ESCAPE participants with PTSD

Table 4.1 lists the baseline characteristics of all patients who participated in the ESCAPE trial. Of 241 participants, 52 (21.6%) screened negative for PTSD without further PTSD symptom assessment (i.e. baseline PCL-17 evaluation) and 189 (78.4%) screened positive for PTSD with further baseline PCL-17 evaluation. Among 189 PTSD-screen positive participants, one patient did not respond to several items on PCL-17. Because of this missing data, this patient will be excluded from analyses resulting in a full sample of 240 patients, and a subsample of 188 patients assessed for PTSD symptoms.

Depending on the availability of measurements required by the analysis, either the full sample (N=240) or the subsample (N=188) was analyzed.

1) Full sample: This sample includes all 240 participants (excluding one patient with PTSD-screen positive but missing PCL-17 total score). If participants screened negative (Prins 2003) for PTSD (N=52, 21.7%), we assumed their PCL-17 total scores were less than 41 (a validated cut point for clinically significant PTSD symptoms) although these patients were not assessed with the PCL-17 according to the study design. In other words, we assumed that participants had either no or mild PTSD symptom which did not meet criteria for clinically

meaningful PTSD symptoms. Table 2 contains the baseline characteristics of participants in the full sample (N = 240). Participants' average age was 36.7 years old. Most participants were male (88.3%) and Caucasian (77.6%). More than half of participants (54.6%) were married and all participants had graduated from high school or received some higher education.

2) Subsample: This sample includes all participants who screened positive for PTSD (N=188) and were subsequently assessed with the PCL-17 instrument for PTSD symptoms. Compared with participants who screened negative for PTSD, participants who screened positive for PTSD were younger (39.9 vs. 35.7 years old), reported less comfort with their level of income and lower employment rate, reported more severe pain intensity, more disability days, and higher pain catastrophizing, anxiety, and depression scores (table 4.1).

Table 4.1: Baseline characteristics: all ESCAPE participants (N = 240)

Characteristic	Overall	PTSD Screening negative (N=52)	PTSD screen positive (N=188)	P value
Age in Years, mean (std)	36.7 (10.2)	39.9 (11.7)	35.7 (9.6)	0.0084
Men, n (%)	212 (88.3)	49 (94.2)	163 (86.7)	0.1345
White, n (%)	184 (77.6)	40 (80.0)	144 (77.0)	0.6517
Black, n (%)	31 (13.1)	8 (16.0)	23 (12.3)	0.4906
High school, n (%)	239 (100.0)	51 (100.0)	188 (100.0)	
Married, n (%)	131 (54.6)	30 (57.7)	101 (53.7)	0.6109
Income, "comfortable", n (%)	88 (36.7)	27 (51.9)	61 (32.4)	0.0099
Employed, n (%)	176 (73.3)	44 (84.6)	132 (70.2)	0.0376
GCPS pain intensity, mean (std)	66.3 (13.7)	62.1 (15.7)	67.5 (12.9)	0.0110

Characteristic	Overall	PTSD Screening negative (N=52)	PTSD screen positive (N=188)	P value
GCPS pain disability, mean (std)	54.4 (24.4)	49.68 (19.4)	55.7 (25.5)	0.1166
GCPS pain disability days, mean (std)	14.1 (22.3)	5.4 (8.3)	16.4 (24.3)	0.0017
GCPS pain severity categories, n (%)				0.0012
1	20 (8.3)	8 (15.4)	12 (6.4)	
2	106 (44.2)	27 (51.9)	79 (42.0)	
3	66 (27.5)	15 (28.8)	51 (27.1)	
4	48 (20.0)	2 (3.8)	46 (24.5)	
GCPS pain severity in (3, 4), n (%)	114 (47.5)	17 (32.7)	97 (51.6)	0.0157
Pain catastrophizing, mean (std)	21.7 (12.3)	16.92 (11.1)	23.0 (12.3)	0.0014
GAD-7 anxiety, mean (std)	8.8 (5.3)	5.2 (4.2)	9.9 (5.1)	<.0001
GAD-7 anxiety \geq 10, n (%)	107 (44.6)	10 (19.2)	97 (51.6)	<.0001
PHQ-9 depression, mean (std)	11.2 (5.9)	7.56 (5.5)	12.2 (5.6)	<.0001
PHQ-9 depression \geq 10, n (%)	137 (57.1)	15 (28.8)	122 (64.9)	<.0001
GAD-7 and PHQ-9 \geq 10, n (%)	96 (40.0)	8 (15.4)	88 (46.8)	<.0001

Correlations of baseline PTSD, pain, health-related quality of life, and psychological factors

To assess the relationships between PTSD, pain, health-related quality of life, and other psychological factors, we first calculated the Pearson correlations

of the variables of interest, including pain, PCL17, GAD-7 anxiety, PHQ-9 depression and SF-36 quality of life. Because participants screened negative for PTSD were not evaluated with PCL17 according to the ESCAPE trial protocol, the subsample (N=188) of participants with PCL-17 score measured were included in this analysis. The results are listed in table 4.2 (Appendix H). In summary, a strong correlation ($r \geq 0.6$ or $r \leq -0.6$) was found between 1) PCL-17 and depression, anxiety, SF-36 mental component summary scores; 2) pain disability and SF-36 physical component scores; 3) depression (PHQ-9), anxiety (GAD-7), and SF-36 mental component scores.. A moderate correlation ($0.4 \leq r < 0.6$ or $-0.6 < r \leq -0.4$) was found between 1) PTSD symptoms (PCL17) and pain catastrophizing; 2) between pain intensity and pain disability, SF-36 physical component scores; 3) between pain disability and depression, SF-36 physical component scores; 4) between depression and pain catastrophizing; 5) between anxiety and pain catastrophizing; 6) between pain catastrophizing score and SF-36 mental component score.

Hypothesis #1: Higher PTSD symptoms will be significantly associated with poorer pain-related and psychosocial outcomes

To test hypothesis #1, we first categorized patients according to clinically significant PTSD symptoms. Clinically significant PTSD symptoms were defined as a PCL17 total score ≥ 41 (yes/no). We then compared baseline characteristics between those with and without clinically significant PTSD

symptoms and fit a logistic regression model to further assess the association of PTSD severity with pain outcomes.

Comparisons of baseline characteristics between patients with and without clinically significant PTSD symptoms

Overall, 68 (28.3%) participants were categorized as having clinically significant PTSD symptoms (PTSD group) (PCL17 total score ≥ 41). Compared to patients without clinically significant PTSD symptoms (those screened negative or with PCL17 total score < 41), the participants in the PTSD group were similar in age, gender, educational attainment, and marital status (all p -value > 0.5). As shown in table 4.3, the PTSD group was more likely to report having an inadequate income, to be unemployed, have more severe and disabling pain, greater pain catastrophizing, and more severe anxiety, depression, and SF-36 mental scores.

These results confirmed our hypothesis that PTSD is associated with poorer pain-related, psychosocial, and quality of life outcomes.

Table 4.3: All ESCAPE participants (N = 240) baseline characteristics: PTSD group vs. non-PTSD group

Characteristic	Overall	Non-PTSD group (N=172)	PTSD group (N=68)	P value
Age in Years, mean (std)	36.7 (10.2)	37.3 (10.6)	35.1 (9.2)	0.1432
Men, n (%)	212 (88.3%)	152 (88.4%)	60 (88.2%)	0.9763
White, n (%)	184 (77.6%)	134 (79.3%)	50 (73.5%)	0.3357
Black, n (%)	31 (13.1%)	24 (14.2%)	7 (10.3%)	0.4197
High school, n (%)	239 (100.0%)	171 (100.0%)	68 (100.0%)	.
Married, n (%)	131 (54.6%)	98 (57.0%)	33 (48.5%)	0.2363
Income, "comfortable", n (%)	88 (36.7%)	74 (43.0%)	14 (20.6%)	0.0012
Employed, n (%)	176 (73.3%)	136 (79.1%)	40 (58.8%)	0.0014
GCPS pain intensity, mean (std)	66.3 (13.7)	63.9 (13.7)	72.3 (11.6)	<.0001
GCPS pain disability, mean (std)	54.4 (24.4)	49.8 (23.8)	66.1 (21.9)	<.0001
GCPS pain disability days, mean (std)	14.1 (22.3)	10.7 (18.4)	22.7 (28.3)	0.0001
GCPS pain severity categories, n (%)				0.0004
1	20 (8.3%)	18 (10.5%)	2 (2.9%)	
2	106 (44.2%)	86 (50.0%)	20 (29.4%)	
3	66 (27.5%)	43 (25.0%)	23 (33.8%)	
4	48 (20.0%)	25 (14.5%)	23 (33.8%)	
GCPS pain severity \geq 3, n (%)	114 (47.5%)	68 (39.5%)	46 (67.6%)	<.0001
Pain catastrophizing, mean (std)	21.7 (12.3)	19.0 (11.2)	28.6 (12.2)	<.0001
GAD-7 Anxiety, mean (std)	8.8 (5.3)	5.2 (4.2)	9.9 (5.1)	<.0001
GAD-7 \geq 10, n (%)	178 (74.2%)	111 (64.5%)	67 (98.5%)	<.0001

Characteristic	Overall	Non-PTSD group (N=172)	PTSD group (N=68)	P value
PHQ-9 depression, mean (std)	11.2 (5.9)	9.2 (5.1)	16.3 (4.5)	<.0001
PHQ-9 depression \geq 10, n (%)	137 (57.1%)	76 (44.2%)	61 (89.7%)	<.0001
GAD-7 and PHQ-9 \geq 10, n (%)	96 (40.0%)	8 (15.4%)	88 (46.8%)	<.0001
SF36 PCS, mean (std)	37.4 (7.5)	37.8 (7.3)	36.5 (7.8)	0.2409
SF36 MCS, mean (std)	41.6 (12.6)	45.9 (11.2)	30.8 (8.9)	<.0001

Note: GCPS pain intensity: ranges 0 to 100, higher scores represent higher pain intensity.
GCPS pain disability: ranges 0 to 100, higher scores represent higher pain disability.
GCPS pain disability days: range 0 to 90 days.
GCPS pain severity: classified to five grades based on both GCPS pain intensity and GCPS pain disability; range 0 to 4, higher grades represent higher GCPS pain intensity (range 0 to 100) and/or higher GCPS pain disability (range 0 to 100).
GAD-7 anxiety: range 0-21, higher scores represent higher anxiety.
PHQ-9 depression: range 0-27, higher scores represent higher depression.

Multivariate ordinal logistic regression models to assess the relationship between PTSD (independent variable) and pain severity grades (dependent variable)

We conducted a multiple ordinal logistic regression analysis to examine if clinically significant PTSD (PCL-17 score \geq 41) is associated with pain severity (according to GCPS severity 4 categories/grades) using two models. The two models differ only in the choice of covariates. The covariates were various comorbidities of pain (depression, anxiety and pain catastrophizing) in the first model, or comorbidities plus socialdemographic factors including income and employment status in the second model. The results of logistic regression analysis are listed in table 5. In the first model, pain catastrophizing and depression were positively associated with pain severity (i.e. more pain catastrophizing thoughts and depression symptoms are associated with more

severe pain). After adding demographic and economic factors in the second model, employment status, pain catastrophizing and depression were all statistically significant ($p < 0.05$). Except for employment status, there were no statistically significant associations between pain severity and other baseline sociodemographic characteristics (table 4.4).

To evaluate the effect of possible colinearity between PTSD and anxiety, we removed anxiety from the covariate list in our models. The results still show PTSD has no significant effect on pain severity (see table 4.4 footnote).

The ordinal logistic regression results therefore did not show PTSD was independently associated with pain severity controlling for depression, anxiety, catastrophizing and social demographic factors.

Table 4.4: Ordinal logistic regression to evaluate associations between GCPS pain severity, PTSD, and other factors in all ESCAPE (n = 240) participants

	Response variable: GCPS pain severity categories (1, 2, 3, 4)			
	Model without socio-demographic characteristics adjustment		Model with socio-demographic characteristics adjustment	
	OR (95% CI)	p-value	OR (95% CI)	p-value
PTSD (PCL17≥ 41)	1.55 (0.86, 2.79)*	0.137	1.37 (0.74, 2.52)**	0.31
pain catastrophizing	1.03 (1.01, 1.06)	0.002	1.03 (1.01, 1.06)	0.004
GAD-7 anxiety ≥10	1.40 (0.69, 2.86)	0.966	1.27 (0.60, 2.66)	0.782
PHQ-9 depression≥10	1.96 (1.05, 3.67)	0.025	1.96 (1.03, 3.75)	0.029
Age			0.98 (0.96, 1.01)	0.173
Male			0.42 (0.2, 0.94)	0.08
white			0.52 (0.29, 0.96)	0.082
Married			1.01 (0.6, 1.68)	0.61
Income, "comfortable"			1.38 (0.8, 2.38)	0.418
Employed			0.3 (0.18, 0.56)	<.0001

*After removing GAD-7 flag from the model without socio-demographic characteristics adjustment, the OR for PTSD is 1.59 (0.88, 2.86)

** After removing GAD-7 flag from the model with socio-demographic characteristics adjustment, the OR for PTSD is 1.39 (0.76, 2.56)

Hypothesis #2: Higher pain severity will be associated with more severe PTSD symptoms and psychosocial outcomes

To test hypothesis #2, we first compared patients with different GCPS pain severity grades at baseline (table 4.5). Next, multiple logistic regression models were developed to further assess the association of pain severity with PTSD.

Baseline characteristics among patients with lower versus higher pain

At baseline, 126 (52.5%) patients had a GCPS pain severity grade 1 or 2 (mild pain group), and 114 (47.5%) patients had a GCPS pain severity grade 3 or 4 (moderate to severe pain group). Pain severity grade, ranging from 1 to 4, was

defined based on the combination of pain intensity, disability score and disability days (see chapter 3). Table 4.5 summarizes the baseline characteristics among patients with lower grades of pain severity (1, 2) versus those with higher grades (3, 4). The two groups did not differ according to demographic characteristics (i.e. age, gender, race, married status). The high pain severity group was less likely to be employed. Moreover, the high pain severity group reported greater pain catastrophizing thoughts, and showed a higher prevalence of clinically significant PTSD, anxiety and depression. These results therefore support our hypothesis that higher pain severity is associated with PTSD and worse psychosocial outcomes.

Table 4.5: Baseline characteristics of patients (n = 240) with low vs. high pain severity

Characteristic	Overall	Low pain group* (N=126)	High Pain group* (N=114)	P value
Age in Years, mean (std)	36.7 (10.2)	37.9 (10.4)	35.3 (9.8)	0.0565
Men, n (%)	212 (88.3)	116 (92.1)	96 (84.2)	0.0584
White, n (%)	184 (77.6)	101 (81.5)	83 (73.5)	0.1399
Black, n (%)	31 (13.1)	16 (12.9)	15 (13.3)	0.9326
High school, n (%)	239 (100.0)	125 (100.0)	114 (100.0)	.
Married, n (%)	131 (54.6)	74 (58.7)	57 (50.0)	0.1749
Income, "comfortable", n (%)	88 (36.7)	51 (40.5)	37 (32.5)	0.1979
Employed, n (%)	176 (73.3)	105 (83.3)	71 (62.3)	0.0002
Pain catastrophizing, mean (std)	21.7 (12.3)	18.2 (11.0)	25.5 (12.6)	<.0001
PCL 17≥41, n (%)	68 (28.3)	22 (17.5)	46 (40.4)	<.0001
GAD-7 anxiety, mean (std)	16.5 (8.7)	13.9 (8.2)	19.4 (8.3)	<.0001
GAD-7 ≥ 10, n (%)	178 (74.2)	80 (63.5)	98 (86.0)	<.0001
PHQ-9 depression, mean (std)	11.2 (5.9)	9.2 (5.3)	13.4 (5.8)	<.0001
PHQ-9 depression ≥ 10, n (%)	137 (57.1)	55 (43.7)	82 (71.9)	<.0001
GAD-7 and PHQ-9 ≥ 10, n (%)	132 (55.0)	51 (40.5)	81 (71.1)	<.0001
GAD-7 or PHQ-9 ≥ 10, n (%)	183 (76.3)	84 (66.7)	99 (86.8)	0.0002

*Low pain group: GCPS severity in (1, 2); **High pain group: GCPS severity in (3, 4).

Logistic regression assessing the relationship between pain severity (independent variable) and PTSD (dependent variable)

We conducted a multiple logistic regression analysis to examine if PTSD can be explained by pain severity using two models. In both models, the

response variable is PTSD status defined as PCL-17 \geq 41 (Y/N). In the first model, the covariates included only the physical and psychological comorbidities of PTSD (i.e. pain, anxiety, depression, and pain catastrophizing). In the second model, socio-demographic factors were also added as covariates. Results for both models are listed in table 4.6. In the first model, almost all parameters included are statistically significant ($p < 0.05$) except pain severity (overall $p = 0.469$). In the second model, pain catastrophizing, anxiety, depression were significant ($p < 0.05$) even after adjustment for socio-demographic factors. There were no statistically significant associations between clinically significant PTSD (PCL-17 score \geq 41) and baseline socio-demographic characteristics (table 4.6).

The multiple logistic regression results therefore did not show pain severity had an independent relationship to PTSD severity in models with and without socio-demographic adjustment.

Table 4.6: Logistic regression to examine associations between PTSD, pain severity, and other factors in all 240 ESCAPE participants

	Response variable: PTSD (PCL-17 \geq 41)			
	Model without socio-demographic characteristics adjustment		Model without socio-demographic characteristics adjustment	
	OR (95% CI)	p-value	OR (95% CI)	p-value
GCPS pain severity categories				
1 vs. 4	0.43 (0.08, 2.39)	0.21	0.58 (0.1, 3.5)	0.545
2 vs. 4	0.63 (0.28, 1.46)	0.7	0.88 (0.35, 2.21)	0.716
3 vs. 4	1.04 (0.45, 2.43)	0.306	1.35 (0.54, 3.39)	0.273
pain catastrophizing	1.04 (1.01, 1.07)	0.011	1.03 (1.004, 1.07)	0.025
GAD-7 anxiety \geq 10	8.9 (1.09, 72.44)	0.038	9.37 (1.12, 78.38)	0.037
PHQ-9 depression \geq 10	4.2 (1.68, 10.54)	0.002	4.15 (1.62, 10.65)	0.003
Age			1 (0.96, 1.04)	0.981
Male			1.05 (0.37, 3)	0.942
white			0.76 (0.34, 1.72)	0.493
Married			0.64 (0.32, 1.3)	0.224
Income, "comfortable"			0.52 (0.24, 1.13)	0.113
Employed			0.62 (0.28, 1.34)	0.212

Hypothesis #3: Besides pain severity, there are other key factors that are associated with PTSD

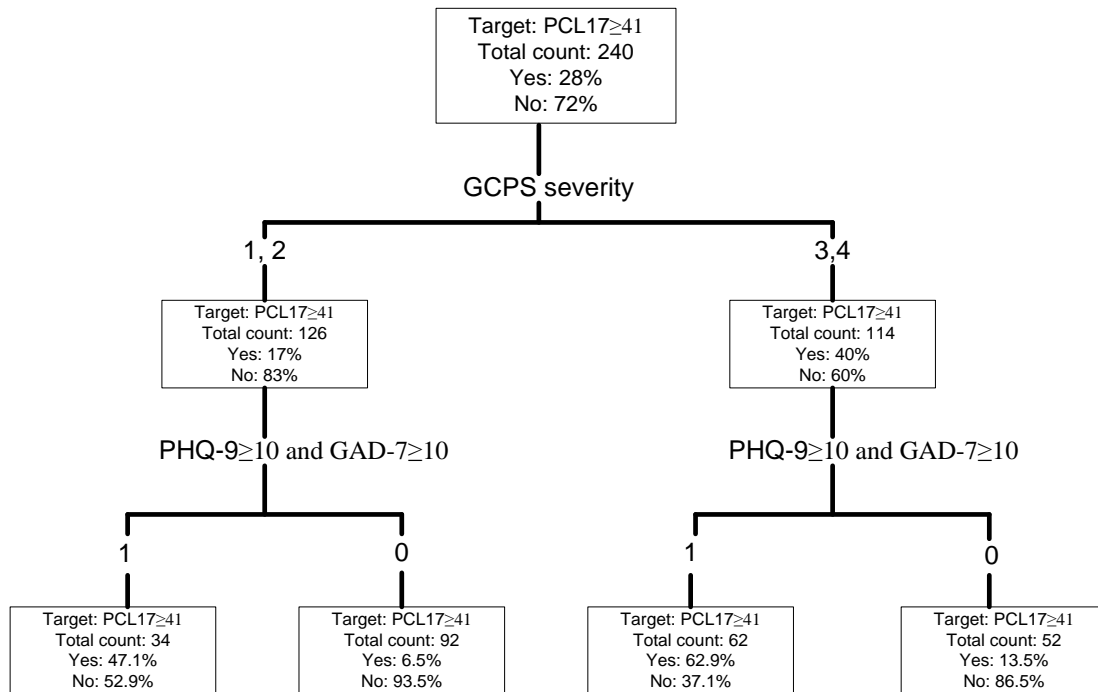
We used CART analysis to test hypothesis #3. CART analysis can be used to uncover the existing interactions or nonlinear relationships among a given response variable and multiple predictor variables, and provide thresholds for each predictor variable, at which its predictive power becomes statistically significant. CART analysis presents a "hierarchy" or decision tree of predictors by finding the best combination of predictors for a given outcome.

In our study, CART analysis was used to identify the most important covariates associated with PTSD besides pain severity. The target variable is PTSD status defined as a PCL-17 score \geq 41 (Yes/No). To identify the

relationship between PTSD and pain severity, pain severity grade (ranges 1 to 4) was “forced” as the first decision variable. The next decision variable was determined by searching all other input variables (i.e. socio-demographic, moderately severe depression, moderately severe anxiety, and pain catastrophizing score). The final decision tree is shown in figure 4.1. In the study baseline data, 68 of 240 patients (28%) had clinically significant PTSD based on total PCL 17 score ≥ 41 . At the first branching level, 240 patients were partitioned based on whether their GCPS severity grade was less than 3. Among patients with GCPS pain severity grade of 3 or 4, 40% had clinically significant PTSD, compared to 17% among the group with GCPS pain severity less than 3. At the next branch point, patients were continually partitioned based on whether both PHQ-9 depression and GAD-7 scores were ≥ 10 (representing moderately severe depression and anxiety symptoms, respectively). The highest PTSD prevalence (62.9%) was identified among patients whose GCPS severity grade was 3 or 4 and who met the second criteria of having moderately severe depression and anxiety symptoms. In contrast, the PTSD prevalence rate was 47.1% among patients who did not meet the first GCPS severity grade criteria but did meet the second criteria of clinically significant depression (PHQ ≥ 10) and anxiety (GAD ≥ 10).

The CART analysis results tended to support our hypothesis that patients with higher pain severity and coexisting depression and anxiety are more likely to have clinically significant PTSD symptoms.

Figure 4.1: Full Sample (N=240): CART analysis to predict clinically significant PTSD (PCL17 \geq 41)



Hypothesis #4: The relationship between PTSD and chronic pain severity will be mediated through depression, anxiety, or pain catastrophizing (4a). Moreover PTSD and pain severity will adversely affect quality of life independently (4b). And patients with high chronic pain (GCPS severity grade \geq 3) and PTSD will have worse quality of life than patients with only one or neither of these conditions (i.e., high chronic pain or PTSD) (4c)

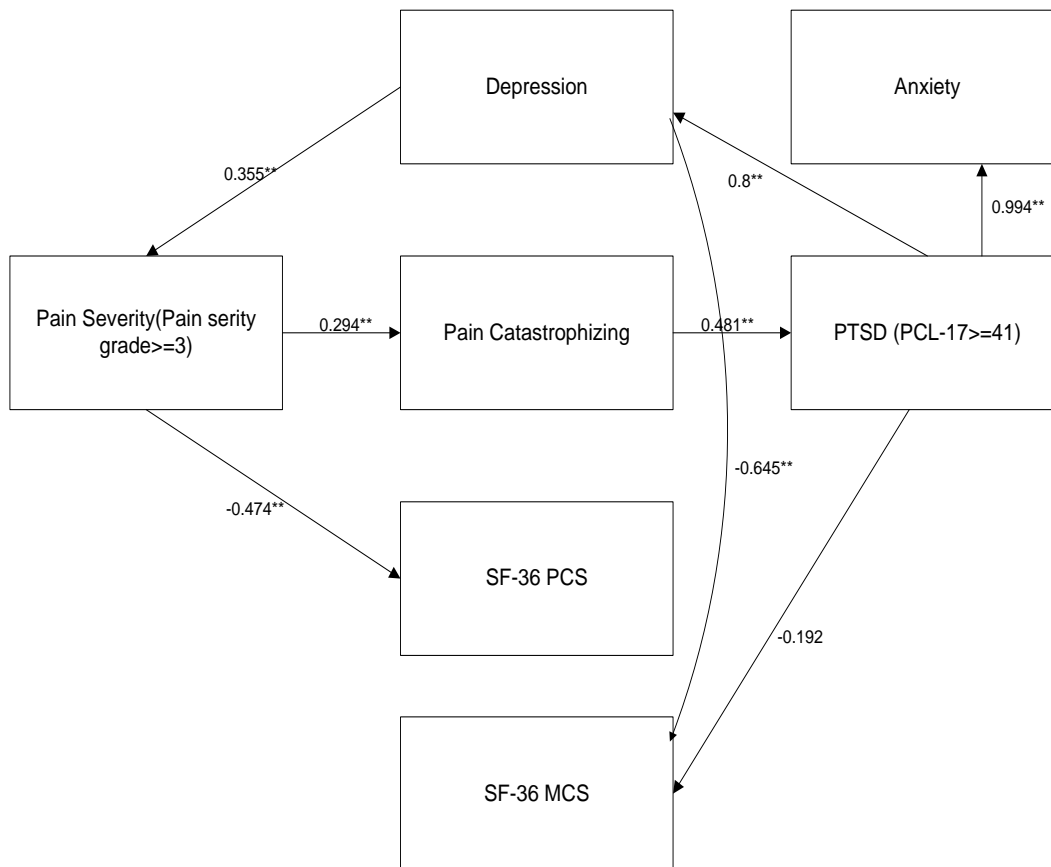
In order to test the first two parts of hypothesis #4 (4a and 4b), we conducted a series of Structured Equation Modeling (SEM) path analysis to test four models (model A to D) pre-specified in chapter 3. All variables included in these models were considered measured. No latent variables were included in

these models. To test the third part of hypothesis #4 (4c), we conducted an ANCOVA analysis to compare the quality of life of chronic pain patients with clinically significant PTSD versus those without.

SEM analysis: model A (N=240)

Model A and its fitting results are depicted in figure 4.2 (full sample). For comparison purpose, the hypotheses and fitting results of this model are also listed in a table in Appendix I along with other models. Model A fits our data fairly (ref. Appendix A: relative Chi-square slightly bigger than the 3:1 cut point, RMSEA =0.092 slightly bigger than the 0.08 cut point, CFI>0.95, TLI>0.9) and provides empirical support for hypothesis #4a and #4b. In particular, this model shows that PTSD is indirectly associated with pain severity through depression, and pain severity is indirectly associated with PTSD through catastrophizing (hypothesis #4a). This model also shows pain severity has a direct negative relationship with quality of life as measured by the SF-36 physical component summary score (SF-36 PCS) (standardized coefficient=-0.474), and PTSD has an indirect negative relationship with the SF-36 mental component summary score (SF-36 MCS) (hypothesis #4b). This indirect relationship is mediated through depression. The model shows PTSD severity is strongly associated with both anxiety (standardized coefficient=0.994) and depression (standardized coefficient=0.8). And depression has a strong negative association with the SF-36 MCS (standardized coefficient=-0.645). The direct relationship between PTSD and quality of life (SF-36 PCS and SF-36 MCS) is, however, not significant.

Figure 4.2: SEM model A related to hypothesis 4. Coefficients reflect standardized path coefficients



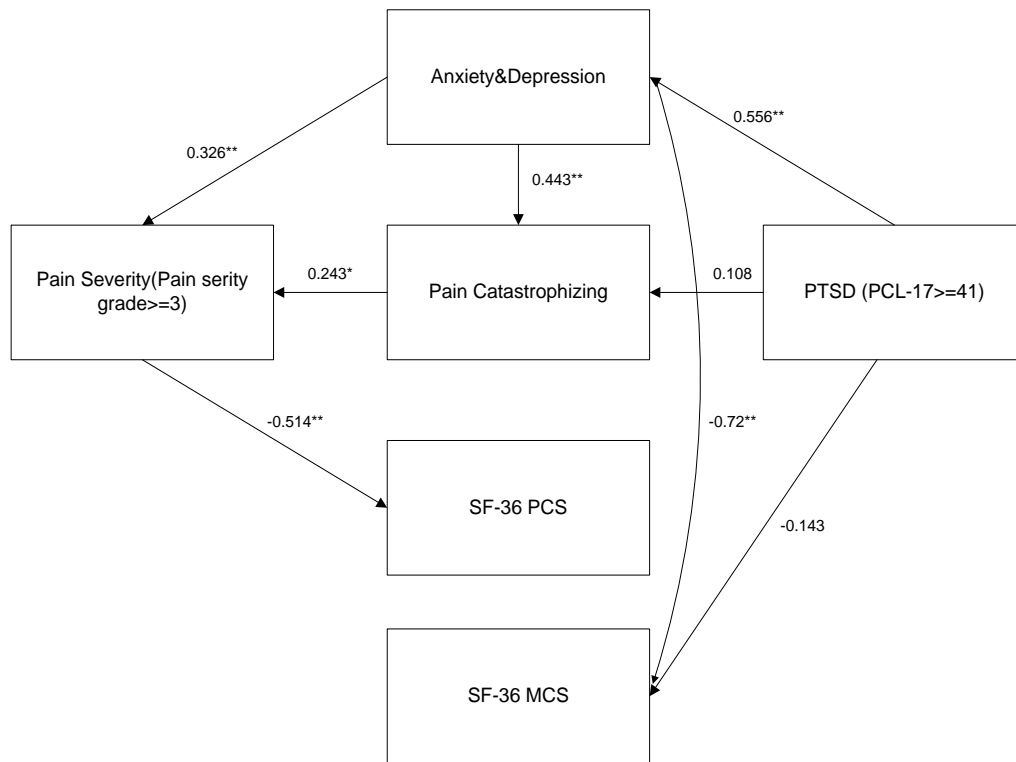
Model fit statistic: Chi-square 30.449, df=10, p<.05; RMSEA 0.092(p<.05); CFI 0.971; TLI 0.939
 *P-value<0.05; **P-value <0.01

SEM analysis: model B (N=240)

Model B and its fitting results are depicted in figure 4.3 (full sample), and are also included in the table of Appendix I for comparison purpose. This model combines anxiety and depression into a single predictor and examines how PTSD is associated with pain severity. The fit is very good in terms of relative chi-square (<2). Other fit indices are also in an acceptable (RMSEA =0.041) or

better (CFI>0.95, TLI>0.95) range. Model B shows PTSD severity has an indirect association on pain catastrophizing through the mediation of the combination of anxiety and depression, and both anxiety/depression and pain catastrophizing are directly related to pain severity (hypothesis #4a). Like model A, model B also shows pain severity has a strong negative association with SF-36 PCS (standardized coefficient=-0.514) (hypothesis #4b). But the hypothesized relationship between PTSD and pain catastrophizing was not significant (standardized coefficient= coefficient < 0.2, p>0.05). The hypothesized direct negative association of PTSD with SF-36 MCS was not significant(-0.143), but indirect negative association was significant (hypothesis4b).

Figure 4.3: SEM model B related to hypothesis 4. Coefficients reflect standardized path coefficients



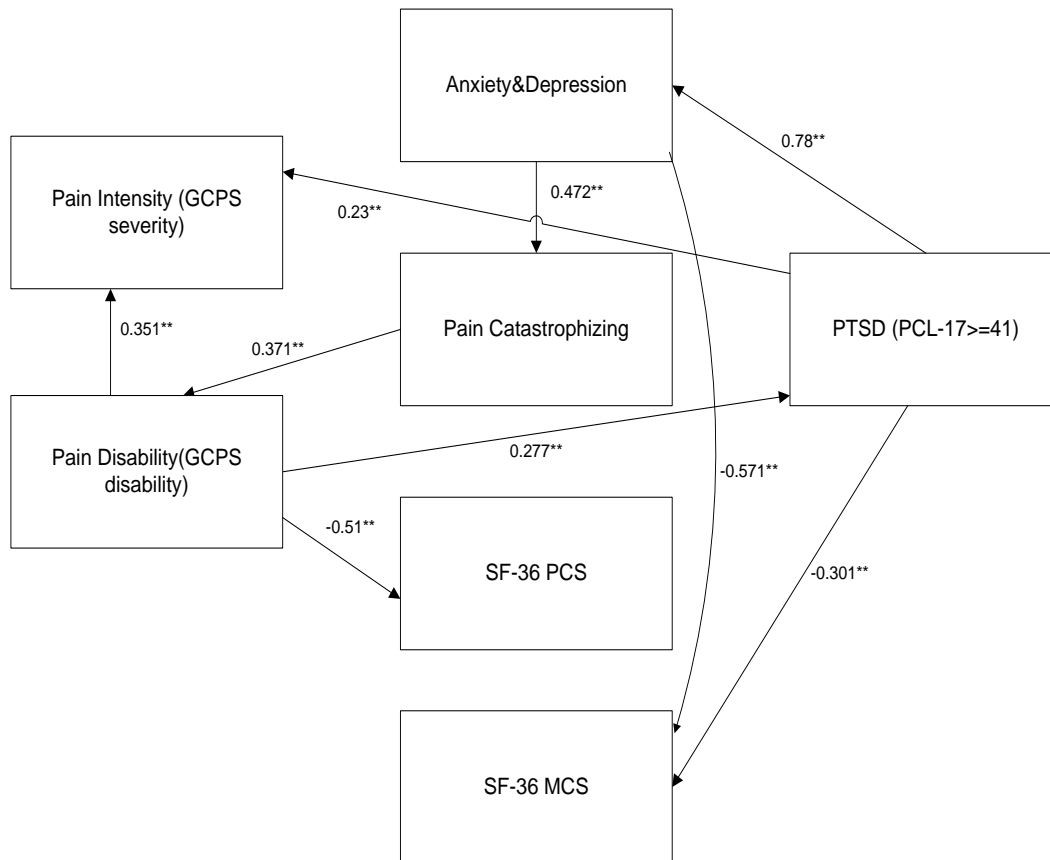
Model fit statistic: Chi-square 8.39, df=6, $p > .05$; RMSEA 0.041 ($p > .05$); CFI 0.992; TLI 0.98
 *P-value < 0.05 ; **P-value < 0.01

SEM analysis: model C (N=240)

Model C and its fitting results are depicted in figure 4.4 (full sample), and are also included in the table of Appendix I for comparison purpose. This model also combines anxiety and depression into a single predictor, but separates pain intensity from pain disability. The model fit is good in terms of RMSEA (0.038). Other fit indices are also in a good fit range (relative chi square < 2 , TLI > 0.95 , CFI > 0.95). All paths are significant at $p < 0.05$. This model shows: 1) Pain disability has direct associations with pain intensity (standardized

coefficient=0.351) , PTSD (standardized coefficient=0.277) and SF-36 PCS (standardized coefficient=-0.51); 2) PTSD has direct associations with pain intensity (standardized coefficient=0.23) and SF-36 MCS (standardized coefficient=-0.301); 3) PTSD also has an indirect association with SF-36 MCS through the mediation of comorbid anxiety and depression (standardized coefficient= -0.571), and an indirect association with pain intensity through the mediation of comorbid anxiety and depression, and catastrophizing (standardized coefficient= -0.371). Like model A, the fitting results of model C supported both hypothesis #4a and #4b. Furthermore, these results highlighted the differential associations of pain intensity and pain disability with PTSD, and with quality of life as assessed by SF-36 PCS.

Figure 4.4: SEM model C related to hypothesis 4. Coefficients reflect standardized path coefficients



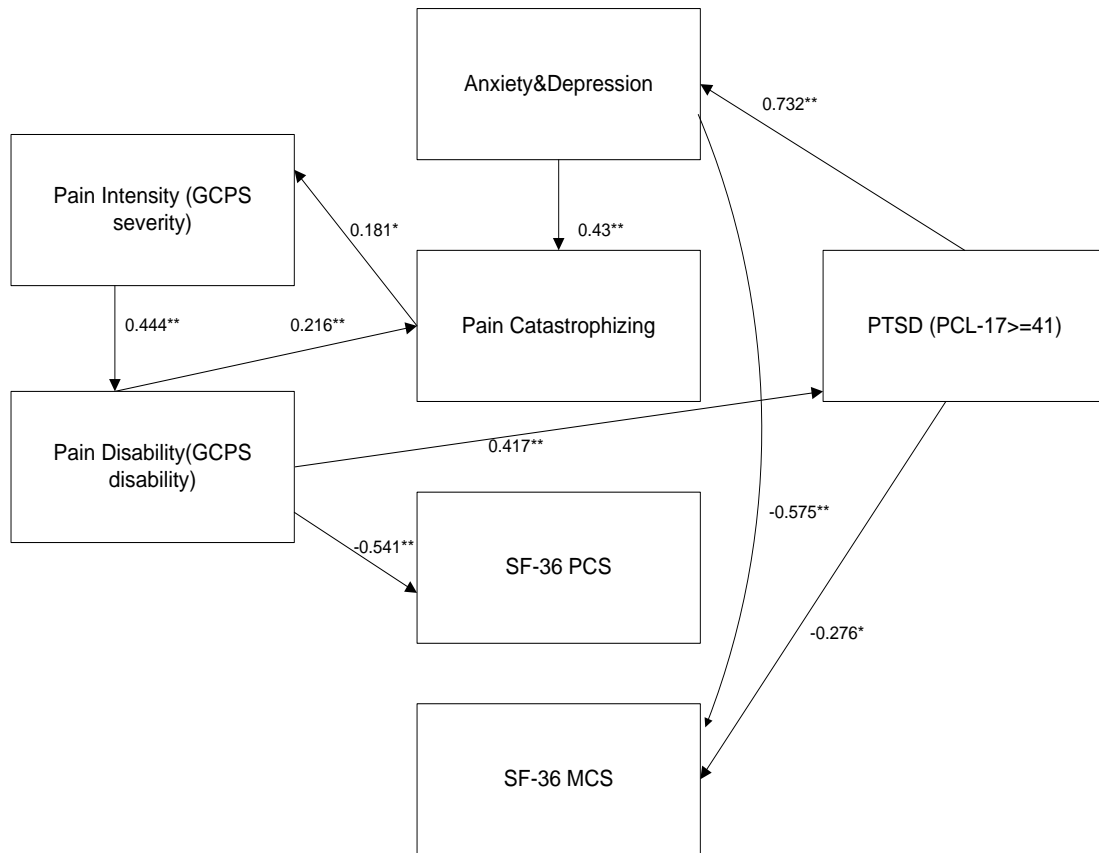
Model fit statistic: Chi-square 12.21, df=9, p<.05; RMSEA 0.038 (p>.05); CFI 0.992; TLI 0.98
 *P-value<0.05; **P-value <0.01

SEM analysis: model D(n=240)

Model D and its fitting results are depicted in figure 4.5 (full sample), and are also included in the table of Appendix I for comparison purpose. This model is very similar to model C except that we hypothesized in model D that 1) pain disability has an indirect association with pain intensity through pain catastrophizing; and 2) pain intensity has a direct association with pain disability.

The fit of model D is good in terms of RMSEA (0.062), and other fit indices are in a good (relative chi square <3, TLI>0.9, CFI>0.95) range. All paths are significant at $p < 0.05$. These test results supported our hypothesis that 1) Pain disability has an indirect association with pain intensity through pain catastrophizing; 2) pain intensity has a direct association with pain disability; 3) pain disability has direct associations with PTSD and SF-36 PCS; 4) PTSD has a direct association (and an indirect association through comorbid anxiety and depression) with the SF-36 MCS, and an indirect association with pain intensity through comorbid anxiety and depression, and pain catastrophizing. Like model C, the fitting results of model D provided additional support for our hypothesis #4a and #4b. Unlike model C, model D demonstrated bidirectional (versus unidirectional in Model C) associations between pain intensity and pain disability through the mediation of pain catastrophizing. In addition, model D showed PTSD has an indirect relationship with pain intensity through comorbid depression and anxiety and pain catastrophizing, while model C demonstrated a direct association of PTSD with pain intensity.

Figure 4.5: SEM model D related to hypothesis 4. Coefficients reflect standardized path coefficients



Model fit statistic: Chi-square 21.118, df=11, p<.05; RMSEA 0.062 (p>.05); CFI 0.973; TLI 0.949
 *P-value < 0.05; **P-value < 0.01

Summary of above four SEM models (model A to D)

To test hypotheses 4a and 4b, four different SEM models (model A to D) were used to examine the possibility of complex bidirectional relationships, and multiple ways of direct and indirect relationships between PTSD, chronic pain and other variables. These relationships cannot be examined with a single SEM model due to sample size limitation of present study. The results of the four SEM

models are instead combined together and summarized below with further detail outlined in Appendix I:

1. PTSD has a direct effect on anxiety (model A).
2. PTSD has an indirect effect on pain severity through depression (model A), or through the combination of depression and anxiety (model B).
3. PTSD has a direct effect on pain intensity (model C), and an indirect effect on pain intensity through comorbid anxiety and depression and pain catastrophizing (model D).
4. PTSD has an indirect effect on pain disability through comorbid anxiety and depression and pain catastrophizing (model C).
5. Pain severity has an indirect effect on PTSD through pain catastrophizing (model A).
6. Pain disability has a direct effect on PTSD (model C and D).
7. The mental health component score is affected by depression (model A) or the combination of depression and anxiety (model B, C, and D), and by PTSD (model C and D).
8. The physical health component score is affected by pain severity (model A and B), or by pain disability (model C and D).

ANCOVA analysis

The patients' quality of life (QOL) was measured by the SF-36 which consists of eight QOL domains that comprise two summary measures – the physical component summary (PCS) and the mental component summary (MCS). At least moderate negative correlations ($r \leq -0.4$) were identified through Pearson correlation analysis between GCPS pain intensity and PCS, GCPS pain disability; between SF-36 PCS and MCS, PCL-17 and SF-36 MCS. The ANCOVA analyses showed that patients with GCPS pain severity grade ≥ 3 and

clinically significant PTSD (PCL-17 ≥ 41) were associated with worse SF-36 PCS (p-value= 0.024) and MCS scores (p-value<0.001) (table 4.7). These results therefore supported our hypothesis #4c that patients with high chronic pain (GCPS severity grade ≥ 3) and PTSD will have worse quality of life than patients with only one or neither of these conditions (i.e., high chronic pain or PTSD).

Table 4.7: ANCOVA analysis to test hypothesis #4c: patients with high chronic pain and PTSD will have worse quality of life than patients with only one or neither of these conditions

SF-PCS			SF-MCS		
Least-Squares Means		p-value	Least-Squares Means		p-value
GCPS pain severity ≥ 3 and PCL-17 total score ≥ 41	GCPS pain severity <3 or PCL-17 total score <41		GCPS pain severity ≥ 3 and PCL-17 total score ≥ 41	GCPS pain severity <3 or PCL-17 total score <41	
34.2	37.2	0.024	38.9	45.2	<0.001

Note: Model adjusted by other factors, including age, gender, marriage, income, employment status, pain catastrophizing, anxiety and depression.

Hypothesis #5: Different PTSD symptom domains will have differential relationships with chronic pain outcomes, either directly, or through mediating factors such as depression or anxiety symptoms

In order to test our hypothesis #5, we conducted a confirmatory factor analysis to find the best factor structures of PTSD, followed by a series of SEM analysis to test two SEM models with latent variables. In these models, individual PTSD symptom domain severity was treated as latent variable measured by

corresponding PCL-17 item scores as determined by the results of confirmatory factor analyses. All models (model E to I) are based on the subsample (N=188) of participants who screened positive for PTSD and had measured PCL17.

Confirmatory factor analysis

Table 4.8 lists the results of confirmatory factor analysis for five factor structure models of PTSD symptoms measured by PCL-17 (model E to I). Among these models, the two models with four factors (Model H and I) have the best fit indices. Both provide good fit for our data as indicated by relevant fit indices (RMSEA <0.08, CFI > 0.9, TFI > 0.9), and Model I fits our data slightly better than Model H. This finding is consistent with that reported in Cyders' study (Cyders, Burris et al. 2010) in patients with PTSD and chronic orofacial pain.

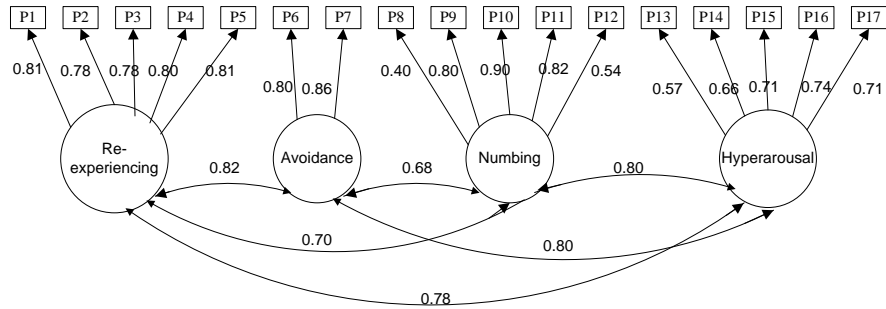
Table 4.8: Confirmatory factor analysis (subsample N=188): summary of factor structures of five models (E-I)

Model	Factors	PCL17	χ^2	DF	RMSEA	CFI	TFI	Adjusted BIC*
E	PTSD	All 17 items	422.41	119	0.116	0.82	0.80	9376.60
F	Re-experience/avoidance	1-7	296.54	118	0.090	0.90	0.88	9252.81
	Numbing/hyperarousal	8-17						
G	Re-experiencing	1-5	299.99	116	0.092	0.89	0.88	9260.40
	Avoidance	6-12						
	Hyperarousal	13-17						
H*	Re-experiencing	1-5	201.55	113	0.065	0.95	0.94	9168.16
	Avoidance	6-7						
	Numbing	8-12						
	Hyperarousal	13-17						
I*	Re-experiencing	1-5	172.43	113	0.053	0.97	0.96	9139.04
	Avoidance	6-7						
	Dysphoria	8-15						
	Hyperarousal	16-17						

Note: * Sample size adjusted Bayesian information criterion (BIC) is a parsimony fit index, with a smaller value representing a better fit (complex model will be penalized).

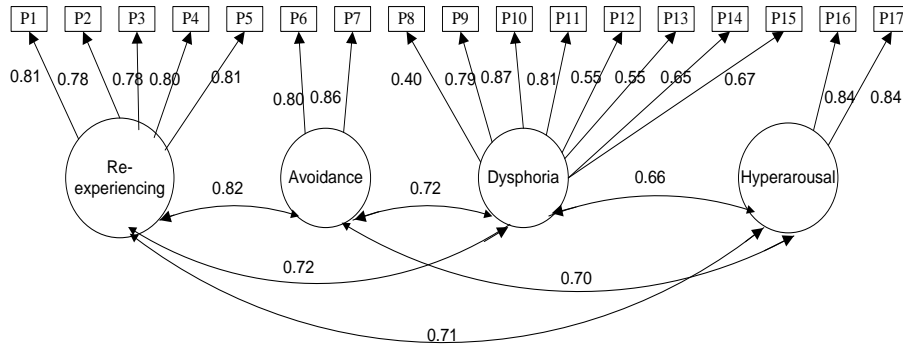
The factor loadings and correlation coefficients of model H and model I were depicted in detail in figure 4.6 and 4.7, respectively.

Figure 4.6: Confirmatory factor analysis for model H



Note: Re-experiencing (PCL-17 items 1–5), Avoidance (PCL-17 items 6–7), Numbing (PCL-17 items 8–12), and Hyperarousal (PCL-17 items 13–17).

Figure 4.7: Confirmatory factor analysis for model I



Note: Re-experiencing (PCL-17 items 1–5), Avoidance (PCL-17 items 6–7), Dysphoria (PCL-17 items 8–15), and Hyperarousal (PCL-17 items 16–17).

SEM analysis based on model H and I

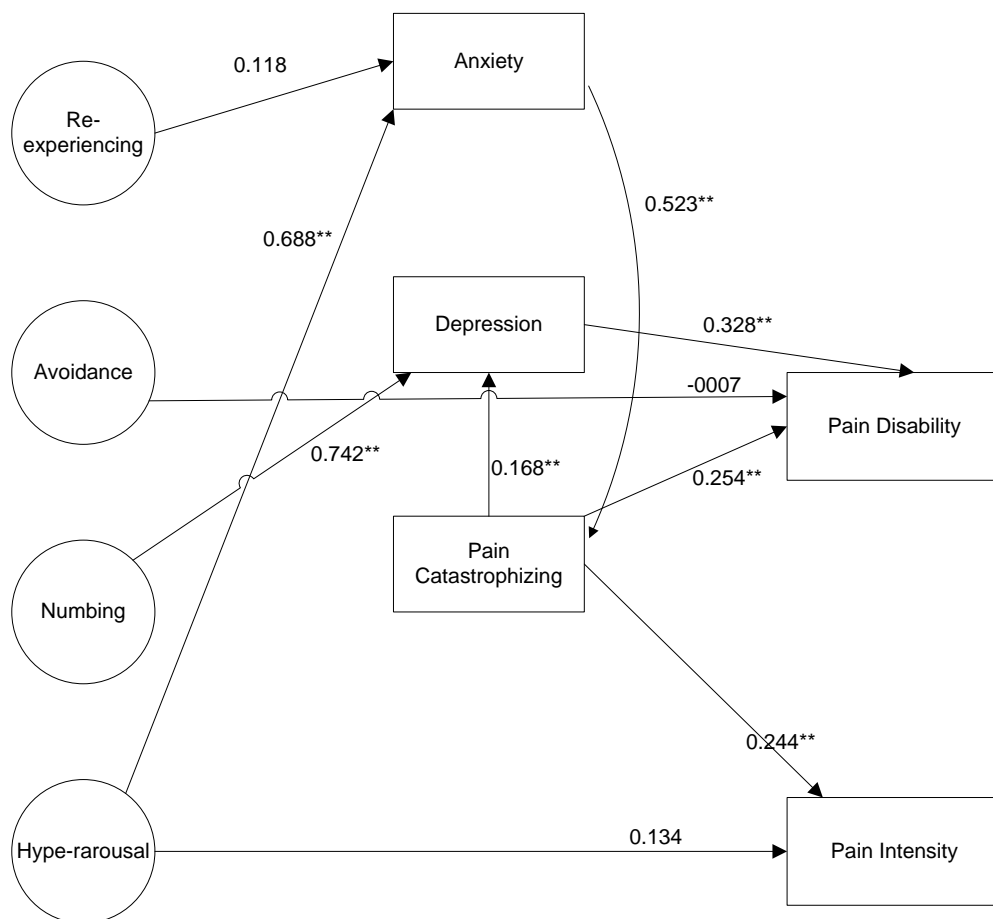
SEM analysis was conducted next to test the hypothesized relationships between the PTSD symptom clusters and pain outcomes (pain intensity and pain

disability), and the mediating roles of depression, anxiety, and pain catastrophizing. Two SEM models (based on factor model H and I, respectively) with latent variables specified were tested.

Figure 4.8 depicts the test results of the SEM model based on factor model H. In this model, we observed the following fit indices: relative chi square <2, CFI=.917, TLI=.903, RMSEA=.072. The hyperarousal symptom cluster was not directly associated with pain intensity, but indirectly related, through anxiety and pain catastrophizing. The numbing symptom cluster was indirectly associated with pain disability through its association with depression. Avoidance was not directly associated with pain-related disability. Re-experiencing was not directly associated with anxiety, while anxiety was indirectly associated with pain intensity through pain catastrophizing. Pain catastrophizing was directly associated with pain intensity, disability and depression.

The results showed that none of the four PTSD symptom clusters has a significant direct relationship with either pain intensity or pain disability. This finding is consistent with the previous analysis based on the SEM model D.

Figure 4.8: SEM path analysis of the relationships among PTSD symptom clusters defined by factor model H



Model fit statistic: Chi-squer 391.298, df=236 (p<0.05); RMSEA 0.072
(p<0.01); CFI 0.917; TLI 0.903

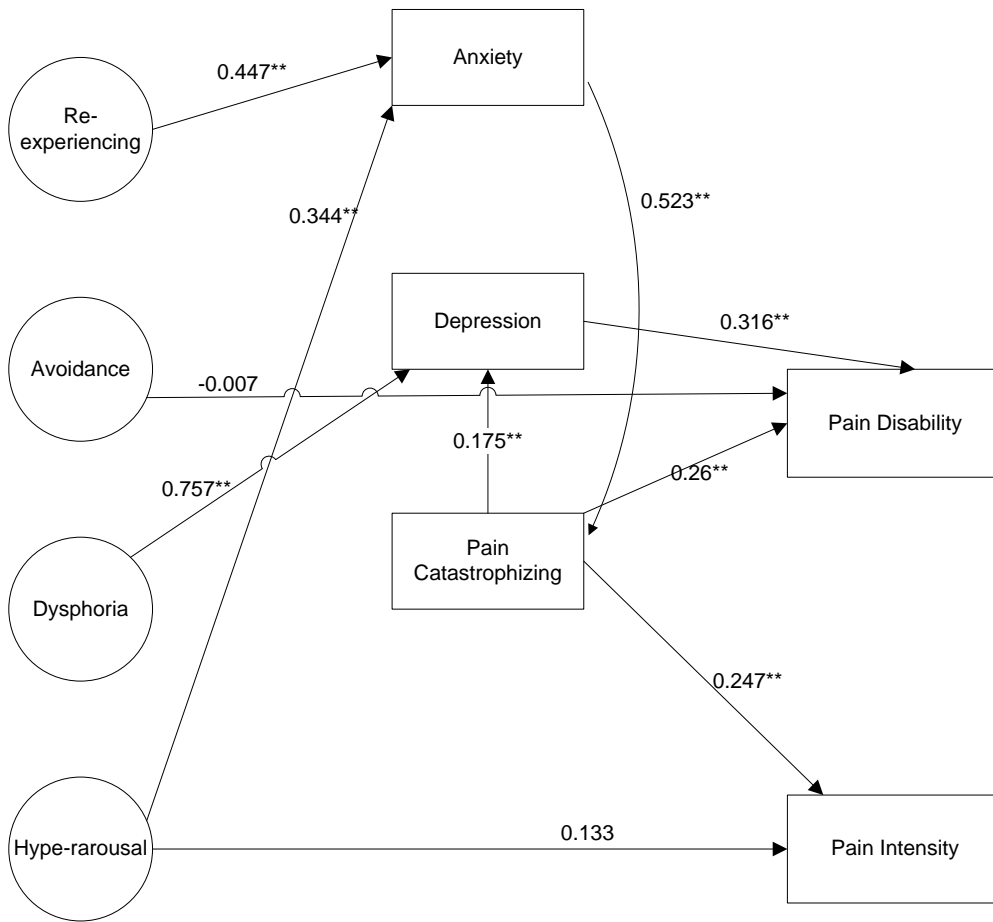
Note: Re-experiencing (PCL-17 items 1–5), Avoidance (PCL-17 items 6–7), Numbing (PCL-17 items 8–12), and Hyperarousal (PCL-17 items 13–17))

SEM analysis: model I

Figure 4.9 depicts the test results of the SEM model based on factor model I. This model's fitting indices were slightly improved (CFI=.925, TLI=.913, RMSEA=0.069) compared to model H. Similar to model H, this model also showed the hyperarousal symptom cluster was indirectly associated with pain intensity and pain disability through anxiety and pain catastrophizing; and avoidance was not directly associated with pain-related disability. Contrary to model H where the relationship between re-experiencing and anxiety is not significant, the model I showed a significant association between re-experience and anxiety. The model I further showed that reexperiencing was indirectly associated with pain outcomes through anxiety's significant association with pain catastrophizing, and catastrophizing's significant association with both pain intensity and pain disability. In addition, dysphoria, like numbing in the previous SEM model, demonstrated an indirect association with pain-related disability through depression.

Thus, compared to model H, model I revealed more statistically significant direct and indirect relationships between PTSD symptom clusters and various pain and psychological outcomes of interest. However, like model H, model I shows none of the four PTSD symptom clusters has a significant direct relationship with either pain intensity or pain disability.

Figure 4.9: SEM path analysis of the relationships among Model I PTSD symptom clusters



Model fit statistic : Chi-square 371.92, df=236(p<0.05); RMSEA 0.069 (p<0.05); CFI 0.925; TLI 0.913

Note: Re-experiencing (PCL-17 items 1–5), Avoidance (PCL-17 items 6–7), Dysphoria (PCL-17 items 8–15), and Hyperarousal (PCL-17 items 16–17))

Hypothesis #6: Baseline PTSD will predict pain severity at 9 months, and baseline pain severity will predict PTSD at 9 months

In the ESCAPE trial, PTSD symptoms were measured at baseline and 9 months. Patients who screened positive for PTSD were evaluated further using the PCL-17 instrument. Patients PTSD were defined as those who were screened positive for PTSD and had a PCL-17 total score ≥ 41 . To test hypothesis #6, logistic regression was conducted first, followed by cross-lagged panel analysis.

Logistic regression analysis

Logistic regression analyses were used to determine whether baseline pain intensity (model 1) or pain disability (model 2), together with baseline PTSD, depression, anxiety symptoms and patients' demographics, predicted PTSD at 9 months. After adjusting for other factors, both baseline pain intensity score (p-value=0.02) and baseline pain disability score (p-value=0.003) were independent predictors of PTSD at 9 months (table 4.9).

Table 4.9: Logistic regression to predict PTSD (PCL-17 total score ≥ 41) at 9 months visit

Effect	Model 1 (pain intensity as predictor)		Model 2 (pain disability as predictor)	
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Baseline PTSD (PCL-17 ≥ 41)	13.9 (5.5, 35.1)	<.0001	14.2 (5.5, 36.6)	<.0001
Baseline GCPS intensity score	1.03 (1.01, 1.06)	0.02	N.A	N.A
Baseline GCPS disability score	N.A	N.A	1.03 (1.01, 1.05)	0.003
Baseline Pain catastrophizing	1 (0.96, 1.04)	0.828	0.996 (0.96, 1.04)	0.826
Baseline PHQ-9 depression ≥ 10	1.9 (0.6, 5.7)	0.261	1.71 (0.55, 5.29)	0.351
Baseline GAD-7 ≥ 10	9.7 (0.995, 93.7)	0.051	7.13 (0.73, 69.6)	0.091
Age	1.03 (0.99, 1.09)	0.133	1.03 (0.98, 1.08)	0.194
Male	1.6 (0.43, 5.9)	0.479	1.7 (0.45, 6.46)	0.434
White	0.6 (0.23, 1.65)	0.342	0.63 (0.23, 1.71)	0.368
Employee	0.7 (0.3, 1.7)	0.437	0.7 (0.28, 1.72)	0.433
Married	1.03 (0.42, 2.5)	0.953	1.12 (0.45, 2.79)	0.809
Income comfortable	1.58 (0.58, 4.25)	0.369	1.36 (0.5, 3.73)	0.548

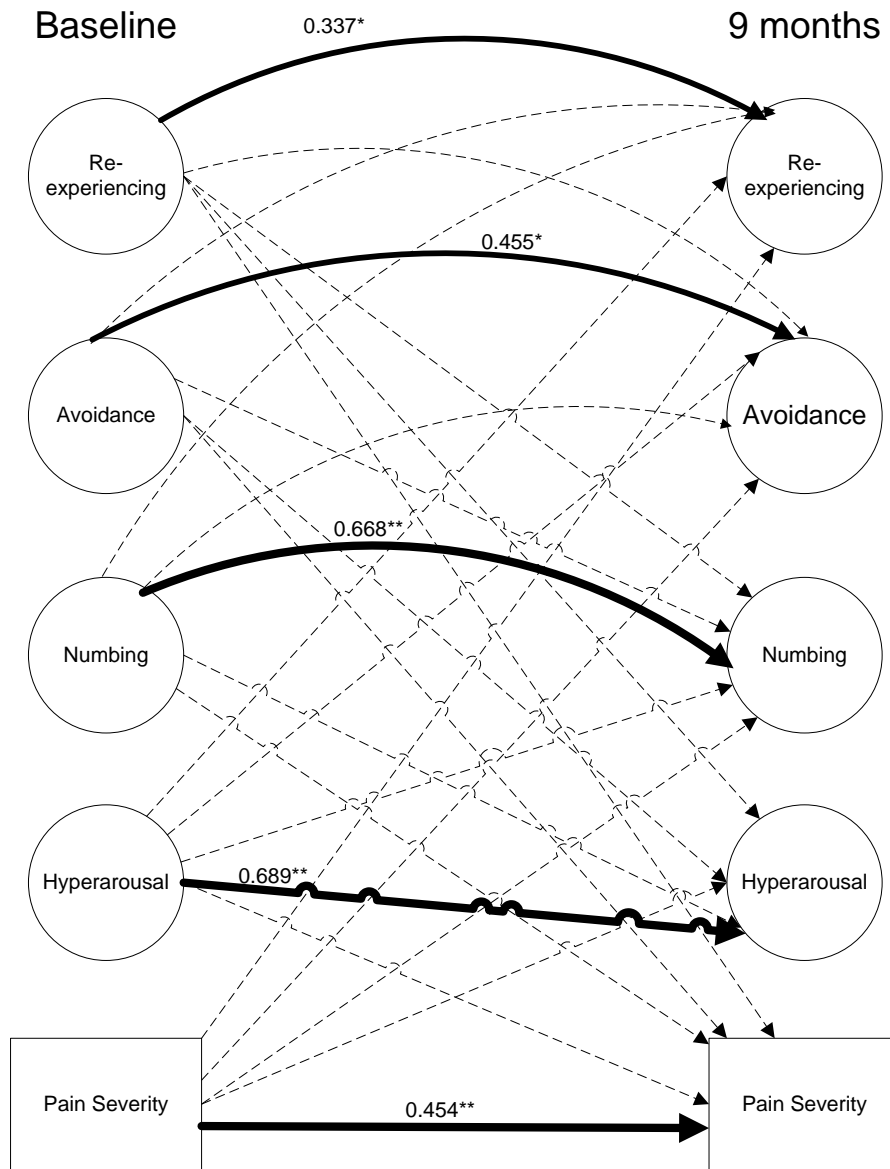
Note: Odds ratio > 1 means the variable is a predictor of PTSD at 9 months visit.

Cross-lagged panel analysis

We examined the cross-lagged relationships between PTSD symptom domains and pain severity grade (ranges 1 to 4), using a sample of 144 persons with PCL-17 scores assessed at baseline and 9 month visit. Structural equation modeling was used to assess the longitudinal relationship between PTSD symptoms and pain severity. Based on the results of previous confirmatory factor

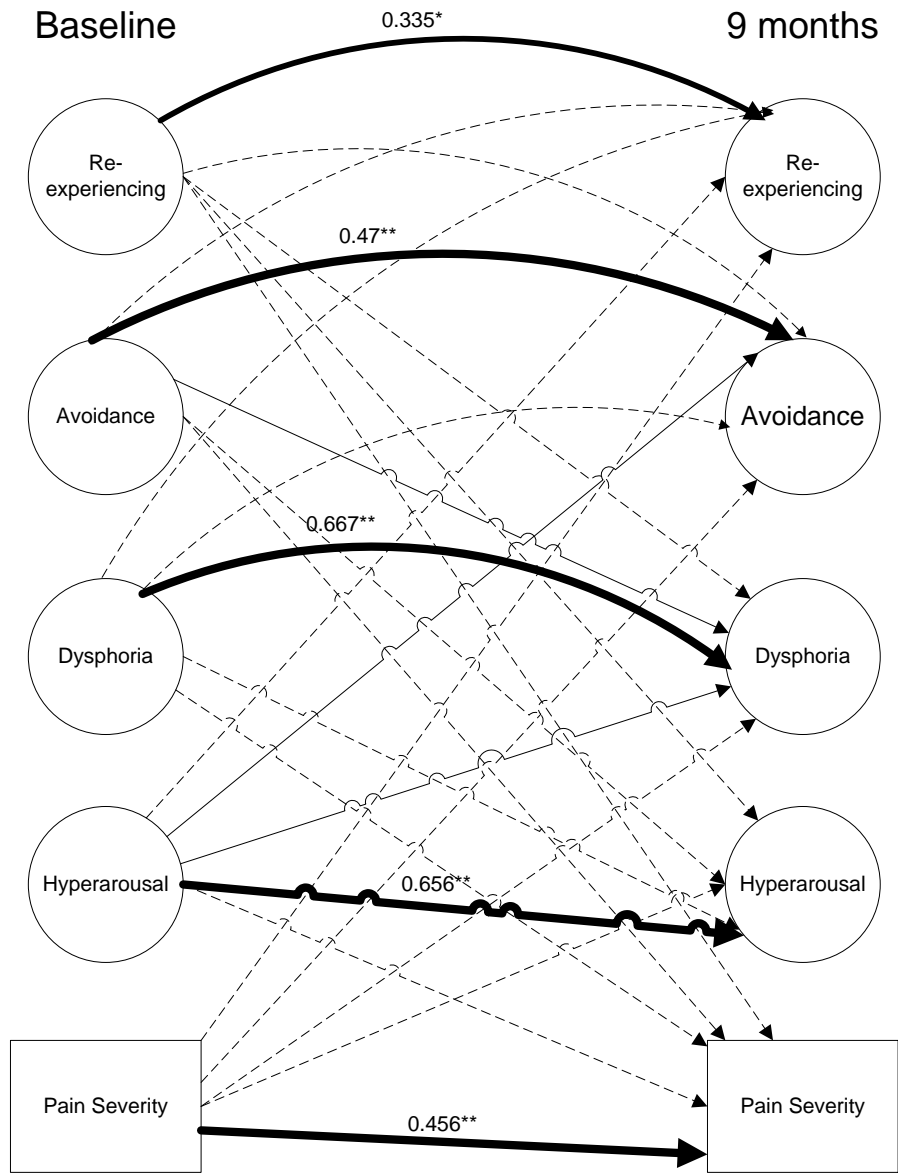
analysis (table 8), we constructed a cross-lagged model using the two four-factor models (model H and I) for PTSD symptoms that provided the best fit of our data. Figure 4.10 depicts the cross-lagged model using PTSD factor model H, including the factors of re-experiencing (PCL-17 items 1–5), avoidance (PCL-17 items 6–7), numbing (PCL-17 items 8–12), and hyperarousal (PCL-17 items 13–17). Figure 4.11 depicts the cross-lagged model using PTSD factor model I, including the factors of re-experiencing (PCL-17 items 1–5), avoidance (PCL-17 items 6–7), dysphoria (PCL-17 items 8–15), and hyperarousal (PCL-17 items 16–17). In figure 4.10 and 4.11, coefficients and arrow thicknesses reflect significance of standardized path coefficients. Dashed arrows represent coefficients that were not significant at $p \geq 0.05$. For the cross-lagged panel analysis based on factor model H, the model fitting is not good, RMSEA=0.087, CFI=0.818 and TLI=0.793. The model fitting is slightly better for the cross-lagged panel analysis based on factor model I, RMSEA=0.074, CFI=0.868 and TLI=0.85. Not surprisingly both models showed the pain severity and PTSD symptom at 9 months are predicted by baseline values of pain and PTSD respectively. None of the PTSD symptom domains were found to be a significant predictor of other PTSD symptom domains or pain severity at 9 months. Baseline pain severity was not a significant predictor of any of the PTSD symptom domains at 9 months either. The results of our cross-lagged panel analysis therefore did not seem to support our hypothesis #6.

Figure 4.10: Cross-lagged panel analysis based on factor model H



Model fit statistic; Chi-square 1160.773, df=555 ($p < 0.05$);
 RMSEA 0.087 ($p < 0.05$); CFI 0.818; TLI 0.793.
 * $P < 0.05$; ** $P < 0.01$

Figure 4.11: Cross-lagged panel analysis based on factor model I



Model fit statistic; Chi-square 993.35, df=555 ($p < 0.05$); RMSEA 0.074 ($p < 0.05$); CFI 0.868; TLI 0.85.
 * $p < 0.05$; ** $P < 0.01$

Hypothesis #7: The longitudinal change in pain severity will be predicted by PTSD at baseline. The PTSD at 9 month will be predicted by pain intensity and disability at baseline

To test hypothesis #7, a repeated measures model analysis was conducted.

Repeated measure model analysis

As shown in table 4.10, two repeated-measures models were conducted to examine if the change from baseline to 9 months in pain intensity and pain disability was predicted by baseline pain, PTSD, comorbid depression, and comorbid anxiety. In model one, the dependent variable is change from baseline of GCPS intensity score at each post-baseline visit and baseline GCPS intensity is included as a covariate. In model 2, the dependent variable is change from baseline of GCPS disability score at each post-baseline visit and baseline GCPS disability is included as a covariate. In both models, the independent variables also include month (visit), baseline GAD flag, baseline depression flag, baseline pain catastrophizing score, and social demographics. After adjustment of patients' demographic effects, the results of the repeated measure model analysis showed patients with severe pain intensity and lower pain catastrophizing score at baseline achieved more improvement in pain severity after 9 months of treatment. Moreover, baseline PTSD symptom severity was found to predict less improvement of pain disability over time, while its impact on the improvement of

pain intensity was not significant. In other words, patients with clinically significant PTSD symptoms did show significantly less improvement on pain disability score (but not pain intensity score) after 9 months.

Table 4.10: MMRM model: baseline demographics and clinical characteristics predict change of pain intensity and disability from baseline by visits

Effect	Change from baseline to 9 months in GCPS intensity			Change from baseline to 9 months in GCPS disability		
	Estimate*	StdErr	p-value	Estimate*	StdErr	p-value
Visits (months)						
3 vs. 9	2.71	1.03	0.009	3.1	1.38	0.026
6 vs. 9	-0.11	0.96	0.907	1.81	1.30	0.166
PTSD (Baseline PCL 17≥41)	2.26	2.11	0.286	6.38	2.94	0.031
Baseline GCPS intensity	-0.28	0.06	<.0001	N.A	N. A	N.A
Baseline GCPS disability	N.A	N. A	N.A	-0.44	0.05	<.0001
Baseline GAD-7≥10	0.78	2.42	0.745	0.07	3.33	0.983
Baseline Pain catastrophizing	0.19	0.08	0.017	0.38	0.11	0.0008
Baseline PHQ-9 depression≥10	-0.32	2.13	0.88	1.21	3	0.69
Age	0.1	0.08	0.252	0.26	0.12	0.031
Male	0.37	2.52	0.02	-2.56	3.54	0.471
White	-2.52	2.02	0.212	-4.07	2.81	0.149
Employee	1.34	1.93	0.488	1.9	2.7	0.482
Married	-0.08	1.7	0.945	-0.85	2.38	0.722
Income comfortable	1	1.78	0.575	2.02	2.49	0.42

Note: *Negative value means positive effect for pain improvement.

Chapter V: Discussion and Conclusion

Overview of significant findings

We conducted a series of statistical analyses based on ESCAPE trial data to test our hypotheses to the following three research questions:

- 1) How strong is the relationship between PTSD and chronic musculoskeletal pain?
- 2) Which factors affect the relationship between PTSD and chronic musculoskeletal pain?
- 3) Do specific PTSD symptom domains affect chronic musculoskeletal pain outcomes differently?

In our analyses and conclusions, PTSD is defined as a positive PTSD screen and a PCL-17 score ≥ 41 . Pain intensity and pain-related disability are measured by the GCPS. Pain severity is defined by 5 grades (ranges 0 to 4) based on the combination of pain intensity and pain-related disability measured by GCPS (see chapter 3).

Table 5.1 (Appendix J) lists the results of our analyses and the corresponding hypotheses and research questions. In summary, we found the following significant findings:

1. PTSD was associated with greater pain severity, more psychological comorbidity (depression and anxiety), worse pain cognitions (e.g. pain catastrophizing), and poorer quality of life.
2. Greater pain severity was associated with a greater likelihood of PTSD, and more depression, anxiety, and pain catastrophizing.

3. The coexistence of PTSD and more severe pain severity grade was associated with worse SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores. In particular, pain disability was directly related to SF-36 PCS scores and PTSD was directly and indirectly related to SF-36 MCS scores.
4. Patients with greater pain severity grade or comorbid depression and anxiety were more likely to have PTSD.
5. Regarding the impact of PTSD on pain, PTSD was related to pain intensity directly and indirectly, to pain disability indirectly, and to pain severity grade (ranges 1 to 4 based on the combination of pain intensity and pain disability) indirectly. The indirect relationships were through the association of PTSD with anxiety, depression or pain catastrophizing.
6. Regarding the impact of pain on PTSD, pain severity grade was related to PTSD indirectly through pain catastrophizing. Pain disability was related to PTSD directly. Pain intensity was related to PTSD indirectly through pain disability. There is a bidirectional relationship between pain intensity and pain disability.
7. In confirmatory factor analyses to examine PTSD symptom domains, the two four-factor models of PTSD provided the best fit of our data. The first model contained reexperiencing, avoidance, numbing and hyperarousal factors. The second model contained reexperiencing, avoidance, dysphoria and hyperarousal factors. While none of the four PTSD symptom domains were directly related to either pain intensity or pain

disability, our analyses showed numbing and dysphoria were indirectly related to pain disability through the influence of depression.

Hyperarousal and reexperiencing were indirectly related to pain disability and pain intensity through anxiety and pain catastrophizing.

8. Patients with PTSD demonstrated less improvement in pain disability over 9 months. No evidence was found to support the hypothesis that any of the four PTSD factors (reexperiencing, avoidance, numbing/dysphoria and hyperarousal) were significant predictors of any other PTSD factor or pain severity over 9 months. However, baseline pain intensity and baseline pain disability were significant predictors of PTSD at 9 months.

Comparisons with findings from other studies

Our first finding (i.e., PTSD was associated with greater pain severity and pain catastrophizing, more depression and anxiety, and poorer quality of life) is consistent with several other published studies. These studies vary in study designs, outcomes, care settings, and sample populations. For example, PTSD was found to be significantly associated with higher rates of psychiatric comorbidity (including depression and anxiety) in a recent cross-sectional study among civilian primary care patients (Lowe, Kroenke et al. 2011). In a prospective study of U.S. veterans with rheumatoid arthritis (RA), patients with PTSD had worse pain than patients with no psychiatric diagnosis (Mikuls, Padala et al. 2012). PTSD was also found to be associated with poor quality of life in a large community sample of patients, after adjusting for sociodemographic

factors, mental disorders, and severity of physical disorders (Sareen, Cox et al. 2007), as well as greater catastrophizing in a study of 194 veterans with chronic pain (Alschuler and Otis 2011).

Our second finding (The cohort of veterans with higher pain severity reported significantly higher pain catastrophizing scores, and significantly higher frequencies and odds of clinically significant PTSD, anxiety and depression) is also consistent with other published studies. For example, the National Comorbidity Survey, in a representative sample of the general US civilian population, found significant positive associations between chronic pain and mood and anxiety disorders including depression, generalized anxiety disorder, and PTSD (McWilliams, Cox et al. 2003). In a sample of VA primary care patients with moderate to severe pain, a sample similar to our ESCAPE study, a high risk for psychological distress (including PTSD and depression) was found (Sherbourne, Asch et al. 2009). The association between pain severity and pain catastrophizing has also been reported in a recent systematic review. In this review, high catastrophizing levels were found to be associated with increased pain severity, an increased incidence of development of chronic pain, and poorer quality of life after surgery (Khan, Ahmed et al. 2011). Another study found both patients and their spouses' catastrophizing was related to pain severity (Cano, Leonard et al. 2005). These findings coupled with finding from our study may imply that catastrophizing is a common moderator or mediator of both PTSD and chronic musculoskeletal pain severity.

Our third finding (*The coexistence of more severe pain and clinically significant PTSD was associated with worse SF-36 PCS and MCS scores. In particular, pain disability was directly related to SF-36 PCS scores and PTSD was directly and indirectly related with SF-36 MCS scores. In addition, the coexistence of PTSD and chronic pain is associated with poorer SF-36 PCS and MCS scores*) is consistent in part with a published study, which found patients with fibromyalgia syndrome and PTSD reported greater pain, lower quality of life, higher functional impairment and suffered more psychological distress than patients with PTSD without fibromyalgia syndrome (Amir, Kaplan et al. 1997). Although our study bears similarity with other studies regarding the general relationship between PTSD, chronic pain, disability and quality of life, our study examined these relationships in the latest cohort of veterans and in the context of clinical trial. Our study also emphasized the relationship of pain disability (rather than pain intensity) with the physical component of quality of life, and the relationship of PTSD with the mental component of quality of life. The differential relationship of PTSD and pain with the mental and physical domains of quality of life seems to complement the finding reported by another study. Palyo and Beck (Palyo and Beck 2005) examined the differential association of co-occurring pain complaints and PTSD symptoms with disability in the domains of psychosocial and physical functioning in participants with motor vehicle accident. Using Structural Equation Modeling, they found more severe PTSD symptoms and greater pain complaints were related to psychosocial impairment. However, only

pain, but not PTSD was significantly related to impairment in physical functioning (Palyo and Beck 2005).

Our fourth finding (*Patients with higher musculoskeletal pain severity grade or comorbid depression and anxiety were more likely to have PTSD*) is consistent with several other studies that reported increased prevalence of PTSD among patients with chronic pain (Bryant 1999; Raphael 2004), or with preexisting anxiety or depression (Breslau, Davis et al. 1991; Breslau, Peterson et al. 2008). Our study is, however, the first one to use CART analysis to identify the most important covariates associated with PTSD among patients with chronic musculoskeletal pain. Our CART analysis showed that patients with GCPS pain severity grades 3 or 4, and comorbid depression and anxiety had the highest proportion (54%) of clinically significant PTSD symptoms.

Our fifth finding (*Regarding the impact of PTSD on pain, PTSD was related to pain intensity directly and indirectly, to pain disability indirectly, and to pain severity grade indirectly. The indirect relationships were through the association of PTSD with anxiety, depression or pain catastrophizing*) is consistent with several other studies. For example, Lowe et al found that adjusting for depression substantially attenuated the association of PTSD and trauma with somatic symptoms including chronic pain (Lowe, Kroenke et al. 2011). In a sample of 130 male veterans seeking assessment or treatment for deployment-related PTSD, PTSD and pain were moderately related ($r = .29$), and this relationship was mediated by depression (Poundja, Fikretoglu et al. 2006). In another cross-sectional, retrospective study of 411 female patients with

orofacial pain, SEM analyses indicated PTSD symptoms likely exert their influence on pain severity through depression and sleep quality (Burris, Cyders et al. 2009). Relative to the large number of studies reporting depression as a mediator of the PTSD-chronic pain relationship, there are much fewer studies reporting pain catastrophizing as a mediator of this relationship. Interestingly, one study among women undergoing a hysterectomy found pain catastrophizing was a full mediator between pre-surgical anxiety (as compared to PTSD) and post-surgical pain intensity (Pinto, McIntyre et al. 2012). The direct association between PTSD and pain catastrophizing seen in our study provides additional support for a possible mutual maintaining relationship between PTSD and chronic pain through catastrophizing.

The first part of our sixth finding (*Pain severity grade was related to PTSD indirectly through pain catastrophizing.*) is consistent with another study, which found pain catastrophizing, rather than pain severity, was a significant determinant of the persistence of post-traumatic stress symptoms (Sullivan, Thibault et al. 2009). The second part of our fifth finding (*Pain disability was directly related to PTSD. Pain intensity was related to PTSD indirectly through pain disability.*) is partially in line with another published study, which found that PTSD symptoms are indirectly influenced by pain intensity through depression severity (Roth, Geisser et al. 2008). Both studies used SEM to assess the relationship between PTSD and pain intensity. However, unlike our present study, which used the Graded Chronic Pain Scale (GCPS) to measure both pain intensity and pain disability, the Patient Health Questionnaire (PHQ-9) to

measure depression severity, and PCL-17 to measure PTSD symptoms, Roth et al. study used the McGill Pain Questionnaire (MPQ) to measure self-reported pain intensity, the Pain Disability Index (PDI) to measure pain disability, the Center for Epidemiological Studies – Depression Scale (CES-D) to measure depression, and the Post-traumatic Chronic Pain Test (PCPT) to measure symptoms of PTSD related to pain. The discrepancy between the findings of these two studies may result from the different choices of measurement for PTSD and pain, which may differ (e.g. PCPT and PCL-17) psychometrically or conceptually. The discrepancy may also be due to the fact that different hypothesized SEM models were tested, both of which fit sample data well. The last part of our sixth finding (*There is a bidirectional relationship between pain disability and pain intensity.*) complements another prospective longitudinal study (Katz, Asmundson et al. 2009), of patients who underwent postero-lateral thoracotomy for intrathoracic malignancies. This study found concurrent pain intensity and emotional numbing, but not avoidance symptoms, made unique, significant contributions at each follow-up to pain disability. Together these findings (i.e. *Pain disability was directly related to PTSD, There is a bidirectional relationship between pain disability and pain intensity. And pain intensity influences subsequent pain disability*) suggest disability may be another mechanism to explain a mutual maintaining relationship between PTSD and chronic pain.

The first part of our seventh finding (*In confirmatory factor analyses to examine PTSD symptom domains, the two four-factor models provided the best*

fit for our data. The first model contained reexperiencing, avoidance, numbing and hyperarousal factors. The second model contained reexperiencing, avoidance, dysphoria and hyperarousal factors.) replicated the results of a cross-sectional SEM study conducted by Cyders et al (Cyders, Burris et al. 2010), who also found the two four-factor models provided the best fit for their data. The second part of our finding (*None of the four PTSD symptom domains were directly related to pain intensity or pain disability*) however differs from Cyders et al who found that avoidance was directly associated with pain disability, and hyperarousal was directly associated with pain severity (intensity). Both Cyders' study and our study found numbing and dysphoria were indirectly related to pain disability through the influence of depression. Cyders et al. found sleep quality mediates the relationships between reexperiencing and hyperarousal, and pain severity. We found anxiety and pain catastrophizing mediates the relationships between reexperiencing and hyperarousal, and pain severity and pain disability. The effects of the four symptom clusters of PTSD on pain intensity and pain disability are further listed in table 5.2 (Appendix K) for Cyders et al study and our present study, for comparison purpose. The differences are primarily due to the inclusion of different mediating variables in the SEM models. In Cyders et al models, sleep quality and general activity level are included, as compared to pain catastrophizing, which is included in our present model. The different choices of pain outcomes measurement (i.e. MPI vs GCPS) may also lead to a slightly different interpretation of pain intensity and pain-related disability, resulting in additional differences of complex relationships.

The first part of our eighth finding (*Patients with PTSD demonstrated less improvement in pain disability over 9 months*) complements the finding from a published cross-sectional study. Dunn et al. reported patients with PTSD (n = 21) experienced significantly less improvement than those without PTSD (n = 119) on self-reported outcome measures of neck and low back disability (Dunn, Passmore et al. 2009). The second part of our finding (*No evidence was found to support the hypothesis that any of the four PTSD factors were significant predictors of any other PTSD factor or pain severity over 9-months. However baseline pain intensity and baseline pain disability were significant predictors of PTSD at 9 months.*) differed from a longitudinal study which found through SEM analyses that the baseline and 12-month pain relationship was mediated by 3-month arousal; baseline and 12-month arousal and re-experiencing relationships were mediated by 3-month pain severity (Liedl, O'Donnell et al. 2010). However, our findings are consistent with a 1-year prospective study of 336 socioeconomically disadvantaged adults treated for orofacial injury. Glynn et al. found pain severity predicted PTSD symptoms at 12 months (Glynn, Shetty et al. 2007). Our study further demonstrated that pain intensity and pain disability are independent predictors of PTSD at 9 months.

Strengths and Limitations

Our findings are supported by several strengths in the original design of ESCAPE trial, including (1) a high interest study population (i.e. OIF/OEF veterans); (2) an explicit decision to include a broad, rather than narrow spectrum

of veterans with musculoskeletal pain, such that the study findings will be maximally generalizable and pragmatic; (3) a comprehensive set of variables collected over time allowing for the evaluation of various theories to explain the PTSD-chronic pain relationship. In addition, our hypotheses were based on a comprehensive review of published studies and conceptual models, making it possible to cross-validate our results against previously published evidence and theories. Finally, our study examined and tested a comprehensive set of hypotheses using various statistical methods. The combination of various findings and use of various statistical methods may give us a more accurate and more comprehensive picture of the PTSD-chronic pain relationship. For example, the use of CART analysis helped to identify the strongest risk factors of clinically significant PTSD symptoms among patients with chronic pain. The use of SEM analyses with latent variables helped to assess the simultaneous relationships between various PTSD symptom domains and other variables of interest and to minimize measurement error in our analyses. In addition, the use of traditional logistic regression and repeated measure model analyses helped to identify the longitudinal relationship between baseline PTSD/Pain severity and PTSD/Pain severity at 9 months.

It is worth noting that we used the full ESCAPE sample (N=240) for CART analysis and most of our structural equation modeling analyses, to ensure sufficient statistical power. While minimum sample size needed is affected by data normality and the desired level of statistical power, the rule of thumb value is 10 participants for every free parameter estimated (Schreiber 2006). Although

there is little consensus on the recommended sample size for SEM, several researchers have (Sivo 2006), (Garver 1999) (Hoelter 1983) proposed a 'critical sample size' of 200 to provide sufficient statistical power for data analysis.

The present study also has its limitations including: 1) a study sample predominantly of white men which may not represent the general population with PTSD or chronic pain; 2) the subsample (N=188) may not be sufficient to support the analysis of some of our SEM models; 3) PTSD was measured at baseline and 9-months rather than every three month, which would have been more informative to assess causal relationships; 4) Not all variables of interest were measured in the ESCAPE study (e.g. anxiety sensitivity, substance abuse), making it impossible to test some relevant theories (e.g. anxiety sensitivity measure to test the Shared Vulnerability model); 5) Only patients with moderate to severe pain were included in the ESCAPE study, which is adequate for measuring the treatment effect, but provide an inadequate range of pain levels for the evaluation of PTSD-pain severity relationship; 6) The cross-sectional nature of baseline data analyses prohibit causal inferences regarding to the relationship between PTSD, pain and other psychological comorbidities; 7) Lack of PCL-17 measurements for all patients (impact of missing data) required additional assumptions in the analysis; 8) No control for multiplicity; 9) Lack of Replication (not big enough N to have a split sample or replication study).

Contributions

Our findings contribute significantly to what is currently understood about the relationship between PTSD and chronic musculoskeletal pain. Although the frequent coexistence of PTSD and chronic musculoskeletal pain, and the positive correlation between PTSD and chronic musculoskeletal pain severity, have been widely reported and examined by various studies, there has been little consensus on the exact causes or influential factors of this relationship. As a result, various conceptual models have been proposed to explain the PTSD-pain relationship. In summary, our findings suggest there is most likely an indirect association between PTSD and chronic musculoskeletal pain severity, which may be explained by their shared, direct relationships with anxiety, depression, pain catastrophizing, and pain disability. Our findings also suggest a stronger relationship between PTSD and each component of chronic musculoskeletal pain (i.e. pain intensity and pain disability) than the composite pain severity variable which combined intensity and disability into 4 grades of chronic pain. While PTSD and the composite pain severity are indirectly related through anxiety, depression and pain catastrophizing (fifth and sixth findings), PTSD is found to be related to pain intensity directly (fifth finding), and pain disability is found to be related to PTSD directly (sixth finding).

In addition, our findings provided additional empiric support for several theoretical models (see the next section: *Theoretical and clinical implication*), especially the Mutual Maintenance model, with data collected from Iraq/Afghanistan war veterans in primary care setting.

Importantly, our study contributes to the medical literature by using various methodologies to examine the relationship between PTSD and chronic musculoskeletal pain. We are not aware of other studies that: 1) combine pain intensity and pain disability (classified into five pain grades) for model construction; 2) use decision tree techniques to identify risk factors for PTSD in patients with chronic pain; or 3) examine mediators or moderators of quality of life by various psychological factors in the complex, simultaneous model of PTSD and chronic pain. Furthermore, our study applied various statistical methods to test a comprehensive set of hypotheses informed by existing conceptual models and theories. A combination of all these tests gave us a more comprehensive picture of the direction and strength of the relationship between PTSD, chronic musculoskeletal pain and other variables. Finally, our study not only examined the relationship between the combined PTSD severity measure and chronic musculoskeletal pain, but also the relationship between individual PTSD symptom clusters and each chronic musculoskeletal pain dimension (pain intensity and pain disability).

Theoretical and Clinical Implications of Findings

Implications and application to mutual maintenance model

Our fifth and sixth findings from cross-sectional analyses are consistent with the mutual maintenance model. According to the mutual maintenance model, PTSD and chronic musculoskeletal pain have a mutual maintaining relationship through the mediation of seven identifiable mechanisms including

attentional and reasoning bias, anxiety sensitivity, reminders of the trauma, avoidance, depression and reduced activity levels, anxiety and pain perception, and cognitive demand from symptoms limiting use of adaptive strategies. In addition to their direct relationship with PTSD and chronic musculoskeletal pain, these seven mechanisms also influence PTSD and chronic musculoskeletal pain indirectly through patient distress and disability according to the mutual maintenance model. Our fifth finding supported the roles of depression and catastrophizing in mediating the relationships between PTSD and chronic musculoskeletal pain. Our fifth finding also revealed a direct association between pain disability and PTSD. Although our seventh finding from the longitudinal, cross-lagged panel analyses found no significant, direct relationship between avoidance or re-experiencing and pain severity over a 9-months period or vice versa. Our findings from both logistic regression and mixed model repeated measure analyses showed that baseline PTSD has a direct effect on pain disability at 9 months, and that both baseline pain intensity and pain disability predict PTSD at 9 months. These latter findings provided further support for the reciprocal and causal relationships posited by the mutual maintenance model. It is worth noting that our cross-lagged panel analysis has inherent limitations due to the lack of PTSD measurement in the ESCAPE trial at intermediate time points such as 3 and 6 months after the baseline visit, making it possible to only conduct a two-wave analysis. However, cross-lagged panel analysis has proved to be more powerful if more than two waves (panels) of data points are available (Finkel and NetLibrary Inc. 1995).

Implications and application to perpetual avoidance model

Our seventh finding (*Hyperarousal and reexperiencing were indirectly related to pain disability and pain intensity through anxiety and pain catastrophizing*) is consistent with part of the perpetual avoidance model. In the perpetual avoidance model, PTSD interacts with pain through hyperarousal to pain sensation and catastrophizing/fear-avoidance beliefs. Our sixth finding suggests that hyperarousal and reexperiencing symptoms of PTSD may be the most important components because of their direct relationship with pain catastrophizing and their indirect relationship to pain intensity and disability.

Implications and application to diathesis-stress model

Our seventh finding (*Hyperarousal and reexperiencing were indirectly related to pain disability and pain intensity through anxiety and pain catastrophizing*) is also consistent with part of the diathesis-stress model. In the diathesis-stress model, anxiety sensitivity results in catastrophizing and fear of pain/injury beliefs, which then leads to disability through avoidance behaviors. Our seventh finding suggests a direct effect of generalized anxiety symptom severity (as compared to anxiety sensitivity) on catastrophizing beliefs, and a direct effect of catastrophizing on the level of disability.

Implications for clinical treatment

Because psychological factors often go unrecognized (Sherbourne, Asch et al. 2009), our first finding highlights the need for providers to be more vigilant

in their assessment of PTSD and other mental health problems in patients experiencing high pain levels (Sherbourne, Asch et al. 2009), especially for veterans seeking primary care treatment. Together, our second and fourth findings imply that effective treatment of traumatic pain to maximize pain relief may reduce the likelihood of PTSD as higher pain severity is associated with clinically significant PTSD symptoms. Treatment of PTSD with cognitive-behavior therapy alone proved to be insufficient in patients with severe pain (Taylor, Fedoroff et al. 2001). Although Tatrow et al. found pain reduction was weakly associated with PTSD symptoms improvement (Tatrow, Blanchard et al. 2003), treatment of acute burn pain with morphine may secondarily prevent PTSD (Saxe, Stoddard et al. 2001).

Our eighth finding indicates that patients with clinically significant PTSD symptoms may show less improvement in pain disability from standard pain treatment; implying the need for assessment and possibly more aggressive treatment for chronic musculoskeletal pain patients with comorbid PTSD. In general, assessment should not only examine the presence and causes of musculoskeletal pain, but also the presence and causes of affective distress. And treatment should focus on both physical and emotional dysfunction (Thieme, Turk et al. 2004). As a result, multidisciplinary collaborative care models of treatment may be necessary to collectively address the full spectrum of postwar physical and neurocognitive health concerns (Wilk, Herrell et al. 2012).

Our fifth finding (*PTSD was indirectly related to pain severity through depression or pain catastrophizing*), sixth finding (*Pain severity grade was related*

to PTSD indirectly through pain catastrophizing), and seventh finding (Numbing and dysphoria were indirectly related to pain disability mediated by depression, and hyperarousal and reexperiencing PTSD symptom domains were indirectly related to pain disability and pain intensity mediated by anxiety and pain catastrophizing) further imply that a comprehensive treatment approach of PTSD and pain in veteran populations should also include careful assessment and regular monitoring of depression (Poundja, Fikretoglu et al. 2006) as well as pain catastrophizing. These findings also point to the importance of unresolved PTSD symptoms in contributing to the level of depression, anxiety, pain, and disability seen in chronic musculoskeletal pain patients and highlights the need to consider directed and primary treatment of PTSD in pain rehabilitation programs (Roth, Geisser et al. 2008).

In summary, the frequent co-occurrence of PTSD and chronic musculoskeletal pain and their mutual influence on each other through various mechanisms as shown in our study provided further support for the Mutual Maintenance model. Our study findings also suggest an integrated treatment approach targeting both physical symptoms including pain and psychological disorders including PTSD simultaneously might be more effective than traditional approach that targets either PTSD or chronic musculoskeletal pain separately, especially for patients with poor outcomes from traditional treatment. Similarly, any clinical trial targeting an intervention for chronic musculoskeletal pain also needs to consider PTSD and other psychological disorders, and vice versa.

Conclusions and Future Directions

Given our findings corresponding to each of our three research questions, we conclude that

- 1) While our cross-lagged panel analyses did not show a mutual maintaining relationship between chronic musculoskeletal pain severity and any of the four PTSD symptom domains over 9 months, our logistic regression analysis and mixed model repeated measure analysis did show that baseline pain intensity and pain disability predicted PTSD at 9 months. Furthermore, the reciprocal relationship was seen; baseline PTSD predicted improvement of pain disability at 9 months. Moreover, our SEM path analyses also demonstrated direct relationships between certain components of chronic musculoskeletal pain and PTSD, and indirect relationships mediated by depression and pain catastrophizing. Together these findings support a mutual maintaining relationship between chronic musculoskeletal pain and PTSD, as proposed by the mutual maintenance model. A longitudinal study which measures PTSD, chronic pain and other variables of interest at more than two points of time will be helpful in increasing our confidence in evaluating the mutual maintenance theory.
- 2) Although our data identified depression, generalized anxiety, and catastrophizing as mediating factors between PTSD and chronic pain, they are by no means the only factors believed to be important. Due to constraints of the ESCAPE trial, other potentially important factors thought to mediate or moderate the relationship between PTSD and chronic pain were not included in our analyses. To increase our understanding of the complex relationship between

PTSD and chronic pain, future research needs to increase the number of variables measured that are hypothesized to influence this relationship.

3) Our SEM path analyses with cross-sectional data revealed differential associations between different PTSD symptom domains and different pain outcomes (pain intensity and pain disability); some mediated by pain catastrophizing, depression, or generalized anxiety. These associations suggest treatment approaches may need to target individual symptom domains to be effective in treating patients with chronic musculoskeletal pain and PTSD. For example, relaxation techniques can be used to treat hyperarousal and pain intensity, while biofeedback and physical activation may be used to treat pain catastrophizing, avoidance and pain disability.

Recognizing the role of depression and pain catastrophizing in mediating the relationship between PTSD and chronic musculoskeletal pain is important in optimizing care for both PTSD and chronic musculoskeletal pain. The high frequency of co-occurring PTSD and chronic musculoskeletal pain and the various mechanisms (including cognitive, affective, behavioral, biological and social factors) through which these two conditions relate to and interact with each other present significant challenges to clinicians in a variety of clinical settings, especially in primary care setting where PTSD and other psychological disorders are often unrecognized. Improving awareness and understanding of these two conditions and their intersection may help clinicians find better treatment approaches for patients seeking treatment for either PTSD or chronic musculoskeletal pain alone. A thorough biopsychosocial history and assessment

for other medical and psychiatric illnesses including PTSD has been recommended to improve pain management (Gibson 2012). Effective management of pain often includes an integrated and multidisciplinary approach involving a team of clinicians with varying expertise and clinical focus to address the physical, social, psychological, and spiritual components of pain in an individualized treatment plan that is specifically tailored to the patient and type of pain condition (Gibson 2012; Smeeding, Bradshaw et al. 2010). More research is needed to identify the most effective way of treating patients with chronic pain, PTSD and other psychological disorders, and to improve existing clinical practice guidelines (VA/DOD 2010) .

Appendices

Appendix A

DSM-IV Criteria for Posttraumatic Stress Disorder

A. The person has been exposed to a traumatic event in which both of the following have been present:

(1) the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others (2) the person's response involved intense fear, helplessness, or horror. Note: In children, this may be expressed instead by disorganized or agitated behavior.

B. The traumatic event is persistently **reexperienced** in one (or more) of the following ways:

(1) recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions. Note: In young children, repetitive play may occur in which themes or aspects of the trauma are expressed.

(2) recurrent distressing dreams of the event. Note: In children, there may be frightening dreams without recognizable content.

(3) acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur upon awakening or when intoxicated). Note: In young children, trauma-specific reenactment may occur.

(4) intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.

(5) physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.

C. Persistent **avoidance** of stimuli associated with the trauma and **numbing** of general responsiveness (not present before the trauma), as indicated by three (or more) of the following:

(1) efforts to avoid thoughts, feelings, or conversations associated with the trauma

(2) efforts to avoid activities, places, or people that arouse recollections of the trauma

- (3) inability to recall an important aspect of the trauma
- (4) markedly diminished interest or participation in significant activities
- (5) feeling of detachment or estrangement from others
- (6) restricted range of affect (e.g., unable to have loving feelings)
- (7) sense of a foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span)

D. Persistent symptoms of increased **arousal** (not present before the trauma), as indicated by two (or more) of the following:

- (1) difficulty falling or staying asleep
- (2) irritability or outbursts of anger
- (3) difficulty concentrating
- (4) hypervigilance
- (5) exaggerated startle response

E. Duration of the disturbance (symptoms in Criteria B, C, and D) is more than one month.

F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:

Acute: if duration of symptoms is less than 3 months

Chronic: if duration of symptoms is 3 months or more

Specify if:

With Delayed Onset: if onset of symptoms is at least 6 months after the stressor

Appendix B

Table 2.1: Prevalence of PTSD in Pain Samples

Author	No. of Patients	Study Setting	Pain Type	Patients with PTSD, %
Muse 1985	64	Pain Clinic	Chronic pain 6-12m	6/64
Benedikt 1986	225	VA pain clinic	Chronic pain	22 (10%)
Amir, Kaplan et al. 1997	29	Psychiatric clinic	Fibromyalgia	21%
Asmundson, Norton et al. 1998	139	rehabilitation program	chronic pain	34.70%
Sherman, Turk et al. 2000	93	Pain Clinic	Fibromyalgia	52(56%)
Cohen, Neumann et al. 2002	77	Rheumatology outpatient clinic	Fibromyalgia	57%
Roy-Byrne, Smith et al. 2004	571	Referral clinic	Fibromyalgia	20%PTSD;42 %MDD
De Leeuw, Bertoli et al. 2005	1478	tertiary care center	chronic orofacial pain	218, 15%
de Leeuw, Schmidt et al. 2005	80 headache patients; 80 muscle pain	Orofacial Pain Center	Headache; muscle pain	51(64%); 42(52%)
Balasubramaniam, de Leeuw et al. 2007	32	Physical Medicine and Rehabilitation Clinic	Fibromyalgia	41.30%
Bertoli, de Leeuw et al. 2007	445; muscle pain=242; joint pain=203			36,14.9%; 20,9.9%
Meltzer-Brody, Leserman et al. 2007	713 women	referral-based pelvic pain clinic	chronic pelvic pain	31.30%
Jenewein, Moergeli et al. 2009	40	Department of Traumatology	accident-related pain Chronic pain	9(22.5%) subsyndramal PTSD
Ifergane, Buskila et al. 2009	92	Headache Clinic	migraine	6(6.5%)
Peterlin, Tietjen et al. 2009	593	6 headache centers.	Migraine; chronic daily headache	22.4%;30.3%
Jenewein, Moergeli et al. 2009	40	Department of Traumatology	accident-related pain Chronic pain	4/40(10%)
Williams, Newman et al. 2009	106	Medical records	hand-injured patients	32/106

Appendix C

Table 2.2: Rates of PTSD among Patients with and without Chronic Pain

Author	No. of Patients	Study Setting	Pain type	With vs. Without Chronic Pain
Bryant 1999	96	Interviews on patients admitted to a major brain injury rehabilitation unit	chronic pain defined as pain that had existed for at least 6 months and that occurred at least once a week	Chi-square analyses indicated that more patients who reported chronic pain (37%) met criteria for PTSD than did those without pain (15%), ($P < 0.05$)
Raphael 2004	1312	telephone survey of Community dwelling women	fibromyalgia	probable PTSD odds >3 (odds=5.18 (2.99, 8.99)) among women with FM-like symptoms
Johnson 2006	1,219 female veterans	Cross-sectional mailed survey	mastalgia	Compared to women without mastalgia, women reporting frequent mastalgia were more likely to screen positive for PTSD (odds ratio [OR] 5.2, 95% confidence interval [CI] 3.2 to 8.4), major depression (OR 4.2, 2.6 to 6.9)
McWilliams, Cox et al. 2003	5877	a sample representative of the general US civilian population	chronic pain	Chronic pain was strongly associated with post-traumatic stress disorder (OR=3.69). The presence of one psychiatric disorder was not significantly associated with pain-related disability, but the presence of multiple psychiatric disorders was significantly associated with

				increased disability
Liebschutz 2007	509	patients awaiting primary care appointments in an urban academic medical center	chronic pain	The prevalence of PTSD, adjusted for age, gender, race, and marital and socioeconomic statuses, was higher in participants with, compared to those without, chronic pain (23 vs. 12%, $p =$.003)

Appendix D

Table 2.3: Effects of chronic pain on patients with PTSD

Key Study	Sample Size	Sample Type	Design	Key Finding
Jenewein, Moergeli et al. 2009	90	Patients with sustained accidental injuries referred to the intensive care unit	prospective longitudinal cohort design	Individuals with chronic pain showed significantly more symptoms of PTSD, depression, and anxiety, more disability, and more days off work. The development of chronic pain is more related to psychological factors, particularly PTSD symptoms
Page, Kleiman et al. 2009)	447	pain and pain-free patients scheduled for major surgery	cross-sectional design	In pain-free patients, PTSD symptoms were best expressed as 2 symptom clusters (re-experiencing/avoidance; emotional numbing/hyperarousal) accounting for 52.4% of the variance. In pain patients, PTSD symptoms were best expressed as a single symptom cluster accounting for 51.1% of the variance
(Van Loey, Maas et al. 2003)	301	Patients with burn injury from six burn centers	prospective longitudinal cohort design	1) pain related anxiety correlated positively with PTSD symptom severity at 2 weeks and 12 months post burn; 2) pain-related anxiety predicted posttraumatic stress symptoms at 1-year after the burn injury

Liedl, O'Donnell et al. 2010	824	Patients admitted to four hospitals following traumatic injuries	longitudinal study	SEM shows baseline and 12-month pain relationship mediated by 3-month arousal; Baseline and 12-month arousal and re-experiencing relationships mediated by 3-month pain
Sullivan, Thibault et al. 2009)	112	Individuals with whiplash injuries who had been admitted to a standardized multidisciplinary rehabilitation program	prospective study	1) pain and pain-related psychological as indicators of injury severity were associated with more severe post-traumatic stress symptoms; 2) Contrary to expectations, indicators of pain severity did not contribute to the persistence of post-traumatic stress symptoms; 3) pain catastrophizing were one of the significant determinants of the persistence of post-traumatic stress symptoms
Glynn, Shetty et al. 2007	336	patients treated for orofacial injury at a Level I trauma center	prospective study	Patient report of pain severity was one of the predictor of PTSD symptoms at 12 months
(Whitehead, Perkins-Porras et al. 2006)	135	patients admitted to four coronary care units	Two-phase prospective study	Severity of chest pain and psychological factors during admission were predictive of PTSD severity
Chossegras, Hours et al. 2011	541	patients hospitalized after a road traffic accident	prospective cohort study	persistent pain 6 months after the accident is associated with PTSD
Bonin, Norton et al. 2000	33+29	patients with comorbid PTSD and substance, or comorbid PTSD and chronic pain	cross-sectional design	Patients with chronic pain and PTSD reported greater severity scores for many indices (i.e., 9 of

				17 PTSD symptoms), whereas patients with SA+PTSD had significantly greater frequency scores (i.e., 8 of 17 PTSD symptoms).
Humphreys, Cooper et al. 2010	84	community-based sample of formerly abused women	cross-sectional design	Compared to women with mild pain, women with moderate to severe chronic pain had higher levels of depressive and PTSD symptoms
Norman, Stein et al. 2008	115	patients admitted to a Level I surgical trauma center	prospective observational study	Peritraumatic pain was associated with an increased risk of PTSD
Palyo and Beck 2005	183	patients with a motor vehicle accident and reported pain due to accident-related injuries	cross-sectional design	more severe PTSD symptoms and greater pain complaints were related to psychosocial impairment, however, only pain was significantly related to impairment in physical functioning
Ponsford, Hill et al. 2008	113+61	orthopedic trauma patients, recruited during rehabilitation, and demographically similar uninjured controls	prospective longitudinal cohort study	pain and PTSD symptoms predict ongoing disability after orthopedic trauma
Amir, Kaplan et al. 1997	29	PTSD patients from a trauma clinic due to mixed types of trauma	cross-sectional design	PTSD subjects suffering from fibromyalgia syndrome were more tender, reported more pain, lower quality of life, higher functional impairment and suffered more psychological distress than the PTSD patients not having fibromyalgia syndrome

Appendix E

SEM Fit Indices and their acceptable thresholds (Hooper 2008, Hoe 2008)

Index (Range)	Guidelines for interpretation	Cutoff for the current study
Chi Square (χ^2)	Nonsignificant χ^2 suggests the model fits the data (i.e., differences are non-significant). Usually significant in larger samples.	> 0.05
Relative χ^2 (χ^2/df)	2:1 (Tabachnick 2007) 3:1 (Kline 2005)	Adjusted for sample size
Root Mean Square Error of Approximation (RMSEA; 0 - ∞)	Values less than 0.08 (Hoe 2008)	<0.08; Values less than 0.05 represent excellent fit.
Comparative Fit Index (CFI; 0 – 1)	Values closer to 1 indicate better fitting model; suggested cutoff is 0.95 (Hu 1999)	≥ 0.90 was initially advanced ; > 0.95 good fit
Non-Normed Fit Index (NNFI; TLI)	An index that prefers simpler models; can go above 1.0 (Hu 1999)	0.90 acceptable fit; > 0.95 good fit

Appendix F

Table 2.4: Conceptual Models on PTSD and Chronic Pain Relationship

#	Model Name	Key Points	Model Classes	Comments
1	Mutual Maintenance Model (Sharp and Harvey 2001)	PTSD and chronic pain maintain each other through increased distress and disability caused by: 1) attentional and reasoning biases; 2) anxiety sensitivity; 3) reminders of the trauma; 4) avoidance of activities and sensations associated with pain and trauma; 5) depression and reduced activity levels; 6) anxiety and pain perception; 7) cognitive demand from symptoms limiting use of adaptive strategies	Class #1: Mutual Maintenance	1. Most widely cited model, validated partially by multiple studies. 2. Unlike other models such as shared vulnerability model, this model focuses on the interaction rather than the cause of PTSD and pain, and offers a simplified view on the inherently complex relationship between PTSD, pain, distress and disability
2	Shared Vulnerability Model (Asmundson, Coons et al. 2002)	People with high level of anxiety sensitivity are vulnerable to develop and maintain both PTSD and chronic pain.	Class #2: Shared Vulnerability	1. Focus on one of the common causes of PTSD and chronic Pain 2. Simple, one-directional relationship 3. Few citations. Not validated by any empirical study

3	Perpetual Avoidance Model (Liedl and Knaevelsrud 2008)	PTSD and chronic pain maintain each other through the interaction between the causal components of PTSD circle including 1) dysfunctional cognition/intrusions, which causes 2) 2) hyperarousal, which causes 3) and 4) 3) avoidance/inactivity, which causes 1) , and the causal components of pain circle including 4) pain sensation, which causes 5) 5) catastrophizing/fear avoidance beliefs, which causes 3) 3) avoidance/inactivity, which causes 1) and 4)	Class #1: Mutual maintenance	1. Involve interplay and mutual maintenance of chronic pain symptoms and PTSD symptoms 2. Complex, one-directional model (except for avoidance<->pain sensation) 3. No mention on the role of anxiety sensitivity and comorbid psychiatric disorders
4	Triple Vulnerability Model (Otis, Keane et al. 2003)	People with an integrated set of triple vulnerabilities are vulnerable to develop and maintain both PTSD and chronic pain: 1) a generalized biological vulnerability, 2) a generalized psychological vulnerability based on early experiences of control over salient events, 3) a more specific psychological vulnerability in which one learns to focus anxiety on specific situations	Class #2: Shared Vulnerability	1. More general than shared vulnerability model but less than diathesis–stress model 2. Lack of evidence to apply the full triple vulnerability model to the development of chronic pain

5	Fear Avoidance Model (Vlaeyen and Linton 2000; Otis, Keane et al. 2003)	Fear can develop and maintain both PTSD and chronic pain through avoidance behavior: <ol style="list-style-type: none"> 1) Fear of pain causes avoidance of painful movement or activities 2) Fear of reexperiencing disturbing thoughts of events causes avoidance of reminders associated with the trauma 3) Avoidance behavior causes the development and maintenance of PTSD and chronic pain symptoms 	Class #3: Shared pathway	Extended from chronic pain model; Focuses on shared symptom (i.e. avoidance) between PTSD and chronic pain
6	Stress System Dysregulation model (McLean, Clauw et al. 2005)	Dysregulation of stress response system after trauma can develop and maintain both PTSD and chronic pain due to its interaction with cognitive-behavioral factors, such as avoidance learning.	Class #3: Shared pathway	<ol style="list-style-type: none"> 1. Involve the interplay between psychological, behavioral and biological factors; 2. Acute stress->stress system dysregulation->PTSD->chronic pain
7	Diathesis-stress model (Dersh 2002; Turk 2002; Martin 2010)	<ol style="list-style-type: none"> 1. People with pre-existing psychopathology vulnerability (i.e. diathesis) are vulnerable to develop PTSD or chronic pain due to acute or constant stress associated with trauma or pain. 2. At the same time, and in a reciprocal manner, PTSD intensifies the pain or traumatic event experience, making it impossible to treat either condition independently of the other. 	Class #2: Shared Vulnerability	<ol style="list-style-type: none"> 1. Extended from chronic pain model; Involve the interplay between predisposing vulnerability factor, pain or traumatic event related stressor, and subsequent psychological factors; More comprehensive than shared vulnerability model and triple vulnerability model ; 2. Trauma or pain ->stress 3. Stress + diathesis -> PTSD -> pain

Appendix G

Table 3.5: List of existing studies supporting our hypotheses

Study	Study population	Sample size	Analytic Methods	Hypothesis Supported	Results
Geisser, Roth et al. 1996	patients with chronic pain referred to a multidisciplinary pain center	241	Used MANCOVA and ANCOVA to examine group differences	#1	Patients with accident-related pain and high PTSD symptoms displayed higher levels of self-reported pain compared to patients with accident-related pain and no or few PTSD symptoms, and to patients with pain that's not accident related and without PTSD symptoms
Beckham, Crawford et al. 1997	combat veterans with PTSD who visited out-patient PTSD clinic	103	Used multiple regression analyses to examine relationship between pain and PTSD symptoms.	#1	B PTSD symptoms (reexperiencing symptoms) were significantly related to pain disability, overall pain index, and depression scores were also significantly related to percent body pain
Van Loey, Maas et al. 2003	Burn center patients	301	Used hierarchical linear regression model to analyze predictors of PTSD symptoms	#7	Increase in pain is associated with increase in PTSD symptom severity

Glynn, Shetty et al. 2007	socioeconomically disadvantaged adults treated for orofacial injury at a Level I trauma center	336	Used univariate analyses to test the predictors of PTSD symptoms	#6	Predictors of PTSD symptoms at 12 months included current and lifetime mental health and social service needs, lifetime social service use, prior trauma exposure, sum of stressful life events in the year preceding injury, patient report of pain severity and inadequate social support at 10 days postdischarge, and PTSD scores at 1 month
Norman, Stein et al. 2008	Level 1 Surgical Trauma Center	115	Used logistic regression to compute unadjusted odds ratio for each of the previously identified risk factors measured in this study	#7	Peritraumatic pain was associated with an increased risk of PTSD, even after controlling for a number of other significant risk factors other than acute stress disorder symptoms. An increase of 0.5 s.d. from the mean in a 0-10 pain rating scale 24-48 h after injury was associated with an increased odds of PTSD at 4 months by more than fivefold, and at 8 months by almost sevenfold. A single item regarding amount of pain at the time of hospital admission correctly classified 65% of participants
Humphreys, Cooper et al. 2010	community-based sample of formerly abused women	84	Used logistic regression analysis to compute odds ratio of PTSD and depression	#2	Women with moderate to severe chronic pain had equally high levels of depressive and PTSD symptoms and multiple trauma exposures

<p>Whitehead, Perkins-Porras et al. 2006</p>	<p>Inpatient with acute coronary syndromes</p>	<p>135</p>	<p>Used chi-square (for categorical measures) and t tests (for continuous measures) to compare patients in PTSD and non-PTSD groups</p>	<p>#6</p>	<p>Severity of chest pain and psychological factors during admission were predictive of PTSD severity; Acute stress symptoms, depression, negative affect, hostility, and pain scores were independent predictors of three-month PTSD symptoms</p>
<p>Jenewein, Wittmann et al. 2009</p>	<p>sustained severe accidental injuries</p>	<p>90</p>	<p>Group comparisons of dimensional variables were performed with independent samples. Used t tests, one-way ANOVA, χ^2, or Fisher's exact test, multivariate analysis of variance, and logistic regression for group comparisons and predictor assessing.</p>	<p>#1, #6</p>	<p>The prevalence of chronic pain in severely injured patients 3 years after the accident is considerably high. The development of chronic pain is more related to psychological factors, particularly PTSD symptoms, in the aftermath of the accident, as compared to sociodemographic and accident-related variables at the time of the accident</p>

Ramchand, Marshall et al. 2008	hospitalized for injuries resulting from community violence	413	Structural equation modeling/cross-lagged structural model	#6	Posttraumatic distress and physical functioning are reciprocally related. Individuals with high levels of psychological distress at 1 week posttrauma have worse physical functioning at 3 months. Psychological distress at 3 months was not significantly associated with subsequent change in physical functioning at 12 months. Individuals with poor physical functioning at 3 months had higher than expected levels of psychological distress at 12 months.
Zatzick, Jurkovich et al. 2008	Combined pediatric-adult level I trauma center; adolescent injury survivors aged 12 to 18 years	108	Mixed-model regression	#1, #6	High baseline PTSD symptom levels were associated with significant impairments in CHQ-87 Role/Social Behavioral, Role/Social Physical, Bodily Pain, General Behavior, Mental Health, and General Health Perceptions subscales. High baseline depressive symptoms were associated with significant impairments in CHQ-87 Physical Function, Role/Social Emotional, Bodily Pain, Mental Health, Self-esteem, and Family Cohesion subscales.

Cyders 2010	female patients with orofacial pain	411	confirmatory factor analysis; structural equation modeling path analyses	#5	The hyperarousal symptom cluster exerted both direct effects and indirect effects on pain severity, through sleep quality. Additionally, the numbing symptom cluster was predictive of pain-related disability and pain severity through its effects on depression. Avoidance had a direct effect on pain-related disability and an indirect effect on pain-related disability through reduced general activity levels. Re-experiencing had direct effects on both hostility and anxiety.
ESCAPE study	War veterans from VA outpatient clinics	242	logistic regression; multiple regression; repeated measures; confirmatory factor analysis; structural equation modeling path analysis; structural equation modeling cross- lagged panel analysis; CART analysis	#1 -#7	See chapter 4 and 5

Appendix H

Table 4.2: Pearson correlations between baseline PTSD, pain, health-related quality of life, and psychological factors among 188 patients who screened positive for PTSD

	PCL 17	GCPS pain intensity	GCPS disability	GCPS disability days	PHQ-9	GAD-7	pain catastrophizing score	PCS	MCS
PCL 17	1	0.26	0.38	0.3	0.74*	0.74*	0.42	-0.06	-0.71*
GCPS pain intensity	0.26	1	0.45	0.3	0.19	0.17	0.29	-0.4	-0.18
GCPS disability	0.38	0.45	1	0.54	0.43	0.35	0.39	-0.6*	-0.4
GCPS disability days	0.30	0.3	0.54	1	0.33	0.29	0.26	-0.38	-0.26
PHQ-9 depression	0.74*	0.19	0.43	0.33	1	0.72*	0.45	-0.15	-0.77*
GAD-7 Anxiety	0.74*	0.17	0.35	0.29	0.72*	1	0.52	-0.06	-0.69*
pain catastrophizing score	0.42	0.29	0.39	0.26	0.45	0.52	1	-0.27	-0.4
PCS	-0.06	-0.4	-0.6*	-0.38	-0.15	-0.06	-0.27	1	-0.13
MCS	-0.71*	-0.18	-0.4*	-0.26	-0.77*	-0.69*	-0.4	-0.13	1

Note: PCS= SF-36 physical component score; MCS= SF-36 mental component score; *strong correlation $0.6 \geq r < 0.8$ or $-0.8 < r \leq -0.6$.

Appendix I

Comparison of different SEM models examining the relationship of PTSD and pain at baseline.

	Depression and anxiety	Pain	PTSD	PTSD and pain relationships (*significant P-value<0.05)	SF-36	Fit indices
SEM Model A (Figure 4.1)	Anxiety and depression are separated	Pain severity is included in the model, which is the combination of pain intensity and pain disability components measured by the GCPS.	PTSD is defined as PCL 17≥41.	1) PTSD has a *direct effect on anxiety), and an *indirect effect on pain severity through depression . 2) Pain severity has an *indirect effect on PTSD through pain catastrophizing.	1) The mental health component score is *affected by depression or the combination of depression and anxiety.	Model fit is acceptable: relative Chi-square = 3.04, RMSEA =0.092, CFI=0.971, TLI=0.939
SEM Model B (Figure 4.2)	Anxiety and depression are combined			1) PTSD has an indirect effect on pain severity through pain catastrophizing or *through comorbid anxiety and depression.	2) The physical health component score is *affected by the severity of pain	Model fit is good: relative Chi-square = 1.40, RMSEA =0.041, CFI=0.992, TLI=0.98

SEM Model C (Figure 4.3)		Pain intensity and pain disability are included in the model separately, assuming pain disability has a *direct effect on pain intensity.		<p>1) PTSD has a *direct effect on pain intensity, and an *indirect effect on pain disability through comorbid anxiety and depression and pain catastrophizing.</p> <p>2) Pain disability has a *direct effect on PTSD.</p>	<p>1) The mental health component score is *affected by the severity of PTSD, and the combination of depression and anxiety.</p> <p>2) The physical health component score is *affected by pain disability</p>	<p>Model fit is good: relative Chi-square = 1.36, RMSEA = 0.038, CFI=0.992, TLI=0.98</p>
SEM Model D (Figure 4.4)		Pain intensity and pain disability are included in the model separately, assuming pain intensity has a *direct effect on pain disability.		<p>1) PTSD has an *indirect effect on pain intensity through comorbid anxiety and depression and pain catastrophizing.</p> <p>2) Pain disability has a *direct effect on PTSD.</p>		<p>Model fit is good: relative Chi-square = 1.92, RMSEA = 0.062, CFI=0.973, TLI=0.949</p>

SEM model based on factor model H (Figure 4.8)	Anxiety and depression are separated	Pain intensity and pain disability are included in the model separately	The following four PTSD factors are included in the model separately as latent variables: Re-experiencing, Avoidance, Numbing, and Hyperarousal	<ol style="list-style-type: none"> 1) The re-experiencing latent variable is indirectly associated with pain intensity through anxiety and pain catastrophizing. 2) The avoidance latent variable is directly associated with pain disability. 3) The numbing latent variable is *indirectly associated with pain disability through its association with depression. 4) The hyperarousal latent variable is *indirectly associated with pain intensity through anxiety and pain catastrophizing. 	Not included in the model	Model fit is good: relative chi square = 1.66, CFI=.917, TLI=.903, RMSEA=.072
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SEM model based on factor model I (Figure 4.9)			The following four PTSD factors are included in the model separately as latent variables: : Re-experiencing , Avoidance, Dysphoria and Hyperarousal	1) The re-experiencing latent variable is *indirectly associated with pain intensity through anxiety and pain catastrophizing. 2) The avoidance latent variable is directly associated with pain disability. 3) The dysphoria latent variable is *indirectly associated with pain disability through depression. 4)The hyperarousal latent variable is directly associated and *indirectly associated with pain intensity through anxiety and pain catastrophizing.		Model fit is slightly better: relative chi square = 1.58, CFI=.925, TLI=.913, RMSEA=0.069
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*Statistically significant relationship was defined as p-value<0.05. In all of the models above, **anxiety** was defined as GAD-7 total score \geq 10; **depression** was defined as PHQ-9 total score \geq 10. In SEM model based on factor model H, **Re-experiencing** was defined as (PCL-17 items 1–5), **Avoidance** (PCL-17 items 6–7), Numbing (PCL-17 items 8–12), and **Hyperarousal** (PCL-17 items 13–17). In SEM model based on factor model I, **Re-experiencing** was defined as (PCL-17 items 1–5), **Avoidance** (PCL-17 items 6–7), **Dysphoria** (PCL-17 items 8–15), and **Hyperarousal** (PCL-17 items 16–17).

Appendix J

Table 5.1: List of findings by each analysis method for each hypothesis and corresponding research question

Research Question	Hypothesis	Analysis	Finding
1) How strong is the relationship between PTSD and chronic pain?	1) Higher PTSD symptoms will be associated significantly with poorer pain-related and psychosocial outcomes	univariate analysis	PTSD was associated with greater pain severity, the coexistence of pain cognitions and psychological disorders including pain catastrophizing, anxiety, and depression, and poorer quality of life. <i>Hypothesis supported.</i>
		Pearson correlation	A strong correlation ($r \geq 0.6$ or $r \leq -0.6$) was found between PCL-17 and depression, anxiety, and SF-36 mental component summary scores. A moderate correlation ($0.4 \leq r < 0.6$ or $-0.6 < r \leq -0.4$) was found between PTSD symptoms (PCL17) and pain catastrophizing. <i>Hypothesis supported.</i>
		logistic regression	PTSD has no significant effect on pain severity. <i>Hypothesis not supported.</i>
	2) Higher pain severity will be associated with more severe PTSD and psychosocial outcomes	univariate analysis	The cohort with higher pain severity reported significantly higher pain catastrophizing scores, and significantly higher rates of clinically significant PTSD, anxiety, and depression. <i>Hypothesis supported.</i>
		Pearson correlation	A strong correlation ($r \geq 0.6$ or $r \leq -0.6$) was found between pain disability and SF-36 physical component scores; and between depression (PHQ-9), anxiety (GAD-7), and SF-36 mental component scores. A moderate correlation ($0.4 \leq r < 0.6$ or $-0.6 < r \leq -0.4$) was found between 2) between pain intensity and pain disability, SF-36 physical component scores; 3) between pain disability and depression, SF-36 physical component

			scores. <i>Hypothesis supported.</i>
		logistic regression	Pain catastrophizing, anxiety, and depression were significantly ($p < 0.05$) associated with PTSD (PCL-17 ≥ 41) after adjustment for patient demographics, but the predictive association between pain severity and PTSD was not significant (PTSD did not have a direct relationship with pain severity). <i>Hypothesis not supported.</i>
	6) Baseline PTSD will predict pain severity at 9 months, and baseline chronic pain severity will predict PTSD at 9 months	cross-lagged panel analysis	The data did not fit the model well (TLI and CFI < 0.9). No support was found for the hypothesis that any PTSD symptom domain was a significant predictor of any other PTSD factor or pain severity over 9-months. <i>Hypothesis not supported.</i>
	7) The longitudinal change in pain severity will be predicted by PTSD at baseline. The PTSD at 9 month will be predicted by pain intensity and disability at baseline	repeated measure analysis	Baseline PTSD symptom severity was not significantly related to pain intensity over time. However, patients with clinically significant PTSD symptoms did show significant negative relationship with pain disability score improvement after 9 months. <i>Hypothesis partially supported.</i>
		Logistic regression	After adjusting for covariates, both baseline pain intensity and baseline disability score were significantly associated with clinically significant PTSD (PCL-17 ≥ 41). <i>Hypothesis supported.</i>
2) Which factors mediate the relationship between PTSD and chronic	3) Besides pain severity, there are other key factors that are associated with PTSD	CART analysis	Patients with higher pain severity or with coexisting depression and anxiety were more likely to have clinically significant PTSD. <i>Hypothesis supported.</i>

pain?	4) The relationship between PTSD and chronic pain severity will be mediated through depression, anxiety, or pain catastrophizing. And moreover, PTSD and pain severity will adversely affect quality of life (SF-36, MCS/PCS components) independently; and chronic pain patients with PTSD will have worse quality of life than those with one or neither of the conditions .	SEM analysis	PTSD was indirectly related to pain severity mediated by depression, and pain severity was indirectly related to PTSD mediated by catastrophizing. There was no direct association between PTSD and pain severity. Moreover, PTSD was directly related to pain intensity, and pain disability was directly related to PTSD. A combination of both anxiety and depression mediates the effect of PTSD on pain catastrophizing, which has a direct relationship with pain disability. Finally, pain disability was directly related to SF-36 PCS and PTSD was directly related to SF-36 MCS component. <i>Hypothesis supported.</i>
		ANCOVA analysis	Patients with more severe pain and PTSD symptoms were associated with worse SF-36 PCS and MCS scores. <i>Hypothesis partially supported.</i>
3) Do specific PTSD symptom domains affect chronic pain outcomes differently?	5) Different PTSD symptom domains will have differential effects on chronic pain outcomes, either directly, or through mediating factors such as depression or general anxiety disorder.	confirmatory factor analysis	The two four-factor models (reexperiencing, avoidance, numbing/dysphoria and hyperarousal) provided the best fit for our data. The four factors/symptom clusters of PTSD were classified as re-experiencing, avoidance, numbing/dysphoria and hyperarousal. <i>Hypothesis supported.</i>
		SEM analysis with latent variables	None of the four factors of PTSD (reexperiencing, avoidance, numbing/dysphoria and hyperarousal) directly related to pain intensity or pain disability. However, numbing and dysphoria were indirectly related to pain disability mediated by depression, and hyperarousal and reexperiencing were indirectly related to pain disability and pain intensity mediated by anxiety and pain catastrophizing. <i>Hypothesis partially supported.</i>

Appendix K

Table 5.2: Comparison between Cyders et al study and our present study in evaluating the relationship of pain outcomes and the four symptom clusters of PTSD.

	Cyders study	Present study
<i>Methods</i>		
Study type	cross-sectional, retrospective	baseline, prospective
Care setting	orofacial pain center	primary care
Population	female patients with orofacial pain and PTSD	veteran patients with musculoskeletal pain and PTSD
Sample size	411	188
PTSD measure	PCL-17	PCL-17
Pain intensity measure	Multidimensional pain inventory (MPI)	Graded Chronic Pain Scale (GCPS)
Pain disability measure	Multidimensional pain inventory (MPI)	Graded Chronic Pain Scale (GCPS)
General activity level measure	Multidimensional pain inventory (MPI)	
Depression measure	Symptom Checklist-90-Revised (SCL-90-R)	Health Questionnaire (PHQ-9)
Anxiety measure	Symptom Checklist-90-Revised (SCL-90-R)	GAD-7
Hostility measure	Symptom Checklist-90-Revised (SCL-90-R)	
Sleep quality measure	Pittsburgh Sleep Quality Index (PSQI)	
Pain catastrophizing measure		Pain Catastrophizing Scale
<i>Results</i>		
Hyperarousal	had both direct and indirect effects on pain intensity, as partially mediated by sleep quality .	had indirect effects on pain intensity and disability as mediated by anxiety and pain catastrophizing .
Re-experiencing	did not predict pain intensity at all, whether through direct or indirect means.	had indirect relationship with both pain intensity and pain disability
Avoidance	predicted pain-related disability through general activity levels and through direct effect on pain-related disability.	did not have a significant relationship with either pain intensity or pain disability.
Numbing/dysphoria	predicted pain-related disability and pain intensity through depression.	had indirect effects on pain-related disability through depression.

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PUBLICATIONS

1. David T. George, Jodi Gilman, Jacqueline Hersh, Annika Thorsell, David Herion, Christopher Geyer, **Xiaomei Peng**, William Kielbasa, Robert Rawlings, John E. Brandt, Donald R. Gehlert, Johannes T. Tauscher, Stephen P. Hunt, Daniel Hommer, Markus Heilig. Neurokinin 1 Receptor Antagonism as a Possible Therapy for Alcoholism. **Science** 14 March 2008: Vol. 319. no. 5869, pp. 1536 - 1539 DOI: 10.1126/science.1153813
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