CHARACTERIZATION OF FIBR OMYALGIA SYNDROME IN OPERATION IRAQI FREEDOM AND OPERATION ENDURING FREEDOM SOLDIERS TREATED AT BROOKE ARMY MEDICAL CENTER SUBSEQUENT TO POST-DEPLOYMENT EXAMINATION

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DEDICATIONS

I would like to dedicate this manuscript to my parents who have provided me with unconditional support, guidance, wisdom, and love, and have served as inspiring models of hard work, diligence, intelligence, and compassion. I would also like to recognize other individuals who have shown me support including Kenneth Kubala and my immediate family members who have supported me throughout the entirety of my lifetime.

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ABSTRACT

CHARACTERIZATION OF FIBROMYALGIA SYNDROME IN OPERATION IRAQI FREEDOM AND OPERATION ENDURING FREEDOM SOLDIERS TREATED AT BROOKE ARMY MEDICAL CENTER SUBSEQUENT TO POST-DEPLOYMENT EXAMINATION

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This study's purpose was to characterize fibromyalgia syndrome (FMS) within a military population; specifically the Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) cohort treated post-deployment at Brooke Army Medical Center (BAMC) during fiscal years 2004-2006. Retrospective and anonymous data were retrieved from BAMC's database for Global War On Terrorism (GWOT) for all OIF/OEF military personnel treated at BAMC for any diagnosis during the fiscal years of 2004-2006. Frequencies were analyzed for the following diagnoses: FMS, PTSD, adjustment disorders, collapsed variables including PTSD collapsed with stress disorders

and brief/acute PTSD, and FMS collapsed with soft-tissue disorders, certain physical disorders including infectious and parasitic disease, musculoskeletal disorders, autoimmune or systemic disorders, burn, cervicalgia, and soft-tissue disorders. Results suggest that increased rates of FMS exist within military populations, along with a high rate of musculoskeletal disorders, as well as inflated rates of PTSD, burn, infectious disease, soft-tissue disorder, and adjustment disorders. Based on these results, services within the military such as combat exposure may play a role in the development of diagnoses that are associated with FMS and have been implicated as precipitants or potential etiologies in the development of FMS.

CHAPTER I

INTRODUCTION

Fibromyalgia Syndrome (FMS) has generated much controversy through the years. Despite mounting scientific research, some critics disregard FMS as a true pain or clinical disorder, claiming it results from psychological illness (Arshad & Ooi, 2007). FMS is a disorder that affects nociception (the system which carries information regarding inflammation and tissue damage to the spinal cord and brain), the immune system, and the stress-regulating system (Henriksson, 2002). Within the general adult population, research indicates FMS is characterized by chronic widespread pain deriving from central sensitization and neurochemical changes (Desmeules, Cedraschi, Rapiti, Baumgartner, Finckh, Cohen, et al., 2003; Larson, Giovengo, Russell, & Michalek, 2000; Russell, 1998) and precipitating factors such as major trauma and illness (Clauw, Engel, Aronowitz, Jones, Kipen, Kroenke, et al., 2003; Shir, Pereira, & Fitzcharles, 2006; Yue, 1999).

Fibromyalgia Syndrome is well described in women in the general population, and less well described in men, given the deviation of their symptoms (Holman, 2005) and potential provider bias to diagnose men with FMS (C. Vriend, personal communication, June 4, 2007). To the author's knowledge, apart from a short preliminary observation of frequency of occurrence of the diagnosis early in Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) soldiers, FMS has not been

characterized in either gender of the post-deployment soldier. Anecdotal evidence suggests that the diagnosis is more common in soldiers with combat exposure than in the general male population and more common in particular groups such as Airborne and Special Forces (Vriend & Hobbs, 2004). Published reports indicate that a significant proportion of soldiers involved in Operation Desert Storm and diagnosed with Gulf War Illness (especially deployed compared to non-deployed veterans) have FMS (Bourdette, McCauley, Barkhuizen, Johnston, Wynn, Joos et al., 2001; Eisen, Kang, Murphy, Blanchard, Reda, Henderson, et al., 2005; Nicolson & Nicolson, 1998). For instance, FMS was reported 3.7 times more often within Kansas Gulf veterans compared to non-Gulf veterans (Steele, 2000). A strong association of FMS and posttraumatic stress disorder (PTSD) exists (Cohen, Neumann, Haiman, & Matas, 2002), along with overlapping symptoms from FMS and Gulf War illness (Borne, 2004); these issues will be explored in this study.

Existing data were retrieved from Brooke Army Medical Center's (BAMC) database for Global War On Terrorism (GWOT) for all OIF/OEF military personnel treated at BAMC for any diagnosis in the fiscal years of 2004-2006. Personnel included were male and female, officer and enlisted for all services in the Armed Forces. Frequencies of FMS and PTSD were analyzed. In addition, because providers have been initially hesitant to diagnose soldiers with PTSD, similar codes were analyzed, including stress disorders and adjustment disorders which are normally diagnosed in lieu of PTSD (C. Vriend, personal communication, June 4, 2007). Collapsed variables were also analyzed; PTSD collapsed with stress disorders and brief/acute PTSD (as these are normally diagnosed before diagnosing standard PTSD), and FMS collapsed with soft-

tissue disorders (as at times patients may be diagnosed with a soft-tissue disorder instead of FMS due to bias or lack of knowledge on the diagnosis of FMS) (C. Vriend, personal communication, June 4, 2007). Certain physical disorders, disease, and trauma were analyzed as well, including infectious and parasitic disease, musculoskeletal disorders (such as degenerative disc disease and osteoarthritis), autoimmune or systemic disorders (such as rheumatoid arthritis), burn, cervicalgia (neck pain), and soft-tissue disorders (e.g., neuralgia and neuritis). A number of these factors have been associated with FMS such as infection (Steere, 1995), musculoskeletal pain (Henriksson, 2003), autoimmune disorders (Staud, 2006) and physical trauma (Staud & Domingo, 2001), and with military populations such as musculoskeletal injuries and PTSD (Huang, Feuerstein, & Arroyo, 2001; Seal, Bertenthal, Miner, Sen, & Marmar, 2007).

It is expected that this study will support the existing hypothesis that there is an increased prevalence of FMS, with a comparable prevalence of PTSD, within the military compared to the general population. In addition, this study will allow for the following: characterization of FMS in the members of the military and contribute to the identification of potential precipitating factors (such as illness or trauma), the generation of a hypothesis of the etiology of FMS, possible prevention and improved treatment of FMS for the military and general population.

CHAPTER II

REVIEW OF RECENT LITERATURE

Characterization of FMS in the General Population

Fibromyalgia syndrome (FMS) is a musculoskeletal and central nervous system (CNS) disorder that generates chronic widespread pain that may be accompanied by symptoms such as fatigue, migraine, non-restorative sleep and insomnia, gastrointestinal symptoms (e.g., Irritable Bowel Syndrome or IBS), memory loss, muscle tension and stiffness, restless leg syndrome, myoclonus (brief, involuntary twitching of a muscle or a group of muscles), dizziness, poor circulation, anxiety and depression (Anderson, 2005; Holman, 2005). FMS is a multisystem disorder that is not confined to one area or system in the body (Martinez-Lavin, 2002). The prevalence of FMS in the general population is approximately 2%, with 3.7% existing in females and 0.5% in males, resulting in a ratio of approximately 9:1 female to male diagnoses (Raphael, Janal, Nayak, Schwartz, & Gallagher, 2006; Vriend & Hobbs, 2004; Wolfe, Ross, Anderson, Russell, & Herbert, 1995; Yue, 1999). Men with FMS may frequently go undiagnosed, as their symptoms deviate from those of women (Holman, 2005). Muscle spasms and widespread pain usually appear more indistinctly in men, which allows for a much later diagnosis in the course of FMS (Holman, 2005). Response rates to pharmacological treatment are also weakened among men (Holman, 2005). Provider bias or lack of thorough diagnostic knowledge may also facilitate the low number of male FMS diagnoses in general and

military populations (C. Vriend, personal communication, June 4, 2007). Individuals with FMS are thought to experience a pain-processing problem. Neuropathic pain, or pain that originates from a damaged nerve or nervous system or dysfunction of a nerve or nervous system, is experienced with FMS (Staud & Domingo, 2001). For FMS sufferers, pain is experienced from non-noxious stimuli (stimuli that is physically non-harmful such as light touch), a phenomenon termed *allodynia*, while also experiencing an increased response to noxious stimuli (physically harmful stimuli such as a sharp pinch), termed *hyperalgesia* (Henriksson, 2002; Russell, 1998; Staud & Domingo, 2001). Research concludes that there are alterations in the ratios of chemical pain mediators in patients with FMS (Russell, 1998). Individuals with FMS experience chemical changes within the cerebrospinal fluid (CSF), such as elevated levels of Substance P (SP), nerve growth factor, and dynorphin, and decreased met-enkephalin-arg-phe (endorphins) (Givengo, Russell, & Larson, 1999; Larson et al., 2000; Russell, 1998; Staud & Domingo, 2001; Vaeroy, Nyberg, & Terenius, 1991; Welin, Bragee, Nyberg, & Kristiansson, 1995). An increase in SP alone induced allodynia within a group of rats in a study conducted by Hoheisel, Mense, and Ratkai in 1996. Individuals with FMS also experience central sensitization, which is hyperexcitability in the spinal cord and sensitivity in the nervous system that can derive from a long-term noxious stimulus, such as chronic pain (Desmeules et al., 2003). This is one mechanism of the neuropathic pain experienced by individuals with FMS.

In addition, individuals with FMS experience a growth hormone (GH) deficiency (Bennett, 2004). Normally within healthy individuals approximately 70% of GH is released at night, particularly during stages three and four non-rapid eye movement sleep

(Jones, Deodhar, Lorentzen, Bennett & Deodhar, 2007). Individuals with FMS experience difficulties reaching stage four sleep, which is one source for GH deficiency in FMS patients. GH is also normally secreted after exercise; however, its secretion is decreased in FMS patients post exercise (Paiva, Deodhar, Jones, & Bennett, 2002). GH is normally responsible for stimulating growth and cell reproduction or rejuvenation (Bennett, 2004). When a GH deficiency is experienced, it may result in decreased muscle strength and size, non-restorative sleep, fatigue, migraines, decreased bone density, a decreased capacity for exercise, and an increase in fractures or osteoporosis. Individuals with FMS also encounter a difficulty with retaining normal sympathetic homeostasis (Holman, 2005). Because of this dysautonomia, autonomic functions such as disturbed sleep and psychiatric arousal (such as posttraumatic stress disorder) are of particular focus with FMS (Holman, 2005).

Finally, the following literature will review various aspects of FMS within the general population, discuss its connections to many of the diagnoses of interest within this study including PTSD, trauma and infection, and psychological diagnoses, among others, and finally describe how FMS appears within a particular military cohort population.

Diagnosing FMS

The American College of Rheumatology provided classification criteria in 1990 that can differentiate FMS from other chronic pain conditions (Wolfe, Smythe, Yunus, Bombardier, Goldenberg, Tugwell et al., 1990). To meet the criteria for FMS, the patient must have a history of widespread pain in all four body quadrants (left and right side, and above and below the waist) for at least three months and experience pain in at least

eleven of eighteen designated cites of tender points (such as on the arms, legs, or shoulders) using a force of roughly four kilograms (Wolfe et al., 1990). The patient will normally react to the pain with a withdrawal behavior or some sort of gasp (Longley, 2006). However, the tender points are by far not the only tender or painful places for many FMS patients (Longley, 2006).

Normally a diagnosis of FMS is provided by a rheumatologist or other pain specialist after other potential symptom causes are ruled out (such as lupus, osteoarthritis, rheumatoid arthritis, polymyalgia, etc.) even though FMS may co-occur with other similar disorders (Goldenberg, 1999; Longley, 2006). Many FMS patients appear healthy and lack signs that may be typically related to pain such as inflammation or bruising (Longley, 2006). It may be helpful for the patient to understand that FMS is not progressive, degenerative, or deforming and can be well-managed by the patient with assistance and education from a provider (Longley, 2006).

Psychiatric Elements of FMS

Psychopathology has played a role in some cases of FMS, as patients have shown somewhat of an increased occurrence of psychiatric comorbidity (Giesecke, Williams, Harris, Cupps, Tian, Tian et al., 2003). Various FMS patients may experience a range of psychiatric conditions which may lead to varying responses to treatment (Abeles, Pillinger, Solitar, & Abeles, 2007); this is one aspect that a provider would want to remain aware of in order to provide appropriate care.

Depression

There is an evident relationship between depression and pain that is not fully understood but they commonly co-occur together (Bair, Robinson, Katon, & Kroenke,

2003), tend to have overlapping symptoms, may respond to treatments that are similar, share certain neurotransmitters and biological pathways (e.g., descending pathways of the central nervous system) and have the ability to affect one another potentially due to their common pathways (e.g., one can exacerbate the other) (Blier & Abbott, 2001; Gallagher & Verma, 1999). One study found over one half of patients in primary care settings who have depression exhibit solely somatic symptoms (Kirmayer, Robbins, Dworkind, & Yaffe, 1993); symptoms that are primarily pain (Kroenke, Spitzer, Williams, Linzer, Hahn, deGruy et al., 1994). Research indicates that FMS patients tend to have elevated rates of depression (Hudson & Pope, 1996); antidepressant medication that aids in normalizing neurotransmitters such as norepinephrine and serotonin are utilized in treating FMS (Abeles et al., 2007). Although depression and FMS may overlap considerably, many FMS patients do not exhibit clinical depression which may signify that FMS is independent yet overlapping (Abeles et al., 2007).

FMS can be differentiated from depression even though the two entities may co-occur. For instance, although FMS may share various symptoms with depression (e.g., fatigue, poor concentration, sleep issues) (Jason, Richman, Friedberg, Wagner, Taylor, & Jordan, 1997), it is more likely that pain and fatigue will become more debilitating in FMS than in depression (Friedberg & Jason, 2001). Indeed, localized pain is prevalent in depression, such as backache or headache (Simon, Von Korff, Piecinelli, Fullerton, & Ormel, 1999), however, pain in FMS is usually severe, widespread, and debilitating; additionally, cognitive issues (e.g., concentration difficulties) are also more intense in FMS as compared to depression; thus, these symptoms are not definitively related to depression (Friedberg & Jason, 2001).

A further example that exhibits the difference between FMS and depression is that within primary depression a loss of interest and/or anhedonia are present, whereas many who are dealing with FMS may immediately list a number of things that they would like to do if not inhibited by their condition (Friedberg & Jason, 2001). Thus, a significant difference is that FMS patients have lost many abilities to accomplish many of the tasks they could previously, whereas in depression, an individual does not desire to complete activities or tasks at all (Friedberg & Jason, 2001).

Anxiety and Somatization

Anxiety is another psychiatric disorder that may accompany FMS (Fischler, Cluydts, De Gucht, Kaufman, & De Meirleir, 1997). Research indicates that the occurrence of tender points within FMS patients is related to current anxiety levels; similarly, patients who have psychological trauma in their history (such as sexual abuse) have displayed an increased tender point count (Katon, Sullivan, & Walker, 2001). It is documented that individuals with FMS are likely to have experienced some type of abuse (Abeles et al., 2007).

However, the experienced anxiety may or may not fulfill requirements for generalized anxiety disorder (GAD) (Friedberg & Jason, 2001). For instance, GAD is characterized as continuous anxiety that does not necessarily co-occur with pain or fatigue, which are elements within FMS (Friedberg & Jason, 2001). It may be difficult to clearly define the relationship between anxiety and FMS; anxiety may be a secondary reaction to the symptoms and debilitation that arises from FMS (Friedberg & Jason, 2001).

Some studies of a cross-sectional nature have revealed somatization within FMS patients (Abeles et al., 2007). However, the studies evaluated the psychiatric profiles of people who already had FMS, thus, only an association existed; to try and differentiate whether the pain and frustration of the condition led to psychiatric suffering or vice versa was not possible (Abeles et al., 2007). There are overlapping symptoms among the disorders (e.g., pain and gastrointestinal issues), yet they can be distinguished (Friedberg & Jason, 2001). For instance, the pain emerging from somatization does not rise to the level of severity that is characteristic of the multiple tender points in FMS (Friedberg & Jason, 2001). Though symptoms may overlap, the relationships among these disorders remain complex. Psychiatric conditions may predispose an individual to FMS; however, these conditions may also develop in response to FMS (Abeles et al., 2007).

Pathophysiology of FMS

Although extensive research within the past three decades has explored the potential mechanisms of FMS and gains have been made, the etiology and pathophysiology of FMS remain complex. Many elements are noteworthy in evaluating this condition, such as the peripheral and central nervous systems along with elements within them, neuroendocrine aspects, stress, hypothalamic-pituitary-adrenal (HPA) axis, and more. These elements aid in attempting to understand the multifaceted condition of FMS. Additionally, those with FMS experience a pain processing problem; thus the concepts of nociception and neuropathic pain will be reviewed below.

The Role of Nociception and Neuropathic Pain

Nociception, which is usually associated with tissue damamge, is described as the physiologic process of conveying stimuli that is painful from the periphery through

afferent nociceptive neurons, the spinal cord, and the thalamus, to the cerebral cortex, which is the location where one is made mentally aware of or consciously recognizes the pain along with where on the body the stimulus is making contact (Russell, 1998). Various chemicals play important roles in the process of nociception, such as excitatory amino acids, neuropeptides, prostaglandins, biogenic amines, and endogenous opioids, among many others (Russell, 1998). A number of these chemicals send or magnify the signal from the stimulus (such as substance P and nerve growth factor), whereas others have the ability to inhibit communication of the signal or decrease its magnitude (such as serotonin) (Russell, 1998). Individuals with FMS experience pain differently than those who are healthy; decreased thresholds for pain are experienced as compared to healthy persons (Abeles et al., 2007).

FMS patients experience neuropathic pain (from the Greek *neuro,* meaning nerves, and *pathy,* meaning abnormality); it is unlike nociceptive pain (a pain that employs defenses to attempt to limit future tissue damage), as it is stimuli-independent pain that originates from a damaged nerve or nervous system or dysfunction of nerve or nervous system (Staud & Domingo, 2001; Woolf & Mannion, 1999), provides no benefit to the individual, and may be difficult to abolish (Fouquet, 2003). It is characterized by elements such as paresthesias (sensations of tingling, prickling, or numbness) (Woolf & Mannion, 1999), reduced thresholds for pain (hyperalgesia), occurrences of pain paired with soft touch or non-noxious stimuli (mechanical allodynia), variations in temperature (thermal allodynia), and/or pain that may occur unexpectedly (Fouquet, 2003).

Central Sensitization

Central pain mechanisms have been implicated in the pathophysiology of FMS (Abeles et al., 2007). The phenomenon central sensitization is viewed as the underlying process to allodynia and hyperalgesia (Henriksson, 2003). An enhanced excitability of neurons within the spinal cord that transmit nociceptive information to the brain defines central sensitization (Abeles, et al., 2007). Nerve activity of a spontaneous nature, a larger pain distribution, and magnified responses to stimuli exist (such as abnormal temporal summation, or 'wind-up'—which is where stimuli are perceived to be more painful after a first experience of a painful stimulus, is increased in FMS patients) (Abeles, et al., 2007).

The *N*-methyl-D-aspartic acid (NMDA) receptor (located at the postsynaptic membrane in the dorsal horn of the spinal cord) is implicated as being responsible for the processes of central sensitization (Abeles et al., 2007; Henriksson, 2003). Research has demonstrated that treating rats with NMDA-receptor antagonists prevent wind-up (Quartaroli, Carignani, Dal Forno, Mugnaini, Ugolini, Arban et al., 1999). FMS patients have shown attenuated wind-up, hyperalgesia, and muscle pain in response to ketamine (NMDA-receptor antagonist) (Graven-Nielsen, Aspegren Kendall, Henriksson, Bengtsson, Sörensen, Johnson et al., 2000). Dextromethorphan, another NMDA receptor antagonist was also discovered to reduce wind-up in FMS and control patients (Staud, Vierck, Robinson, & Price, 2005).

Finally, this body of research suggests that FMS patients experience an abnormal magnification of pain at the spine (Abeles et al., 2007). Central sensitization is viewed as a part of the pathophysiology of allodynia and hyperalgesia in most FMS sufferers

(Henriksson, 2003). Further research in specific abnormalities that may lead to pain magnification within the general and military populations may be helpful for understanding and better treating FMS.

Chemical Pain Mediators/Role of Neurotransmitters

Certain chemical pain mediators play an important role in the process of allodynia, hyperalgesia, and the pathogenesis of nociception for FMS (Russell, 1998). Many of these chemical mediators, including neurotransmitters, have been shown to stimulate allodynia (Russell, 1998). Some of these vital pain mediators include serotonin, substance P, nerve growth factor (NGF), Calcitonin gene-related peptide (CGRP), and Dynorphin A (Russell, 1998).

Early research indicated that serotonin may play a part in the pathogenesis of FMS, as serotonin was viewed as a deep sleep inducer and a pain perception regulator, both of which are issues with FMS (Moldofsky, 1982; Russell, 1998). Serotonin has a wide distribution within the body and has effects on various pain pathways; with elevated levels of serotonin in the brain, pain signals are blunted by a decrease in the release of substance P within the spinal cord (Abeles, 2007). It is now understood that FMS patients have decreased levels of serotonin in the periphery (Russell, Vipraio, & Acworth, 1993). Other research exhibits decreased levels of serotonin's immediate precursor (5-hydroxy-tryptophan) in the CSF of FMS patients (Russell & Vipraio, 1994). Research on the serotonin transporter gene (5-HTT) suggests altered serotonin metabolism in some FMS patients (Offenbäecher, Bondy, de Jonge, Glatzeder, Krüger, Shoeps, et al., 1999). For example, FMS patients have exhibited a significantly elevated frequency of the genotype at a rate of 31% compared to healthy controls at a rate of 16%

(Offenbäecher et al., 1999). These findings suggest that serotonin may have pathological effects in FMS (Russell, 1998).

Substance P, a neuropeptide, also holds a key role in the process of nociception (Russell, 1998). It supports nociception by 'alarming' neurons in the spinal cord of incoming pain signals from the periphery (Russell, 1998). Animal models have exhibited an induced allodynia in response to increased substance P; one study revealed this phenomenon in a group of rats (Hoheisel et al., 1996). A number of studies support increased levels of substance P (two to three times higher) in the CSF of those with FMS compared to normal controls (Bradley, Alberts, Alarcon, Alexander, 1996; Russell, Orr, Littman, Vipraio, Alboukrek, Michalek et al., 1994; Vaeroy, Helle, Førre, Kass, & Terenuis, 1988; Welin et al., 1995). This evidence indicates a likely role of substance P in increased pain levels within FMS patients. Thus, those who have elevated substance P will likely have amplified levels of pain. One study noted an increase in CSF substance P concentration that directly correlated with clinical changes in pain and tenderness during the same time period within FMS patients, which suggests a direct association among CSF substance P and changes in the severity of FMS pain (Russell, 1998).

Moreover, nerve growth factor (NGF) is a peptide neurotransmitter that has also exhibited elevated levels within the CSF in FMS patients (Giovengo et al., 1999). It remains a complex element, as it is not known why NGF is increased within FMS CSF (Russell, 1998). NGF is thought to support the growth of neurons that contain substance P (Donnerer, Schuligoi, & Stein, 1992; Otten, Goedert, Mayer, & Lembeck, 1980) and to play a role in neuroplasticity (Andreev, Dimitrieva, Koltenzburg, & McMohon, 1995;

Woolf, Shortland, & Coggeshall, 1992). Given these data, NGF may indeed play a vital role in the development and/or maintenance of FMS (Russell, 1998).

Calcitonin gene-related peptide (CGRP) is a neuropeptide that co-localizes with substance P within afferent neural pathways (carry impulses toward CNS). Though the role of CGRP remains somewhat uncertain in the pathology of FMS, one important study did show intriguing relationships with FMS CSF (Russell, 1998). It was found that CGRP in FMS CSF was inversely correlated with a threshold for pain, directly associated with tender point count and depression, and indirectly related to the concentration of CSF hydroxyindoleacetic acid (5-HIAA) (the primary metabolite of serotonin) (Russell, 1998). Thus, these data suggest that with an increase of CSF CGRP, a FMS patient's pain tolerance may decrease with an increase in depressive affect and tender points. Further research would be beneficial for the potential development of treatment options regarding this chemical mediator.

Another peptide dynorphin A appears related to allodynia in several studies (Long, Rigamonti, Oleshansky, Wingfield, & Martinez-Arizala, 1994; Vanderah, Laughlin, Lashbrook, Nichols, Wilcox, Ossipov et al., 1996) through an interaction with *N*-methyl-D-aspartate (NMDA) receptors (Russell, 1998). Additionally, elevated dynorphin A expression is associated with spinal cord constriction or injury (Faden, 1990); which suggests that spinal trauma may lead to increased dynorphin A (Russell, 1998). This is relevant to members of the military who may experience trauma to the spine, as many members of the military experience musculoskeletal disorders of the back due to injury (Huang et al., 2001), which could potentially lead to an increased likelihood of developing FMS. Similarly, one study showed that automobile accidents involving

whiplash to the neck had an increased likelihood of resulting in FMS compared to accidents involving fractures of a lower extremity (21% compared to 2%) (Buskila, Neumann, Vaisberg, Alkalay, & Wolfe, 1997); this is an interesting link as it suggests that mild spinal injury could lead to increased dynorphin A, which could lead to the development of FMS (Russell, 1998).

Finally, FMS research reveals variations in nociception and CNS functioning (Russell, 1998). Recognizing allodynia as an expression of abnormalities in pain processing has led to important research that evaluates nociceptive neurotransmission in patients with FMS (Russell, 1998). These data serve as immensely important, as they aid in characterizing the pathogenesis of FMS which may lead to improved treatment options for FMS patients. Further research that evaluates concepts underlying FMS and symptoms of FMS is needed not only in the general population but within the military population as well, as much of this research is relatively novel within the overall population and virtually absent within military populations.

Neuroendocrine Dysfunction

Many individuals with FMS experience functional aberrations within the hypothalamic-pituitary-adrenal (HPA) axis (Crofford, Pillemer, Kalogeras, Cash, Michelson, Kling et al., 1994). It has been shown that responses of the adrenocorticotropin (ACTH) to corticotrophin releasing factor (CRF) are abnormal; ACTH responses to ovine corticotrophin-releasing hormone (oCRH) shown a tendency toward exaggeration, while the cortisol response to oCRH was decreased; an indication of adrenal hyporesponsiveness (Crofford et al., 1994). It has been concluded that although further research is needed to clearly identify the cause of HPA axis

abnormalities in association with FMS symptoms, it is understood that HPA axis functioning with FMS patients is perturbed (Crofford et al., 1994).

Another study found altered responsiveness of growth hormone, thyroid hormone, and prolactin in FMS patients, along with hypersecretion of ACTH in response to acute stressors (Geenen, Jacobs, & Bijlsma, 2002). The results suggested a central origin of endocrine variations (Geenen et al., 2002). Other research has shown that female FMS patients who noted a history of physical or sexual abuse exhibited lower CSF Corticotropin-releasing factor (CRF) (which mediates stress response) levels compared to women without such history, which suggests certain FMS patients may embody varying neurobiological characteristics based on experiences of stress (McLean, Williams, Stein, Harris, Lyden, Whalen, Park et al., 2006). Furthermore, childhood physical abuse has been shown to predict blunted cortisol rhythms (diurnal), including increased cortisol responses to awakening within FMS patients; sexual abuse has served as a second predictor of higher responses of awakening cortisol (Weissbecker, Floyd, Dedert, Salmon, & Sephton, 2006). These data suggest traumatic experiences in childhood may affect neuroendocrine dysregulation in adult FMS patients (Weissbecker et al., 2006).

Finally, FMS patients should always be assessed for trauma experiences or history before the implementation of treatment, as the experience of trauma may affect FMS patients biologically differently than those FMS patients who may not have experienced certain traumas, including those in childhood. Members of the military are likely to experience certain types of trauma (e.g., combative injury) (Huang, 2001) which may be implicated in the development of FMS and PTSD symptoms.

Autonomic and Sympathetic Nervous System Dysfunction

Individuals with FMS may experience dizziness, fainting, orthostatic fatigue, or other symptoms of dysautonomia (or dysfunction of the autonomic nervous system (ANS) (Russell, 1999) such as vasoconstriction. The sympathetic nervous system (SNS), which is a branch of the ANS, is thought to maintain FMS due to a relentless sympathetic hyperactivity (Martinez-Lavin, 2004), as heart studies have shown that FMS patients experience heart rate variability changes that are consistent with persistent sympathetic hyperactivity (Cohen, Neumann, Shore, Amir, Cassuto, & Buskila, 2000; Martinez-Lavin, Hermosillo, Mendoza, Ortiz, Cajigas, Pineda, et al., 1997). Additionally, research has shown that individuals with FMS experience norepinephrine-evoked pain, along with pain remission in response to sympathetic blockade, which also indicates that FMS may be a sympathetically maintained pain syndrome (Martinez-Lavin, 2004; Martinez-Lavin, Vidal, Barbosa, Pineda, Casanova, & Nava, 2002), as norepinephrine underlies the stress response which increases heart rate and skeletal muscle readiness. Sympathetic hyperactivity induces the secretion of norepinephrine that may consequently sensitize pain receptors and in turn provoke widespread pain and tenderness (Martin-Lavin & Hermosillo, 2000). Thus, it is thought that dysautonomia may underlie the multisystem aspects of FMS such as allodynia and paresthesias (Martin-Lavin et al., 2002).

Sympathetic hyperactivity has been shown in Gulf War Veterans (GWVs) who suffered from Gulf War Syndrome (GWS) (a syndrome which has overlapping features of FMS such as diffuse musculoskeletal pain, fatigue of a chronic nature, and cognitive difficulties) (Bourdette et al., 2001). For example, high-frequency spectral power (which is an indicator of parasympathetic activity) has been blunted at night in GWVs compared

to healthy control veterans (Haley, Vongpatanasin, Wolfe, Bryan, Armitage, Hoffmann et al., 2004). This indicates an over-expression of sympathetic activity, as sympathetic and parasympathetic systems have antagonistic effects on the heart (specifically, the sinus node, which is an element that helps control heart rate) (Haley et al., 2004). Additionally in a subgroup of these GWVs, a tendency emerged for the veterans to have increased values of nerve sympathetic activity, which also signifies potential dysautonomia (Haley et al., 2004). GWVs have also experienced sympathetic driven symptoms that are also found in FMS such as gastrointestinal difficulties (e.g., irritable bowl and/or bladder syndrome), hot flashes, night sweats, syncope, esophageal reflux, and raynaud's syndrome (Baker et al., 2001; Bennett, 2002; C. Vriend, personal communication, July 6, 2007). This area of research indicates that sympathetic hyperactivity may be an underlying mechanism for FMS pain and symptoms. It is suggested that ANS dysfunction may also be the common underlying pathogenesis for overlapping multisystem illnesses (such as FMS, GWS, and chronic fatigue syndrome) (Martinez-Laven & Hermosillo, 2005).

Potential Precipitants or Etiologies of FMS

A definitive cause for the development of FMS is not known; however there are environmental, genetic, and psychosocial factors that have been implicated as potential influential factors (Staud & Domingo, 2001). Various risk factors for developing FMS may include a prior history of physical trauma, infection (Amir, Kaplan Neumann, Sharabani, Shani, Buskila, 1997; Berg, Naides, & Simms, 1993), being of female gender (Forseth, Førre, & Gran, 1999), heredity (Arnold, Hudson, Hess, Ware, Fritz, Auchenbach et al., 2004), longstanding musculoskeletal localized pain (Henriksson,

2003), and growth hormone (Bennett, Clark, Campbell, & Burckhardt, 1992). Military members also seem to be at risk, as many of these factors are experienced within war, combat, or other military duty.

Trauma

Physical trauma has been noted as a precedent of chronic pain by some FMS patients (Staud & Domingo, 2001). For instance, one study noted that out of sixty seven FMS patients, many reported symptoms of FMS after certain traumas which included, motor vehicle accident (60% reported generalized pain), work-related injury (12.5% experienced pain), post-surgery (7.1% reported pain), sports related trauma (5.4%), and other unspecified events (14.3%) (Waylonis & Perkins, 1994).

Another similar study evaluated a population of FMS patients and found reports of abuse that included experiences of sexual trauma (Castro, Barrantes, Tuna, Cabrera, Garcia, Recinos et al., 2005). The researchers found that 70.7% of the FMS patients reported abuse that included 14.8% sexual, 60.9% physical, and 24.3% verbal (Castro et al., 2005). These studies suggest an association of trauma in the development of FMS may be plausible; however, some authors note that the explicit role is still in question (Castro et al., 2005). Some research has noted that location of injuries may play an important part in FMS development. For instance, chronic and generalized pain has been seen to occur up to thirteen times more often after neck trauma (e.g., whiplash) as compared to lower extremity injuries (Buskila et al., 1997; Friedman & Weisberg, 2000). However, the role and mechanism of trauma influencing the onset of FMS remains unclear (Staud & Doming, 2001).

Within the military, upper extremity and back-related diagnoses have emerged as prevalent (e.g., cervicalgia, neck sprain, and lumbago) (Huang et al., 2001). This is important in that these types of injuries and diagnoses may predispose military populations to the development of FMS. Additionally, trauma may be experienced at a higher rate within the military compared to the general population, especially within the personnel who are deployed for combat. One study found that 49% of male patients with combat-related PTSD met the criteria for FMS (Amital, Fostick, Polliack, Segev, Zohar, Rubinow et al., 2006); thus, there may be a strong link between combat trauma and FMS in the military. More recently, a major portion of the military personnel deployed to Iraq and Afghanistan undergo severe guerilla warfare and threats of bombs and other explosive devices (Friedman, 2005); due to this type of environment, many soldiers experience traumatic injury and many are wounded survivors (Gawande, 2004; Hoge, Castro, Messer, McGurk, Cotting, Koffman et al., 2004). Because trauma is prevalent within military members, and trauma may precede FMS, and military personnel experience co-morbid PTSD and FMS, it is vital to study FMS within military populations to facilitate pain management, PTSD treatment, and prevent a high occurrence of FMS.

Infections/Illness

Research indicates that certain infections and disease may be associated with or precede the onset of FMS in some patients. For instance, elevated rates of FMS as compared to the general population have been found in patients who were diagnosed with hepatitis C (Buskila, Shnaider, Neumann, Zilberman, Hilzenrat, Sikuler, 1997; Rivera, de-Diego, Trinchet, & García Monforte, 1997) and HIV (Buskila, Gladman, Langevitz,

Urowitz, & Smythe, 1990). Other infections have been implicated in the role of FMS as well, such as Lyme disease (Steere, 1995) and parvovirus B19 infection (Berg et al., 1993). It is thought that infections of this nature may at least predispose individuals to developing FMS (Buskila et al., 1990; Buskila et al., 1997; Rivera et al., 1997).

Similar to trauma, it remains uncertain as to how or why infections may precede or trigger FMS (Abeles et al., 2007). However, some research indicates that immune response to various infections may be associated with the etiology of FMS. Specifically, cytokine activation in both immune cells and CNS glia may play an important role (Holguin, O'Connor, Biedenkapp, Campisi, Wieseler-Frank, Milligan et al., 2004; Milligan, O'Connor, Nguyen, Armstrong, Twining, Gaykema et al., 2001). One recent study found an elevated level of cytokines in FMS patients (Bazzichi, Rossi, Massimetti, Giannaccini, Giuliano, De Feo et al., 2007). This exaggerated inflammatory response system (IRS) may be implicated in FMS (Bazzichi et al., 2007).

As previously noted, glial activation may play a role in pathological pain. Glia in the spinal cord exhibit similar characteristics with immune cells in that they both respond to infectious agents as well as neural trauma with releases of proinflammatory cytokines, which in turn may cause pathological pain (Watkins, Milligan, & Maier, 2001). The glia in the spinal cord are activated by signals that originate from the periphery, signal cytokines, and in turn pathological pain and hyperalgesia (a major element of FMS) develops (Sommer & Kress, 2004; Watkins et al., 2001). This research suggests that glial activation may play a significant role in the pain from FMS and that the neuropathological dysfunction is actually neuroimmune in nature.

War veterans have displayed certain chronic infections such as mycoplasmal or bacterial infections (Nicolson & Nicolson, 1998; Vriend & Hobbs, 2004). Regarding the recent war, Acinetobacter infection (an infection that is rare in the general population and can cause pneumonia, skin and wound infections, urinary tract infection, central nevous system infections, and blood-stream infections) have been common in the military operations in Iraq during 2003-2005 (e.g., Acinetobacter was found in 23 admitted wounded soldiers, 18 soldiers had osteomyelitis, 3 had deep wound infection, and 2 had burn infection) (Davis, Moran, McAllister, & Gray, 2005; Deployment Health and Family Readiness Library, 2005). Leishmaniasis (a parasitic disease that may cause skin sores or affect internal organs casuing sever health problems and a weakened immune system) has also occurred in soldiers deployed to certain areas of the world such as in the Middle East, Southwest Asia, Central and South American, and East and North Africa (Deployment Health and Family Readiness Library, 2007). Based on literature that implicates the immune system responding to illness and infection and potentially leading to FMS, exposure to infections and parasitic disease within the military may be another explanation for the occurrence of FMS within this population. If there is an increased exposure to infection/illness/disease within the military population, that may increase one's likelihood of developing FMS and associated symptoms.

A number of autoimmune disorders have also been linked to FMS. For instance, systemic lupus erythematosus (SLE) has been noted as a potential risk factor for FMS (Stuad, 2006). Up to 47% of SLE patients fulfilled FMS criteria in a particular study (Stuad, 2006). However, widespread chronic pain, weakness, and distress do not serve as risk factors for SLE (Staud, 2006). The autoimmune activity against receptor systems

such as NMDA may trigger pain, cognitive difficulties, and chronic pain conditions such as FMS (Staud, 2006). Autoimmune disorders have been noted within military populations such as systemic lupus (Arbuckle, McClain, Rubertone, Scofield, Dennis, James, et al., 2003), multiple sclerosis (Wallin, Page, & Kurtzke, 2000), diabetes (Sane, Rautuoja, Mäkelä, Westerberg, & Lehesjoki, 2007), and Graves disease (Burch, Bernet, Plotkin, McCord, Howard, Solomon et al., 2002).

Gender and Hereditary Factors

Research indicates that factors such as gender and heredity may play roles in the etiology of FMS. For example, two studies noted a familial occurrence of FMS (Pellegrino, Walonis, & Sommer, 1989; Stormorken & Brosstad, 1992), one of which also reported a predominance of FMS within females and posited the possibility of a muscle consistency of which was abnormal (Pellegrino et al., 1989). Another study that evaluated 58 offspring of 20 mothers who were diagnosed with FMS and found that 16 offspring, or 28%, had FMS; a male/female ratio emerged at 0.8 compared to 1.5 in the entire group (Buskila, Neumann, Hazanov, & Carmi, 1996). The offspring did not show differences in mental health disorders (anxiety and depression) or in global well being, quality of life, and functioning compared to offspring who did not have FMS; thus genetic factors were attributed to the occurrence of FMS, as neither psychological nor familial factors differed between healthy offspring and those with FMS (Buskila et al., 1996).

A more recent study found similar results regarding a genetic factor. When evaluating relatives of probands (or those who have a disorder under investigation in a family history study) of FMS it was discovered that FMS and decreased thresholds for

pressure pain are found within families; major mood disorder co-aggregated with FMS in the families (Arnold et al., 2004). Additionally, the serotonin transporter gene (5-HTT) has also been implicated as potentially playing a role in FMS. For example, out of 62 FMS patients compared to 110 healthy controls, a significantly higher frequency of the genotype was found in the individuals with FMS (31%) compared to the healthy individuals (16%) (Offenbäecher et al., 1999). Furthermore, polymorphisms of the 5-HT2A receptor gene have been associated with low pain thresholds (Gürsoy, Erdal, Herken, Madenci, & Alasehirli, 2001). This research suggests a potential familial component in FMS and sensitivity to pain; inherited elements may also pertain to co-occurring mood disorders and FMS (Arnold et al., 2004).

The role of gender in relation to FMS is another area of investigation. It is viewed as a potential risk factor for developing FMS (Forseth et al., 1999). Research indicates that females are more likely than males to be diagnosed with FMS; older data suggested that females are seven times more likely, while more recent numbers place females at 1.64 times more likely to be diagnosed (Weir, Harlan, Nkoy, Jones, Hegmann, Gren et al., 2006). Some researchers suggest that healthy females maintain decreased pain thresholds compared to healthy males in the general population, which may indicate that levels of risk for musculoskeletal pain disorders are unbalanced between males and females (Clauw & Crofford, 2003). Also, as previously mentioned, men's symptoms of FMS, such as mechanical allodynia, may deviate from those of women in that muscle spasms and widespread pain normally appear more indistinctly (Holman, 2005). Pain pressure thresholds have been found to be lower in healthy females compared to healthy

males (Maquet, Croisier, Demoulin, & Crielaard, 2004). These factors may lead to a much later diagnosis in the course of FMS for males.

Furthermore, sex hormones have been studied in relation to having a potential role in the prevalence of FMS in women as well. Some studies have found limited or no evidence of a role for sex hormones in FMS, widespread pain, and allodynia (e.g., Macfarlane, Blinkhorn, Worthington, Davies, & Macfarlane, 2002; Okifuji & Turk, 2006), though animal studies have shown that estrogen receptors in enkephalinergic neurons in the spinal cord (Amandusson, Hermanson, Blomqvist, 1996). Because enkephalins play various roles in pain regulation and pain sensitivity, it is hypothesized that decreased estrogen levels may be an element that supports the process of allodynia and hyperalgesia (Henriksson, 2003).

Another factor that may contribute to an increased risk of FMS may be the type of work positions in which women are overrepresented (Frankenhauser, 1991; Henricksson, Liedberg, & Gerdle, 2005). For example, out of the twenty-five vocational positions where the risk of obtaining a musculoskeletal disorder is most prominent, eighteen of those over represent women; some areas of work include food processing, cleaning, manufacturing, packing and storage (Henricksson et al., 2005). Additionally, women prominently reside in occupational areas that carry the most frequently reported accidents of musculoskeletal nature occur, such as personal care givers (Henricksson et al., 2005). A potential link between the type of work performed, static muscle work, and the development of musculoskeletal disorders such as FMS among women. Although, upper body muscle mass can be considered as well. Strength training has shown to decrease symptoms of FMS in women (Rooks, Silverman, & Kantrowitz, 2002); thus, males who

embody more upper body muscle than women in general may be less likely to develop symptoms of FMS compared to women with less muscle size and strength. However, if musculoskeletal injury occurs to a male or female, as it does frequently within the military population (Huang et al., 2001), it may contribute to the development of FMS in persons regardless of gender.

In relation to the military population, a bias may exist that inhibits providers from diagnosing males with FMS, even though they may meet the criteria and may have PTSD (which has been seen to overlap with and co-occur with FMS) or related diagnoses (stress and adjustment disorders) (C. Vriend, personal communication, June 4, 2007). Gulf war veterans have reported symptoms that are common with FMS along with PTSD (Borne, 2004), and over half of gulf war veterans met the criteria for FMS in a certain study (Bourdette et al., 2001). Additionally, as mentioned, a high rate of musculoskeletal disorders occurs within the military population, whether male or female (Huang, 2001), which may predispose this population to FMS. Thus, FMS may occur at a higher prevalence within males than what is currently suggested or documented.

Growth Hormone/Sleep Deficiency

Achieving restorative stage four sleep is a difficult task for many FMS patients and may in part be responsible for the decrement in GH secretion (Bennett, 2004). GH, which is normally released during deep sleep stages (III and IV), is responsible for stimulating growth and cell reproduction or proliferation in a healthy individual (Bennett et al., 1992; Bennett, 2004; Staud & Domingo, 2001). Significant to the exercise intolerance which develops with FMS, muscle repair (such as repairing micro tears associated with resistance exercise) would not be completed in a timely manner in FMS

patients, thus resulting in muscle pain (not soreness as a result of pain amplification) for an extended period. One study found a distinct disruption of somatomedin C, a main mediator of GH's anabolic actions which is necessary for normal muscle homeostasis (Bennett et al., 1992). Another study found decreased secretion of GH to post-exercise compared to healthy controls (Paiva, Deodhar, Jones, & Bennett, 2002), which suggests that the nighttime decrease of GH may not be solely due to lack of stage four sleep. This research suggests an overall decrement of GH within FMS patients, which may indeed contribute to, or predispose one to, muscle pain and exercise intolerance.

Regarding the military population, traumatic brain injury (TBI) has been noted to highly occur within military personnel who are involved in war, such as in the Vietnam war (e.g., 75% of mortality occurred from TBI) and in combat in Iraq and Afghanistan in the current war (e.g., 22% or greater of soldiers have experienced TBI) (Okie, 2005). Growth hormone insufficiency (GHI) has been noted to develop within those who experience TBI, which makes consequences of GHI relevant to the military population as well. Furthermore, GHI within those who have experienced mild, moderate, and severe TBI has been associated with depression and reduced quality of life (Kelly, McArthur, Levin, Swimmer, Dusick, Cohan, et al., 2006). This research highlights the potential importance that the war, and war injuries, may play in the development of generalized pain or symptoms of FMS.

Musculoskeletal Primary Pain Generators

Research has shown that FMS is frequently preceded by localized musculoskeletal pain (Henriksson, 2003). There are various possibilities as to why this could be the case. For instance, muscle pain of varying origins may potentially initiate

neuroplastic changes in nociceptive neurons within the CNS according to some authors (Henriksson, 2003). Additionally, a potential exists that pathological minor muscle variations may sustain pain after allodynia has been established (Henriksson, 2003). One study revealed changes in the tissue oxygen pressure among FMS patients that signified a disrupted regulation of intramuscular microcirculation (Lund, Bengtsson, & Thorborg, 1986). In another study hypoxia (a shortage of oxygen) was implicated, as within a group of FMS patients insufficient relaxation between muscle contractions was noted (Elert, Kendall, Larsson, Mansson, & Gerdle, 2001), which may be sympathetically driven. It is possible that hypoxia may result in sensitization of intramuscular nociceptors (Henriksson, 2003).

Several cases within retrospective and prospective studies reveal longstanding localized musculoskeletal pain preceding the development of FMS. For instance, one retrospective study found 87% of FMS patients reported some type of localized pain that emerged before FMS; at least 55% had low back pain prior to developing pain of a widespread nature (Bengtsson, Henriksson, Jorfeldt, Kagedal, Lennmarken, & Lindström, 1986). Similarly, another study discovered that over 80% of its FMS patient population noted that localized pain steadily turned into widespread pain (Henriksson, Carlberg, Henriksson, Kjällman, & Lundberg, 2000). A further study showed that 25% of women who had dealt with chronic pain in the lower back developed FMS (Lapossy, Maleitze, Hrycaj, Mennet, & Muller, 1995). Though these studies were retrospective, they do show a strong relationship between chronic localized musculoskeletal pain and FMS. One prospective study longitudinally evaluated individuals who had experienced a neck injury; at a three month mark, at least 21% of those individuals met the diagnostic criteria

for FMS (Buskila et al., 1997), while three years later half of those who had chronic neck pain after the injury had FMS (Buskila & Neumann, 2002).

This research suggests that localized musculoskeletal pain may increase one's risk for, or precede, allodynia and widespread pain (Henriksson, 2003). This is relevant to the military population as many military personnel may experience and maintain a localized injury such as degenerative disc or joint disease, or chronic lower back pain (Huang et al., 2001). Additionally, as noted, military personnel experience TBI at relatively high rates; musculoskeletal pain has commonly occurred within individuals who have experienced TBI (Young, 2007). Thus, military personnel seem to be at increased risk for developing FMS or symptoms of FMS.

In summary, there are several potential pathways in the etiology of FMS. Many studies of retrospective nature do not adequately identify temporal relationships (e.g., Waylonis & Perkins, 1994) (Abeles et al., 2007). With regard to military personnel, certain aspects of military duty may increase one's vulnerability to develop FMS and related conditions, as it is likely that one may encounter trauma (e.g., combat-related burn, back injury, or TBI) or certain illness (infectious or parasitic disease) at a higher rate compared to the general population (Baker, McQuarrie, Murray, Lund, Dashevsky, & Mendenhall, 2001).

Disease Co-Morbidity and Overlapping Symptoms

Chronic Fatigue Syndrome (CFS) and FMS

Chronic Fatigue Syndrome (CFS) is defined by at least six months of continuous, debilitating, and unexplainable fatigue not attributable to exertion, not relieved by resting, and causing loss of function in work, social, and personal life (Fukuda, Straus, Hickie,

Sharpe, Dobbins, & Komaroff, 1994). Additionally, at least four secondary symptoms must emerge such as disturbance of sleep, flu-like symptoms, joint or muscle pain, and neurocognitive difficulties (Fukuda et al., 1994). Diagnosis of CFS depends on self-reported symptoms and the elimination of alternative medical or psychological conditions, as there are no characterizing physical signals or laboratory results that clearly indicate a diagnosis of CFS (Reeves, Heim, Maloney, Youngblood, Unger, Decker et al., 2006).

CFS and FMS are disorders that are both enigmatic, manifest similar symptoms including medical and psychological, both somewhat controversial, and share clinical features (e.g., symptomatology and disability) (Friedberg & Jason, 2001). The symptoms that both FMS and CFS share may include elements such as fatigue (more prominent in CFS), pain (more typical in FMS), sleep disturbances, neurocognitive problems, and debilitation, and many similar treatment approaches are utilized for both disorders (e.g., pharmacologic, complementary approaches, physical activity, CBT, etc.) (Friedberg & Jason, 2001; Taylor, Jason, & Schoeny, 2001).

Moreover, there are similar attempted explanatory models that exist for CFS and FMS. Various theories suggest that compulsive overworking and overachieving behaviors arise in FMS and CFS (Friedberg & Jason, 2001). For instance, those with CFS have been characterized by the conversion model (Abbey & Garfinkel, 1991) as feeling compelled to successfully accomplish in many areas of life (e.g., vocational, family, social, etc.) by a "do everything" drive that push them into a conversion-like disorder that allows for obtained social support from loved ones and an exemption from overwhelming responsibilities (Friedberg & Jason, 2001).

Similarly, individuals with FMS have also been characterized by a "pain-prone personality" (Blumer & Heilbron, 1981) premise that notes habitual tendencies to overachieve, along with other behaviors such as a lack of being assertive, issues with identifying anger and other negative emotions, and altruism at one's own expense in order to obtain a high self-esteem and recognition from others (Friedberg & Jason, 2001). This desire for achievement paired with lack of assertiveness may cause increased stress levels that may lead to increased illness susceptibility according to the model (Friedberg & Jason, 2001). As previously noted, other aspects that may increase susceptibility include negative experiences in childhood (e.g., trauma, sexual or physical abuse, poverty, etc.) (Friedberg & Jason, 2001).

Some studies do provide examples of the co-morbidity among FMS and CFS. For example, one study evaluated women who met the criteria for FMS and found that the participants exhibited high lifetime rates of CFS, migraine, IBS, depression, and panic disorder in addition to reporting increased rates of familial major mood disorder (Hudson, Goldenberg, Pope, Keck, & Schlesinger, 1992). The authors concluded that these co-morbid symptoms and disorders may share common physiological abnormalities (Hudson et al., 1992). It was likely that panic disorder was found, as research suggests that lifetime trauma may also serve as a risk factor for developing the disorder (Leskin & Sheikh, 2002). Another study found that compared to controls, patients who were already diagnosed with either FMS, CFS, or temporomandibular disorder (TMD) were more likely to satisfy lifetime symptom and diagnostic criteria for numerous other conditions including CFS, FMS, IBS, multiple chemical sensitivities, and migraine (Aaron, Burke, & Buchwald, 2000). Those with FMS, CFS, and TMD shared universal

symptoms such as sensitivity to generalized pain, issues with sleep and cognitive functioning, migraine and bowel problems (Aaron et al., 2000).

As later outlined in this review, Gulf War (GW) veterans report unexplained symptoms such as memory loss, confusion, insomnia, emotional fluctuations, headaches, and fatigue, while their health related quality of life is inadequate (Baker et al., 2001; Borne, 2004; Bourdette et al., 2001; Eisen et al., 2005; Escalante & Fischbach, 1998). These features are similar and overlap with FMS, PTSD, and CFS (Cohen et al., 2002; Friedberg & Jason, 2001). Ten years after the Gulf War, FMS and CFS occurred significantly more in deployed compared to non-deployed veterans (Eisen et al., 2005). For CFS, the rate was 1.6% in deployed soldiers versus 0.1% in non-deployed, while for FMS, the occurrence was 2% for deployed personnel compared to only 1.2% of non-deployed veterans (Esien et al., 2005). This research indicates an overlap of multisystem illnesses, especially for those persons involved in military duties such as combat.

PTSD and FMS

PTSD is a pathologic response to experienced traumatic events characterized by functional, emotional, behavioral, and physiologic elements (Bland, O'Leary, Farinaro, Jossa, & Trevisan, 1996; Cohen et al., 2002). In existing research, studies suggest that at least 5% of men and 10% of women in the United States who are under the age of 55 have had PTSD that resulted from exposure to traumatic experiences (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). Other risk factors for PTSD are a history of child abuse, psychological disorders, repeated trauma (Breslau, Chilcoat, Kessler, & Davis, 1999; Shalev, 1996; Yehuda, 1999) ethnicity (i.e., Hispanic origin) (Galea, Ahern, Resnick, Kilpatrick, Bucuvalas, Gold et al., 2002; Schnurr, Lunney, & Sengupta, 2004),

experiencing panic attacks and loss of possessions (Galea et al., 2002), family instability, severe punishment as a child, war-zone exposure, antisocial behavior during childhood, post-war trauma (Schnurr et al., 2004), reduced cognitive ability (Kremen, Koenen, Boake, Purcell, Eisen, Franz et al., 2007), and a perceived lack of social support (Johansen, Wahl, Eilertsen, & Weisaeth, 2007).

PTSD has shown to be relatively prevalent within military populations. A recent example involves the military operations within Iraq and Afghanistan. The operations are reported to be the most sustained ground combat actions that include American military personnel since the time of Vietnam; consequently, a preponderance of military members undergo severe guerrilla warfare along with continual threats of mortars, rocket propelled grenades (RPGs) and other devices of explosive nature such as improvised or vehicle borne explosive devices (Friedman, 2005). Due to this kind of environment, soldiers experience intense traumatic injuries and many of the wounded are surviving at high rates (Gawande, 2004; Hoge, Castro, Messer, McGurk, Cotting, & Koffman, 2004). Also, rates of PTSD, along with other mental health issues such as depression, are at increased levels (Seal et al., 2007). In a particular study that analyzed mental health disorders among OIF/OEF veterans during the fiscal year of 2003, it was found that out of those diagnosed with a mental health disorder (25%), PTSD emerged at a rate of 52%, representing 13% of the OIF/OEF veterans (Seal et al., 2007). Other studies have found higher rates. One study evaluated post-deployed soldiers from Iraq and found a PTSD rate of 16.6% (Hoge, Terhakopian, Castro, Messer, & Engel, 2007), while another found a 15.6% to 17.1% rate in post-deployed soldiers from Iraq and a 11.2% in those post-deployed from Afghanistan (Hoge, et al., 2004).

Research supports a strong association between FMS and posttraumatic stress disorder (PTSD) (Amir et al., 1997; Cohen et al., 2002; Sherman, Turk, & Okifuji, 2000). In the general population, PTSD symptoms have been found in 57% of individuals who have FMS (Cohen et al., 2002). Some of the overlap of FMS and PTSD may be explained by precipitants such as traumatic life events (Cohen et al., 2002; Rapheal, Janal, & Nayak, 2004). Previous research concludes that FMS patients with PTSD experience a higher degree of symptoms of anxiety and depression compared to FMS patients who have not been diagnosed with PTSD (Cohen et al., 2002).

As previously mentioned, one recent study indicated that PTSD is highly related to FMS within male patients (Amital et al., 2006). The study evaluated one hundred and twenty-four males; fifty-five who had PTSD, twenty with major depression, and forty-nine controls (Amital et al., 2006). Interestingly, all of the traumatic events in all of the PTSD patients were combat-related (Amital et al., 2006). The results showed that forty-nine percent of PTSD patients, compared to only five percent of major depression patients (and none of the controls) fulfilled the criteria for FMS provided by the American College of Rheumatology (Amital et al., 2006). This study in particular suggests that males who have experienced traumatic combative events (e.g., within the military, from war, etc.) may have a high likelihood for meeting FMS criteria as well.

A physiological measure that exhibits relatively similar changes in both FMS and PTSD is cortisol secretion. For instance, FMS has previously been assoicated with decreased cortisol (Crofford, Pillemer, Kalogeras, Cash, Michelson, Kling et al., 1994), while those with PTSD have also displayed hypocortisolism in the circumstance of elevated negative feedback sensitivity of the HPA axis (Yehuda, Southwick, Krystal,

Bremner, Charney, & Mason, 1993). Because PTSD has been associated with FMS, a recent study evaluated whether or not an increased HPA axis feedback sensitivity was present in FMS patients (Wingenfeld, Wagner, Schmidt, Meinlschmidt, Hellhammer, & Hein, 2007). The study found an elevated sensitivity to glucocorticoid (stress hormone) feedback at the level of the adrenal only, not at a pituitary level regarding adrenocorticotropin hormone (ACTH) secretion (Wingenfeld et al., 2007). Though FMS and PTSD do overlap in some areas, this study did not conclude that similarities exist in the negative feedback loop of the HPA axis. It was suggested that FMS may be characterized by a pattern of HPA axis dysfunction that distinctly varies from the pattern in PTSD (Wingenfeld et al., 2007)

One study found increased associations of FMS and PTSD within those patients who displayed a history of lifetime major depression disorder (MDD) (Roy-Byrne, Smith, Goldberg, Afari, & Buchwald, 2004). This specific study, along with the aforementioned research, suggests that careful evaluations should be made of FMS patients; assessments of PTSD or trauma and potential co-occurrences of MDD or other affective diagnoses should be made (Roy-Byrne et al., 2004).

In summary, PTSD is a relatively frequent occurrence within military personnel (Amital et al., 2006; Seal et al., 2007). PTSD and FMS have been found to be highly associated and co-occurr (Amital et al., 2006; Cohen et al., 2002). However, military personnel may currently be under-diagnosed with these disorders due to provider bias (or lack of knowledge of the disorders, especially FMS) and stigmas of PTSD in the military and FMS in males.

Gulf War Illness (GWI) and FMS

Previous research notes a significant overlap of symptoms for Gulf War Illness (GWI), FMS, and PTSD (Borne, 2004; Bourdette, et al., 2001; Clauw et al., 2003; Vriend & Hobbs, 2003). GWI is similarly characterized as FMS and PTSD. As previously cited, individuals with GWI experience widespread musculoskeletal pain, chronic fatigue, gastrointestinal symptoms (Clauw et al., 2003; Marinez-Lavin & Hermosillo, 2005), memory loss, confusion, insomnia, emotional fluctuations, headaches, sexual dysfunction, and breathing difficulties (Baker et al., 2001; Borne, 2004; Bourdette et al., 2001; Eisen et al., 2005; Escalante & Fischbach, 1998). These symptoms are most common with FMS. Autonomic dysfunction is significant in both FMS and GWI (Borne, 2004), as well as in PTSD (Olff, Langeland, Draijer, & Gersons, 2007). A particular study analyzing GW veterans found that over half of the veterans with unexplained musculoskeletal pain met the criteria for FMS (Bourdette et al., 2001). In addition, research has shown that 82% of GW veterans who were diagnosed with GWI were exposed to more combat, displayed more primary symptoms such as muscle pain, fatigue, and memory problems, and scored higher on assessments of depression, PTSD, and FMS (Baker et al., 2001).

Evidence supports that war veterans are at a heightened risk of unexplained illness and symptoms, while findings are similar among individuals within the general population who experience other catastrophic events (Clauw et al., 2003). Because war veterans display similar and overlapping symptoms of FMS and PTSD, and because PTSD and FMS are highly correlated post-combative trauma, it is important to analyze and characterize FMS within the military.

Treatment Modalities for FMS

Over the years treatment for FMS and reducing the impact of symptoms of FMS has significantly improved (Meisler, 2000). Numerous methods of treatment have been employed throughout time in attempts to decrease the symptoms of FMS, many of which have shown to be helpful. Methods such as physical and aerobic exercise, hydrotherapy (Mannerkorpi, Ahlmén, & Ekdahl, 2002), pharmacologically and psychologically-based treatments, education and self-management programs, stress management, biofeedback, and alternative or complementary therapies have been tested and utilized (Adams & Sim, 2005). It is currently recommended by researchers and clinical experts that clinicians implement multimodal methods of treatment (Meisler, 2000). The objectives of treatment for FMS include aspects such as pain reduction, restoration of physical and social function, and to improve sleep and mood (Russell, 2006).

Pharmacologically-Based Treatments

There are various types of medications that have shown effectiveness in regards to FMS symptoms such as pain, insomnia, depression, anxiety, and fatigue (Rooks, 2007; Russell, 2006). Many categories of medications used for FMS treatment include analgesics, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitor (SNRI), serotonin receptor antagonists, N-methyl-D-aspartate (NMDA) receptor antagonists, anticonvulsants, and muscle relaxers (Russell, 2006).

Analgesics, colloquially known as painkiller medications, are often utilized in the treatment of FMS in attempts to relieve pain and facilitate the effects of other medications (Bennett, Kamin, Karim, & Rosenthal, 2003; Russell 2006). Analgesic

drugs include acetaminophen, nonsterodial anti-inflammatroy drugs (NSAIDs), and opioids (Russell, 2006). However, individuals with FMS may have limited responses to analgesic medications (Staud & Domingo, 2001) while other drug therapy, such as a tricyclic antidepressant, seems more effective in reducing FMS symptoms (Russell, 2006). Opioids are more likely to be used if FMS is complicated by a severe co-morbid pain generator such as severe degenerative disk or joint disease (C. Vriend, personal communication, July 6, 2007). Because opioid use among FMS patients remains controversial and lacks formal testing, clinical and research expert I. J. Russell (2006) recommends that if upon using opioids as a portion of treatment, the patient's physical functioning should increase, side effects should remain controllable, maladaptive behavior should not emerge; if this criteria is not met, it is suggested that the drug be discontinued in use.

Tricyclic antidepressants have served as a popular drug treatment option over time for FMS. Tricyclics have been utilized primarily in low doses to enhance sleep and the effects of certain analgesics (Russell, 2006). Many of the widely-used tricyclics include amitriptyline and nortriptyline (mainly for improving sleep), other drugs with triclyclic effects such as cyclobenzaprine or tramadol are commonly prescribed (Russell, Kamin, Bennett, Schnitzer, Green, & Katz (2000).

SSRIs were initially created for treating depression and have shown promising effects for individuals with FMS who are depressed or have issues with insomnia (Russell, 2006). Fluoxetine is an example of an SSRI that effectively aids with sleep, especially when paired with amitriptyline (Goldenberg, Mayskiy, Mossey, Ruthazer, & Schmid, 1996). Newer medications developed serotonin and norepinephrine reuptake

inhibitors (SSNRIs) with similar reuptake activity at a range of doses have proven more effective in reducing pain (Russell, 2006). Duloxetine is an example of an SSNRI that is utilized in treating pain from FMS (Russell, 2006) and is FDA approved for treating diabetic neuropathy and post-herpetic neuralgia (C. Vriend, personal communication, July 6, 2007). Milnacipran is another SSNRI that is utilized in Europe for treating depression and various symptoms of FMS, such as pain (Russell, 2006). Additionally, serotonin receptor antagonists are currently being examined for their potential roles in the treatment of FMS. For instance, in one study, the drug tropisetron, a 5-hydroxytryptamine3 (5-HT3) antagonist, was found to reduce pain, improve sleep, weakness, and morning stiffness (Stratz, Farber, Varga, Baumgartner, Haus, & Muller, 2001).

Because individuals with FMS experience central sensitization, which may result in an increased sensitivity to harmful stimuli (Staud & Domingo, 2001), it may be significant to incorportate N-methyl-D-aspartate (NMDA) receptor antagonist drug therapy for FMS treatment, as these antagonists can aid in inhibiting central sensitization (Russell, 2006). Examples of NMDAs include ketamine and dextromethorphan, which have both resulted in positive outcomes regarding pain and allodynia stemming from FMS (Clark & Bennett, 2000; Henriksson & Sorensen, 2002).

Anticonvulsant medications, or otherwise known as antiepileptic drugs, which also work at the level of the NMDA receptor have shown to be effective for FMS sufferers (Russell, 2006). Pregabalin is an example of an anticonvulsant that has been FDA approved for treating neuropathic pain in diabetic individuals and postherpetic neuralgia (Rooks, 2007). It inhibits or creates a reduction in the releasing of

neurochemicals such as glutamate, norepinephrine, and substance P, which carry the pain signal (Russell, 2006). Pregabalin has improved FMS patients' pain, weakness, sleep, and life quality (Crofford, Rowbotham, Mease, Russell, Dworkin, Corbin et al., 2005).

Sleep aids, such as zolpidem, lunesta, and tricyclics, are another class of drugs that may be utilized in treating aspects of FMS. Sodium oxybate for example, aids in treating narcolepsy and daytime sleepiness (Russell, 2006) and has also been documented to reduce pain and increase growth hormone production (Scharf, Baumann, & Berkowitz, 2003). A more recent study maintained these results with similar findings of pain relief and sleep improvement (Russell, Bennett, & Michalek, 2005). Seroquel is used if PTSD is co-morbid with FMS (C. Vriend, personal communication, July 6, 2007).

Finally, implementing a combination of medications (rational polypharmacy) is useful for those with FMS; however, if this method is utilized it must be carefully monitored and individually tailored to each patient (Russell, 2006). For instance, for a FMS patient who suffers from pain, sleep issues, and depression may be treated with both oxybate and duloxetine (Russell, 2006). With continued monitoring, this combination is viewed as safe, as the mechanisms of the drugs work very differently and should not cause any adverse effects (Russell, 2006).

Physical Exercise

Physical exercise modalities such as walking and strength training aid in increasing physical aerobic abilities and protect individuals who are burdened by FMS from becoming physically deconditioned (Meisler, 2000). This proves to be an important aspect, as many FMS patients are physically deconditioned (Bennett, Clark, Goldberg, Nelson, & Binafede, 1989) and experience a decrease in muscle capacity (Bengtsson,

2002); ordinary physical and social activities can become difficult and result in increased pain, resulting in further immobility and deconditioning (Vøllestad & Mengshoel, 2005). Additionally, because FMS patients experience vasoconstriction in regards to blood flow, low levels of exercise seem helpful in normalizing muscular perfusion (Delp, 1998) and providing improvements in oxidative ability of muscles; Thus decreasing pain and aversion to activity (Piepoli, Clark, Volterrani, Adamopoulos, Sleight, & Coats, 1996).

This physical activity not only aids in physical improvements, but psychological and emotional improvement as well. For example, a particular study found that routine exercise was correlated with a decrease in depressed mood and an improved general health status, along with positive physical benefits such as decrements in weakness and disability (Da Costa, Dobkin, Drista, & Fitzcharles, 2001).

A number of studies that incorporated aspects of exercise such as aerobic, stretching, strength training, flexibility, and cardiovascular elements found a decrease in tender point count, a concurrent increase in mood (Dawson, Tiidus, Pierrynowski, Crawford, & Trotter, 2003; Martin, Nutting, MacIntosh, Edworthy, Butterwick, & Cook, 1996), improvements in physical fitness (Verstappen, van Santen-Hoeuftt, Bolwiin, van der Linden, & Kuipers, 1997), walking speed (Tiidus, Pierrynowski, & Dawson, 2002), muscle strength (Valkeinen, Häkkinen, Hannonen, Häkkinen, & Alen, 2006), cardiovascular stamina, muscle strength, and functional status as measured by the Fibromyalgia Impact Questionnaire (FIQ) (Rooks, Silverman, & Kantrowitz, 2002), maximal strength (Häkkinen, Häkkinen, Hannonen, & Alen, 2001), and muscle strength along with voluntary muscle activation (Valkeinen, Häkkinen, Pakarinen, Hannonen, Häkkinen, Airaksinen et al., 2005).

Other studies have focused solely on aerobic exercise. For example, improvements in threshold scores for pain and in cardiovascular health (McCain, Bell, Mai, & Halliday, 1988), distribution and severity of pain, ability for energy and work (Wigers, Stiles, & Vogel, 1996), and on tender point count and the FIQ (Richards & Scott, 2002) have been observed in studies that implement aerobic exercise for FMS patients.

Hydrotherapy (or the use of water for treatment, such as warm water pools) has shown to be effective as well, as the low-impact force (Offenbächer & Stucki, 2000), appropriate amount of resistance, and warmth aids in reducing pain while individuals are exercising (Adams & Sim, 2005). For those who are deconditioned, water exercise also serves as suitable place to begin physical activity (Offenbächer & Stucki, 2000). Walking in warm water has elicited benefits for FMS patients' muscle strength, health-based life quality, and pain compared to controls (Gusi, Tomas-Carus, Häkkinen, Häkkinen, & Ortega, 2006). Similarly, deep water running paired with land-based fitness training has shown to be effective at improving female FMS sufferers' pain, affect, fitness, life quality, and functioning (Assis, Silva, Alves, Pessanha, Valim, Feldman et al., 2006). Also, pool exercise therapy paired with education has revealed decreased magnitude of FMS symptoms, and improved physical and social functioning, distress (e.g., depression and anxiety), capabilities for walking (Mannerkorpi et al., 2002), relaxation, and serenity (Mannerkorpi & Gard, 2003). Additionally, aerobic exercise and stretching within the water has elicited significantly better performance in a walking task, on the Beck Depression Inventory (BDI) compared to controls along with favorable changes in anxiety, scores on the Mental Health Inventory, FIQ ratings, and self-efficacy

(Gowans, deHueck, Voss, Silaj, Abbey, & Reyonlds, 2001). Thus, numerous studies have revealed beneficial effects of hydrotherapy for FMS patients.

Physical exercise activities that primarily involve gentle movements may be of value as well (Burckhardt, 2002). Such exercises may include yoga, Tai Chi, and qigong; these activities highlight the importance of one's body awareness, the control of painful movements, and assessment of body signals (Burckhardt, 2002). For example, Tai Chi use among FMS patients has revealed significant improvements in symptom management and health-based life quality, as measured by both the FIQ and Short Form-36 (SF-36) (Taggart, Arslanian, Bae, & Singh, 2003). Also, qigong therapy has demonstrated improvement in functioning, pain, tender point count, and depressed mood for FMS patients (Chen, Hassett, Hou, Staller, & Lichtbroun, 2006). Thus, while more studies are needed regarding these particular types of exercise, preliminary studies do provide hope that they may be useful to FMS sufferers.

Finally, while some treatment methods may not prove to be successful for various individuals with FMS, research demonstrates that a number of physical activity treatment modalities have served as beneficial and may provide hope to those who live with FMS. Though low exercise adherence issues may emerge (Dobkin, Da Costa, Abrahamowicz, Drista, Du Berger, Fitzcharles et al., 2006), continuance of physical exercise can aid in one avoiding decrements in one's tolerance for physical activity in general (Mannerkorpi & Iverson, 2003) and becoming further physically de-conditioned (Meisler, 2000). It has been noted that improved adherence to regular physical exercise has arisen from addressing issues such as pain, stress, exercise barriers, and creating an individualized

exercise program for one's appropriate fitness level and physical restrictions (Dobkin, Abrahamowicz, Fitzcharles, Drista, & Da Costa, 2005; Dobkin et al., 2006).

Education, Combination, and Self-Management Strategies

Education programs and treatment modalities enable individuals with FMS to reduce anxiety and control stress and negative symptoms that result from FMS (Burckhardt & Bjelle, 1994). Other beneficial outcomes have emerged as well from the implementation of education, a combination of education and other treatment modalities, and self-management education programs (Adams & Sim, 2005).

Education combined with exercise has shown beneficial effects for FMS patients. For instance, self-efficacy, or believing in one's own capacity to manage and reduce pain (Bandura, 1997) has been shown to increase within participants who engaged in an education and physical therapy group, compared to an education-only group and a control group (Burckhardt, Mannerkorpi, Hedenberg, & Bjelle, 1994). Increasing self-efficacy in individuals who have FMS is vital, as many FMS patients believe they have no control over their pain (Adams & Sim, 2005). Additionally, a combined education and water-based activity group compared to a control group has demonstrated a superior improvement in the areas of physical function, general well-being, and weakness (Gowans, deHueck, Voss, & Richardson, 1999).

Self-management strategies prove to be vital treatments for individuals with FMS as well (Adams & Sim, 2005). A very significant aspect to self-management strategies or programs encompasses an educational aspect (Burckhardt & Bjelle, 1994). Improved pain ratings within FMS patients have resulted from programs that include FMS education, exercise schedules, engaging in group discussions, setting goals, relaxation

exercises, and daily-living suggestions (Mengshoel, Forseth, Haugen, Walle-Hansen, & Førre, 1995).

This reviewed research suggests that education and self-management programs and treatments, along with education and self-management combination programs that may include a multitude of treatment elements, provide hope for improving the condition of those individuals who live with FMS. Self-management and educational means of treatment may empower the patient by providing him or her with an increased amount of control over the management and treatment of the diagnosis or condition of FMS, reducing the stress of living with the disorder. Other self-directed activities may include heat therapy via shower or bath and relaxation exercises and techniques (Burckhardt, 2002). Support groups that are resource-based may also aid FMS patients in dealing with their condition (Russell, 2006).

Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) has also been apart of treatment for managing symptoms of FMS (Burckhardt, 2002; Russell, 2006). Among the goals of implementing CBT include, aiding FMS patients in understanding that they can play a main role in the management of their symptoms, demonstrating the effect that one's thoughts, behaviors, and anticipations can have on symptoms, and help the patients learn cognitive and behavioral management techniques (Keefe & Caldwell, 1997). For example, managing time for certain daily activities would be a valuable behavioral skill for patients with FMS to learn and implement (Burckhardt, 2002). Numerous studies have produced effective and positive results from implementing CBT in treating symptoms of FMS. For instance, as measured by the FIQ, CBT only was found to be

superior to pharmacologically-based treatment only or a combined group of both CBT and medical management, as symptom improvement (pain, weakness, and stiffness), well-being, and activities (work and daily) were positively altered by the CBT (García, Simón, Durán, Canceller, & Aneiros, 2006). Reductions in pain and insomnia and improvements in functioning, mood, and overall health (Singh, Berman, Hadhazy, & Creamer, 1998), along with improvements in pain, coping, pain behaviors, depression scores, and physical functioning (Goldenberg, Kaplan, & Nadeau, 1994; Nicassio, Radojevic, Weisman, Schuman, Kim, Schoenfeld-Smith et al., 1997; Wigers et al., 1996; Williams, Cary, Glazer, Rodriguez, & Clauw, 2000) have been shown in response to treating symptoms of FMS with CBT.

Complementary Therapies

Various types of complementary and alternative medicines are utilized in the treatment of FMS and research on these treatments is expanding (Burckhardt, 2002). The terms, complementary and alternative, are many times thought of as the same concept (Burckhardt, 2002). However, it is important for patients and providers to understand that complementary strategies refer to treatments that may be implemented concomitantly with regular medical treatment; whereas alternative therapies are primarily utilized in stead of traditional treatment (Burckhardt, 2002). Many patients with FMS tend to employ the use of unconventional treatement methods in a complementary way (Pioro-Boisset, Esdaile, & Fitzcharles, 1996), thus, providers and patients need to fully communicate about these options to optimize outcome and reduce risk (Burckhardt, 2002). Some of the complimentary therapies that are being utilized by FMS patients may include acupuncture, electromyographic (EMG) biofeedback training, massage, and

chiropractic and osteopathic manipulation, among others (Adams & Sim, 2005; Burckhardt, 2002)

Acupuncture is one treatment that has been employed in symptom treatment of FMS (Rooks, 2007). Though some studies found acupuncture to be ineffective in treating symptoms of FMS (e.g., Assefi, Sherman, Jacobsen, Goldberg, Smith & Buchwald, 2005; Harris, Tian, Williams, Tian, Cupps, Petzke et al., 2005), other research has found positive results in measures such as pain threshold, quality of sleep, morning stiffness, number of analgesic pills taken, and pain scores compared to a sham group (Deluze, Bosia, Zirbs, Chantraine, & Vischer, 1992). Currently the results of acupuncture's role in the treatment of FMS lack clarity, and further randomized controlled trials are needed (Rooks, 2007). However, because FMS patients tend to utilize complimentary therapies (Pioro-Boisset et al., 1996), and previous acupuncture studies have failed to report issues of safety, acupuncture could serve as an option and opportunity for some patients (Rooks, 2007).

Electromyographic (EMG) biofeedback training is another complementary therapy that may be incorporated into FMS treatment. It has been previously utilized in the management of chronic musculoskeletal pain separate from FMS, such as low back pain (Flor & Birbaumer, 1993; Newton-John, Spence, & Schotte, 1995), but has also shown effectiveness with symptoms of FMS (Adams & Sim, 2005). Improvements in tender point count, pain severity, and morning stiffness, maintained at six months (Ferraccioli, Ghirelli, Scita, Noili, Mozzani, Fontana et al., 1987), and decreases in pain sensitivity, affective and sensory aspects of pain, insomnia, and migraine and an increase in general quality of life (Mur, Drexler, Gruber, Hartig, & Günther, 1999) have been

found in response to biofeedback. Because EMG biofeedback aids individuals in becoming aware of their physiological tension, it may facilitate FMS patients' knowledge of learning how and when to relax their muscles, even under stressful circumstances.

Physical manipulation is another category of complimentary treatment that a number of FMS patients may employ that includes massage and chiropractic manipulation. Regarding massage therapy, its evaluation within clinical trials is somewhat lacking (Burckhardt, 2002), however, FMS patients continue to experiment with massage (especially gentle massage) (Pioro-Boisset et al., 1996). Studies that have assessed the potential benefits of massage for FMS symptoms do exist. For example, massage has resulted in decrements in anxiety and depression, a rise in the number of hours slept, a decline in movements while asleep, decreased levels of substance P, and reports of lower disease, pain, and tender points by physicians for FMS patients (Field, Diego, Cullen, Hernandez-Reif, Sunshine, & Douglas, 2002). Although additional studies are needed, therapies such as massage and guided relaxation may aid in inhibiting pain and stress for FMS patients (Lund, Lundeberg, Carleson, Sönnerfors, Uhrlin, & Svensson, 2006).

Chiropractic manipulation and osteopathy are treatments that employ the manipulation of joints, and continue to be considered alternative or complimentary medicine (Adams & Sim, 2005). The techniques are primarily utilized to decrease pain, improve muscle strength and joint movement, and decrease further damage to joints or muscles (Crofford & Appleton, 2001). Chiropractic manipulation has elicited lumbar and cervical mobility, improved straight-leg raise, and improved levels of pain compared to controls (Blunt, Rajwani, & Guerriero, 1997) while osteopathy has shown improvements

in pain, daily activities, and some features of chronic pain (Gamber, Shores, Russo, Jimenez, & Rubin, 2002). Regarding complimentary or alternative therapies, patients and providers should fully communicate about these options and understand that some methods may hold potential costs and risks, especially for repeated therapies (Burckhardt, 2002).

Multimodal/Comprehensive Strategies

Multimodal approaches of treatment utilize multiple treatment options in combination, many of which were previously reviewed here. Thus, many components may include physical activity, education, CBT, medication, stress management, complementary therapies, or more (Adams & Sim, 2005; Sim & Adams, 1999). Because FMS is truly a syndrome and multiple factors that contribute to symptom load such as physiological, psychological, and sociological facets, and goals of improvement and rehabilitation may include increased daily activity and functional ability, and decreases in socio-economic stressors, treatments should target symptoms at a biopsychosocial level, or approach treatment in a multi-disciplinary manner (Berker & Dincer, 2005).

Studies have evaluated the use of comprehensive programs specifically. For example, FMS patients have reported improvements in pain intensity, control of pain, emotional distress, and functional capabilities (Nielson, Walker, & McCain, 1992), decrements in tender point count and improved FIQ scores, weakness, stiffness, and physical functioning (Bennett, Burckhardt, & Clark, 1996), and improvements in anxiety, depression, and general affective distress (Turk, Okifuji, Sinclair, & Starz, 1998) in response to multimodal programs that included elements such as relaxation assisted by biofeedback, cognitive techniques, aerobic exercise and stretching, pacing and improving

pain tolerance, education (Nielson et al., 1992), physical and occupational therapy, CBT (Turk et al., 1998) behavior modification, techniques to reduce stress, and support sessions for significant others (Bennett et al., 1996). More recent studies also show support for multimodal or comprehensive treatment programs (e.g., Gustafsson, Ekholm, & Broman, 2002; Pfeiffer, Thompson, Nelson, Tucker, Luedtke, Finnie et al., 2003).

An example of a multimodal program that serves active duty military and beneficiaries is a comprehensive FMS treatment programat Brooke Army Medical Center in San Antonio, TX. The ongoing treatment group meets once weekly for eight weeks per group and includes aspects such as education about FMS and its physiological mechanisms and effects, CBT, psychopharmacology and medication management, developing and implementing behavioral contracts for pain management, exercise education (e.g., learning about effective strength training, stretching, warm water walking or hydrotherapy, light aerobic workouts, Tai Chi, and more, while developing a personalized exercise program), stress management, relaxation techniques (e.g., deep diaphragmatic breathing, guided imagery, and self-hypnosis), and information on various complementary therapies (e.g., massage and acupuncture) for which there is evidence of efficacy.

These multimodal therapies target multiple aspects of FMS compared to one or two treatments only, which provides patients and providers with an increased number of approaches to manage and reduce symptoms of FMS. Although single treatment methods may prove useful for some FMS patients, comprehensive treatment programs may serve as the most useful in reducing the most symptoms of FMS.

Conclusions

Research indicates that FMS is well characterized in the general population with a majority of female patients, and less well characterization of FMS in the military where male patients are in the majority. Research does conclude that Gulf War veterans experienced overlapping and co-occurring symptoms of Gulf War Illness, PTSD, and FMS (Bourdette et al., 2001) and that PTSD resulting from combat-related trauma is highly associated with FMS (Amital et al., 2006). Research has indicated a higher prevalence of FMS within Gulf War veterans compared to non-Gulf War veterans (Steele, 2000) while a preliminary study evaluating a cohort of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) soldiers treated at Brooke Army Medical Center (BAMC) in San Antonio during fiscal year 2003 found a higher prevalence of FMS in this population (overall and among both males and females) with a comparable rate of PTSD (Vriend & Hobbs, 2003).

Furthermore, research notes that factors such as trauma, illness, and primary pain generators appear to be associated with the development of FMS (Berg et al., 1993; Henriksson, 2003; Staud & Domingo, 2001) and that these potential etiological factors are frequently experienced within the military population due to general and combative responsibilities. Additionally, because Gulf War Illness, PTSD, and FMS overlap, the links between injury/trauma/illness and military duty, and the correlation among PTSD and FMS, it is essential to analyze and characterize FMS within the military.

Also, because of the impact of FMS on function, quality of life, and medical resources, it is vital to highlight and characterize FMS in the military to recognize its increased presence and ensure correct diagnosing and treatment; if soldiers are not

correctly diagnosed or treated at the Veterans Administration upon developing FMS, this will account for significant increases in medical costs, as occurred post Gulf War (Baker et al., 2001). For example, Gulf War Veterans were perceived as being "difficult" patients by physicians upon a veteran exhibiting a mental health disorder, more than five somatic symptoms, and severe symptoms, as many physicians wished to strictly follow the biomedical model (Baker et al., 2001). This lead to the "difficult" patients having poorer functional status, noting increased unmet expectations, expressing less satisfaction with care received, and having a higher use of health care services (Baker et al., 2001), which leads to increases in medical costs. It is hoped the current post-deployed soldier will receive adequate diagnosing and treatment in order to avoid increased health care costs and other noted negative experiences that occurred among Gulf War Veterans. Finally, this study will allow for the characterization of FMS in the members of the military and potentially support the identification of precipitating factors and etiologies of FMS.

Hypotheses

It is hypothesized that an increased prevalence of FMS will be found in the OIF/OEF military cohort treated during fiscal years 2004-2006 at BAMC as compared to the rate in the general population, with a comparable rate of PTSD. It is also hypothesized that correlations will reveal significant positive associations among FMS and physical injury and infection.

CHAPTER III

METHOD

Population

All Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) military personnel treated at Brooke Army Medical Center (BAMC) for any *ICD-9-CM* diagnosis/code requested by the author in the fiscal years of 2004-2005 and 2005-2006 are included in the statistical analysis; diagnoses of interest are described below (see, *Procedure*). Personnel included a total of 1259 individuals; 1143 males (90.8%) and 116 females (9.2%). Ages for the overall population ranged from 19 years of age to 62 years of age with a mean age of 32.9; the age range for males varied from 19 years to 62 years of age with a mean age of 32.6, while the range for females varied from 21 years to 61 years of age with a mean age of 35.7. Ages were not available for 13 out of 1259 individuals. Officer and enlisted soldiers for all services in the Armed Forces were active duty and included: 563 from the United States Army, 254 from the United States Army Reserve, 243 from the Army National Guard, 150 from the United States Marine Corps, 14 from the United States Air Force, 14 from the United States Navy, 12 from the Active Guard Reserve, 3 from United States Navy Reserve, 3 civilians, 1 from the Air National Guard, 1 from the United States Coast Guard, and 1 family member (dependent). Neither rank, ethnicities nor race of the personnel were provided to the author in the data.

Measures/Instruments

Existing retrospective data were retrieved from BAMC's standalone database for GWOT (Global War On Terrorism) for all OIF/OEF military personnel treated at BAMC for diagnoses of interest in the fiscal years of 2004-2005 and 2005-2006.

Procedure

Because the current study is descriptive and somewhat exploratory, the analyses were limited to the calculations of frequencies, co-morbidities, and correlations. The data were provided in the form of the number of encounters per individual per diagnosis (i.e., each visit to a provider for a given diagnosis was documented), instead of solely listing each person with his or her given diagnoses. During the two fiscal years of interest, the number of visits or encounters ranged from 1 to 486. On average, individuals were seen 52.18 times; males were seen an average of 52.65 times while females were seen an average of 47.57 times. In order to calculate frequencies, co-morbidities, and correlations regarding the diagnoses of interest, the data for each person were aggregated by utilizing the aggregate function in the Statistical Package for Social Sciences (SPSS) software program in order to obtain the within person mean for any given diagnosis. Absolute one's or zeros were allocated, depending on the within person mean. If the mean was zero, an absolute zero was provided; if the mean was greater than zero, a one was provided. No range was utilized. Thus, if an individual had been seen in an encounter for a certain diagnosis one or more times, he or she was given a one (meaning he or she had the diagnosis of interest); if an individual had not been seen or had no encounters for a diagnosis, then he or she was given a zero in order avoid including him or her in a particular diagnostic group. Those with zeros were not included in the analyses. This

allowed for collapsing encounters and for delineating who had been diagnosed with a diagnosis of interest and who had not been diagnosed; however, the extent of one's diagnosis (e.g., mild, moderate, severe, etc.) was not determined.

The diagnoses of interest were chosen based on the diagnoses included in the preliminary report completed for post-deployed OIF/OEF soldiers treated at BAMC for fiscal year 2003-2004 (which included PTSD, infectious and parasitic disease, burn, and musculoskeletal disorders) (Vriend & Hobbs, 2004). The diagnoses were also chosen due to the literature that indicates associations among FMS and certain disorders (e.g., PTSD and musculoskeletal disorders such as cervicalgia, among others) (Amital et al., 2006; Henricksson, 2003), along with an elevated rate of musculoskeletal disorders within the military population (Huang et al., 2001). Adjustment disorders, brief/acute PTSD, and stress disorders were included in the study due to the tendency of some providers to diagnose military personnel with a diagnosis such as these before utilizing standard PTSD, (C. Vriend, personal communication, June 4, 2007). Soft-tissue disorders with and without FMS were included, as at times patients may be diagnosed with a soft-tissue disorder instead of FMS due to bias or lack of information on the diagnosis of FMS (C. Vriend, personal communication, June 4, 2007). Autoimmune disorders, trauma (such as burn), and infection were analyzed as well, as these have been noted among risk factors for developing FMS (Staud, 2006; Steere, 1995; Waylonis, & Perkins, 1994).

Within SPSS, the diagnoses of interest for which frequencies, correlations, and crosstabs (or co-morbid diagnoses) were calculated included FMS (the standard FMS diagnosis along with a variable that included standard FMS collapsed with other soft

tissue disorders), PTSD (the standard PTSD diagnosis along with a variable that included standard PTSD, brief/acute PTSD, and the stress disorders collapsed; the stress disorders included acute stress, unspecified acute reaction to stress, and acute reaction to stress with predominant disturbance of emotion), infectious and parasitic diseases (including a range from intestinal infectious diseases, bacterial diseases, and viral diseases, to "other" infectious and parasitic), burn (including upper and lower body with varying extents of body surface from less than 10% or less, or unspecified, to 90% or more of body surface, along with varying degrees ranging from unspecified to deep third degree burn), cervicalgia (neck pain), adjustment disorders (including adjustment disorder with depressed mood, with anxious mood, with mixed emotional features, other, with predominant disturbance of conduct, with mixed disturbance of emotions and conduct, with physical symptoms, and unspecified), soft tissue disorders (collapsed with and without FMS), autoimmune disorders (systemic and inflammatory disorders such as rheumatoid arthritis), and musculoskeletal disorders (non-inflammatory, excluding FMS, and degenerative diseases such as degenerative disc and joint disease and osteoarthritis).

CHAPTER IV

RESULTS

Descriptive Statistics

Refer to Table 1 to view the frequencies (overall and for gender breakdown of those who were diagnosed) for diagnoses of interest. Among these diagnoses, many of the most salient frequencies include the following: 3.8% of personnel were diagnosed with FMS; of these, 31.25% were female and 68.75% were male. For PTSD, 12.0% were diagnosed. 52.8% of personnel were diagnosed with some type of musculoskeletal disorder, 30.1% of personnel were diagnosed with some type of burn, 14.7% of personnel were diagnosed with an infectious or parasitic disease, 14.7% of personnel were diagnosed with some type of adjustment disorder, 18% of personnel were diagnosed with a soft-tissue disorder, 20.6% of personnel were diagnosed with FMS collapsed with soft-tissue disorders, and 17.7% of personnel were diagnosed with PTSD collapsed with stress disorders and acute PTSD.

In summary, many of the largest frequencies were found among the diagnoses of musculoskeletal disorder (52.8%), burn (30.1%), the collapsed FMS variable (20.6%), and the collapsed PTSD variable (17.7%). The rate of FMS was elevated from approximately 2% in the general population to 3.8% within this specific military cohort, which is a 90% increase. Males carried a higher percentage of each diagnosis, although females did embody 31.25% of the FMS diagnosis and 22.7% of the autoimmune

disorder; this may suggest for females that out all of the diagnoses analyzed, females were most impacted by those diagnoses in particular compared to other diagnoses. Percentages for males ranged from 68.75% to 95.3% for all of the diagnoses; this was most likely the case as a larger male population compared to females was included in the study.

Table 1

Frequencies of Diagnoses

Diagnosis	**Overall %**	**Female %**	**Male %**
FMS	3.8%	31.25%	68.75%
PTSD	12.0%	9.3%	90.7%
Infectious/Parasitic Disease	14.7%	13.5%	86.5%
Burn	30.1%	4.7%	95.3%
Cervicalgia	5.5%	10.1%	89.9%
Adjustment Disorder	14.7%	10.3%	89.7%
Musculoskeletal Disorder	52.8%	10.8%	89.2%
Autoimmune Disorder	1.7%	22.7%	77.3%
Soft-Tissue Disorder	18.0%	11.1%	88.9%
FMS Collapsed with Soft-Tissue	20.6%	12.7%	87.3%
PTSD Collapsed with Brief PTSD and Stress Disorder	17.7%	9.9%	90.1%

Note: The gender breakdown includes only those who were diagnosed with the diagnoses overall.

Co-Morbidities/Crosstabs

Personnel were diagnosed with both FMS and PTSD at a rate of 0.87%. The largest co-morbidity for FMS occurred among FMS and musculoskeletal disorder with a rate of 3.7%, with the second largest co-morbidity for FMS at 1.6% with cervicalgia. The larger co-morbidities for PTSD included the 9.2% who were diagnosed with PTSD and a musculoskeletal disorder, the 4.5% diagnosed with PTSD and collapsed FMS variable, 3.9% diagnosed with both PTSD and a soft-tissue disorder (compared to FMS and soft-tissue at 1.2%), and 2.8% diagnosed with both PTSD and some type of burn. Additionally for the collapsed variables, elevated co-morbidities included the 16.6% who were diagnosed with collapsed FMS and musculoskeletal disorder, the 12.6% diagnosed with collapsed PTSD and musculoskeletal disorders, and 6.4% diagnosed with both collapsed PTSD and collapsed FMS. Again, males accounted for much larger percentages for the co-morbid diagnoses. However, females did account for 54.5% of co-morbid FMS and infectious/parasitic disease, 46.7% for co-morbid FMS and other soft-tissue disorders, 27.3% of co-morbid FMS and PTSD, and 36.4% for co-morbid FMS and adjustment disorders. Thus, these diagnoses in particular seemed to impact females most compared to other diagnoses.

Correlations

Phi correlations were performed for all diagnoses of interest for the overall sample, male, and female. Refer to Table 2 to view all correlations for the overall population and to Table 3 for correlations by gender. Most significant correlations were significant at the $p < .01$ level, although a number were significant at the $p < .05$ level. Here the significance level at .05 is approached in a conservative manner and considered

marginal due to the large population (n = 1259) within this study. For the overall population, FMS was positively correlated with PTSD $r(1259) = .067, p < .05$, musculoskeletal disorders $r(1259) = .180, p < .01$, autoimmune disorders $r(1259) = .195$, $p < .01$, soft-tissue disorders $r(1259) = .069, p < .05$, and cervicalgia $r(1259) = .317, p < .01$, while negatively correlated with burn $r(1259) = -.113, p < .01$. Unlike many of the other significant correlations, each time that burn was significantly correlated with another variable, it was negatively associated; this indicates that when burn is present, the other variable of interest (including FMS, PTSD, musculoskeletal disorders, infectious disease, cervicalgia, and adjustment disorders) would be less likely to be co-morbid. The effect sizes of these significant correlations are considered small and thus hold little predictive value, as many are at the .1 level or below. The males carried the largest number of significant correlations; however, again, the male population was considerably larger than the female population (1143 compared to 116).

Table 2

Overall Correlations

	FMS	PTS	I/P Dis	Burn	Cervi	Adjus Dis	Musc Dis	Autoi Dis	Softti Dis	FMS Coll	PTSD Coll
FMS	1	.067*	.046	-.113**	.317**	.046	.180**	.195**	.069*	.391**	.038
PTS		1	.006	-.056*	.072*	.082**	.177**	.044	.139**	.157**	.796**
I/P Dis			1	-.087**	-011	.107**	.109**	.030	.122**	.127**	.042
Burn				1	-.120**	-.043	-.084**	-.074**	-.036	-.068*	-.046
Cervi					1	.028	.228**	.101**	.115**	.197**	.062*
Adjus Dis						1	.078**	.065*	.192**	.183**	.137**
Musc Dis							1	.114**	.235**	.284**	172**
Autoi Dis								1	.096**	.142**	.033
Softti Dis									1	.919**	.168**
FMS Coll										1	.176**
PTSD Coll											1

Note: ** Correlation is significant at the .01 level (2-tailed)
* Correlation is significant at the .05 level (2-tailed)

Table 3

Correlations by Gender

	FMS	PTS	I/P Dis	Burn	Cerv	Adj Dis	Mus Dis	Auto Dis	Softt Dis	FMS Coll	PTS Coll
FMS	1	.065* .094	.006 .173	-.095** -.165	.328** .334**	.033 .107	.156** .301**	.151** .298**	030 .235*	.347** .611**	.044 .010
PTS		1	.006 -.001	-.071* .134	.090** -.094	.100** -.092	.177** .181	.044 .052	.134** .192*	.148** .236*	.799** .766**
I/P Dis			1	-.073* -.167	-.019 .043	.106** .108	.116** .021	.013 .095	.125** .082	.123** .134	.045 .014
Burn				1	-.121** -.109	-.045 .003	-.076** -.107	-.068* -.091	-.037 .007	-.063* -.059	-.057 .096
Cerv					1	.022 .083	.231** .198*	.130** -.054	.113** .131	.201** .084	.082** -.123
Adj Dis						1	.079** .058	.031 .250**	.201** .108	.201** .031	.149** .024
Mus Dis							1	.104** .166	.233** .237*	.276** .335**	.164** .242**
Auto Dis								1	.076* .198*	.139** .148	.038 .006
Softt Dis									1	.930** .831**	.161** .228*
FMS Coll										1	.169** .231*
PTS Coll											1

Note: Gender breakdown as follows: M/F
Asterisks below numbers are relevant to numbers above them (due to formatting)
** Correlation is significant at the .01 level (2-tailed)
* Correlation is significant at the .05 level (2-tailed)

Conclusions

Results indicate an increased frequency of FMS exists within this military cohort compared to the general population (3.8% vs. approximately 2%) (Raphael et al., 2006). This increased rate exists despite the preponderance of males within the population and provider bias in diagnosing males with FMS. It is also consistent with Gulf War studies that show increased rates of FMS (e.g., Steele, 2000) and recent preliminary report evaluating FMS in OIF/OEF soldiers (Vriend & Hobbs, 2004). Modest positive correlations with other disorders known to be associated with FMS emerged as well despite not only provider bias, but also that the soldiers were assessed shortly after deployment; FMS develops over time and would thus be likely show a higher prevalence after a longitudinal follow-up with the soldiers (Vriend & Hobbs, 2004); which also applies to the frequency of FMS that was found. Finally, although a more conservative two-tailed significance statistical test was employed, a majority of the correlations among FMS and other disorders emerged at a significance level of $p < .01$ compared to a $p < .05$ level, and, in fact, may be an underestimate of the relationships.

CHAPTER V

DISCUSSION

As hypothesized, the overall findings of this study demonstrate an elevated rate of FMS in post-deployed OIF/OEF soldiers treated at Brooke Army Medical Center during fiscal years 2004-2005 and 2005-2006 as compared to FMS in the general population (3.8% vs. approximately 2%) (Raphael et al., 2006), which is a rate that increased by 90%. This finding is consistent with both the preliminary report that found elevated rates of FMS (3.9%) within the OIF/OEF cohort treated post-deployment during fiscal year 2003-2004 (Vriend & Hobbs, 2004) and other published research that indicates a significant presence of FMS within Gulf War Veterans (e.g., occurring 3.7 times more often within veterans compared to non-Gulf veterans) (Bourdette et al., 2001; Steele, 2000). Normally FMS is characterized as a syndrome that primarily affects women (Wolfe et al., 1995; Yue, 1999); however, the current study exhibited an overall elevated rate of FMS despite provider bias to diagnose men with FMS and despite that the study's population consisting of 90.8% males and only 9.2% females (a predominately male population). Out of those diagnosed with FMS, 68.75% of those were male, while 31.25% were female. This supports the idea that a higher rate of FMS diagnoses may exist in military populations, regardless of gender and bias.

Upon hypothetically applying this 3.8% rate to all active duty military in the United States, this increased rate may potentially affect over 54,000 members, as approximately 1,426,713 personnel are currently on active duty in the military (not including the additional 1,259,000 personnel in the reserve areas). Medical costs for FMS are considerable and remain at higher rates for the average recipient of health care (e.g., FMS claimants in the general population have been shown to pay $5945 versus $2486 for the typical beneficiary) (Robinson, Birnbaum, Morley, Sisitsky, Greenberg, & Claxton, 2003). This increased rate of FMS has the potential to greatly increase medical costs for the military and Veterans Association if left unaddressed, especially if soldiers are not properly diagnosed and treated.

As earlier outlined, the reason that military members, especially those involved in direct combat, may be more likely to develop FMS may be due to the traumatic experiences and injuries to which soldiers are exposed. Musculoskeletal disorders (such as lower back pain, cervicalgia, and degenerative disc and joint disease) have been noted at high frequencies within military populations (Huang et al., 2001); similarly within the current study, musculoskeletal disorders were found at 52.8%. Longstanding musculoskeletal pain (or primary pain) generators have been implicated in preceding FMS (Henriksson, 2003). The current study found a 3.7% rate of co-morbid FMS and musculoskeletal disorders, along with a positive correlation among the two variables, significant at the $p < .01$ level ($r(1259) = .180, p < .01$). These findings partially support current literature, as the prevalence rate for musculoskeletal disorders were high, a co-morbid rate emerged among both variables (at 3.7%), and significant positive correlations

were found; however, the co-morbidity rate was fairly low and effect sizes for the correlations were small, so it is difficult to imply that one may predict the other.

Trauma is another factor that has been noted as a potential precipitant of FMS (Friedman & Weisberg, 2000). Burn, considered to be a traumatic experience, was evaluated in the current study and found at a relatively high rate of 30.1%, while a low rate of co-morbidity emerged between FMS and burn at .16%. Burn was significantly correlated with FMS and other diagnoses; however, unlike many of the other significant correlations, each time that burn was significantly correlated with another variable, it was negatively associated; this indicates that when burn is present, the other variable of interest (including FMS, PTSD, musculoskeletal disorders, infectious disease, cervicalgia, and adjustment disorders) may be less likely to be present. Because burn results in immediate and severe pain, it precludes consideration of any pain related diagnosis including FMS. Both burn and FMS share hyperalgesia (a lower threshold for pain) (Henriksson, 2002; Summer, Romero-Sandoval, Bogen, Dina, Khasar, & Levine, 2007). It may be interesting to follow-up after the cessation of burn treatment in order to evaluate those who experienced burn trauma, to assess whether or not FMS criteria were met. However, as already noted, the significant correlations that emerged held low effects sizes; thus little predictive implications can be made.

The current study also discovered a 12% prevalence of PTSD, which is relatively consistent with other rates of PTSD within military populations, if not an under-representation (Amital et al., 2006; Seal et al., 2007). More notably, PTSD has been found to be highly associated and co-occur with FMS (Amital et al., 2006; Cohen et al., 2002). For example, PTSD symptoms have been noted in 57% of individuals within the

general population who had FMS (Cohen et al., 2002), along with a rate of FMS found in 49% of combat-related trauma patients with PTSD (Amital et al., 2006). Thus, a high co-morbidity was expected among FMS and PTSD in the current study. However, this was not supported, as only 0.87% of all personnel were diagnosed with both FMS and PTSD. Out of those males who were diagnosed with FMS, 32% were also diagnosed with PTSD, and out of those females who were diagnosed with FMS, 25% were also diagnosed with PTSD.

Of those diagnosed with FMS, 68.75% were male and 31.25% were female, while out of those diagnosed with PTSD, 90.7% were male and 9.3% were female; the low rate of PTSD among females was most likely due to the likelihood that they would be less involved in direct field combat, which may contribute to the low rate of PTSD and FMS co-morbidity. However, due to the high association of PTSD and FMS noted in other literature, it would be expected that a larger number of males would have been diagnosed with FMS within the current study, especially since a large number were diagnosed with PTSD. Additionally, the preliminary investigation of OIF/OEF soldiers from fiscal year 2003-2004 discovered a rate of PTSD (3.6%) comparable to that found of FMS (3.9%) (Vriend & Hobbs, 2004). However, FMS (and PTSD) tend to develop over a period of time (for both men and women) from various symptoms into a full syndrome that meets the American College of Rheumatology criteria and autonomic system disturbances (Vriend & Hobbs, 2004). For instance, signs and symptoms of Gulf War Illness (which overlap those of FMS and a high number of Gulf War veterans met criteria for FMS) began to emerge between six months to one year or more after the close of Operation Desert Storm (Nicolson & Nicolson, 1998). This indicates that the OIF/OEF soldiers

may not have developed the full diagnosis of FMS, or even PTSD, as their data were obtained shortly after post-deployment.

Moreover, males may also be under-diagnosed with FMS in part due to the diagnostic criteria for FMS, as it is very dependent upon tender points, which was developed for research purposes and based primarily upon a female population (C. Vriend, personal communication, June 4, 2007). The symptoms displayed by males deviate from those of women, such as mechanical allodynia (Holman, 2005). Muscle spasms and widespread pain usually appear more indistinctly for males, which allows for a much later male diagnosis in the course of FMS (Holman, 2005). This difference in the manifestation of pain may have also contributed to a lower number of male FMS diagnoses as compared to male PTSD diagnoses (68.75% vs. 90.7%), as well as the low overall co-morbidity rate among these two diagnoses.

It is also speculated that a provider bias exists that allows for a low number of FMS diagnoses among men, as providers may assume the diagnosis must be something alternative other than FMS, such as a soft-tissue disorder or connective tissue disorder, as it is historically thought that males do not develop FMS; it has been historically viewed as a female disorder. Thus, FMS among men is somewhat stigmatized. A similar pattern for not diagnosing soldiers with PTSD has existed as well, resulting in personnel being likely to obtain diagnoses of adjustment and stress disorders instead of PTSD, at least initially. Additionally, a lack of thorough knowledge and understanding of FMS criteria or of the most current research regarding the diagnosis and diagnostic criteria may also exist among providers, which may contribute to negative attitudes toward the diagnosis of FMS in males.

Regarding the collapsed variables for FMS and PTSD, as expected, higher frequencies were found for these variables as compared to their standard variables (standard FMS and PTSD). For instance, FMS collapsed with soft-tissue disorders emerged at a 20.6% frequency rate, out of the total population (compared to 3.8% for standard FMS), while PTSD collapsed with stress disorders and brief/acute PTSD emerged at a 17.7% rate (compared to 12% for standard PTSD). As noted, there is a provider tendency to diagnose personnel (especially males) with something other than FMS such as soft-tissue disorder, and also diagnose personnel with a stress disorder or brief/acute PTSD before utilizing standard PTSD, even if criteria are met. These increased numbers of the collapsed variables may represent these biases. Although, the collapsed PTSD variable was more strongly correlated (positively) with adjustment disorders than standard PTSD was with adjustment disorders, suggesting a link between PTSD, brief/acute PTSD, stress disorders, and adjustment disorder diagnoses. Additionally, 6.4% of personnel were diagnosed with both collapsed PTSD and collapsed FMS, showing a higher rate of co-morbidity compared to the co-morbidity among the standard diagnoses (of 0.87%). Thus, if providers are using alternative diagnoses for FMS and PTSD (soft-tissue/autoimmune or stress/adjustment disorders), then these numbers may represent this.

Regarding significant correlations, the hypothesis was supported in that significant positive correlations did emerge between FMS and physical disorders (injury), which included cervicalgia, musculoskeletal disorders, autoimmune disorders, soft-tissue disorders, and FMS collapsed with soft tissue disorders. However, these significant correlations hold little predictive value, as the effect sizes were small (.1 or less). Thus, it

is difficult to suggest that when one such physical disorder diagnosis is present that FMS will be present as well. Because the variables were binary (1 or 0), the Phi correlation was employed, which is equivalent to the Pearson correlation. If a tetrachoric correlation had been utilized, correlation effect sizes would have emerged at an increased rate. However, though the correlations emerging from the Phi correlation coefficient may hold little predictive value, they do hold significance, as many were significant at a $p < .01$ level, even using a more conservative two-tailed significance approach compared to a one-tailed. This reveals associations among FMS and other diagnoses, which supports previous research. Also, infection and parasitic disease was not significantly correlated with FMS, which does not support the outlined hypothesis. Although infection and illness/disease have been implicated as precedents of FMS, the correlations and co-morbidities within this study does not seem to support that literature. However, infectious and parasitic disease did occur at a rate of 14.7%, which is a notable prevalence. It may be that given this sizable rate, criteria for FMS may later be met by those diagnosed personnel, given that FMS may slowly develop.

Limitations and Future Research Directions

Limitations emerge in the current study. First, a limited number of females were included in this military cohort population in particular. Of course it is understood that on average a higher percentage of males are normally enrolled within military services as compared to females, making the issue an inherent one that may or may not be resolved when evaluating other military cohorts. Second, the diagnosis of FMS may be misused among providers in that a lack of knowledge on the diagnostic criteria or the syndrome itself, which may cause providers (such as physical medicine doctors or others who are

not rheumatologists) to utilize FMS as a 'wastebasket' diagnosis (i.e., diagnosing male or female personnel with FMS when he or she is suffering from solely a locialized pain issue or mental health issue such as anxiety, depression, or PTSD). This serves a limitation, as the data may not correctly represent the actual diagnoses that soldiers embody. Third, the degree of severity of the diagnoses of interest were unknown (e.g., mild, moderate, severe, etc.), as individuals were marked as either having a certain diagnosis or not having a diagnosis. FMS is not a progressive disorder once its established but does slowly develop over time with some symptoms present for sometime, thus this may have had little impact on the FMS diagnosis in particular; however, if someone showed a number of FMS symptoms, yet did not meet the full-fledged criteria, again, then this issue mainly may have caused an under diagnosis of FMS. However, it may have been helpful to know the degree of severity of some of the other diagnoses (e.g., infection, musculoskeletal disorders, and soft-tissue) in order to more clearly establish their relationship with FMS and pathophysiological mechanisms. Given this study design, the degree of severity of a given diagnosis was not obtainable; how many times an individual was seen compared to others would have been possible to analyze. However, how many times an individual is seen for a given diagnosis compared to the number of times another individual has been seen for the diagnosis does not automatically reveal who experienced the most or least severity of a disorder. Other measures would have been necessary to obtain this information, such as a Fibromyalgia Impact Questionnaire (FIQ) among others.

Future research directions are many. First, soldiers should be followed longitudinally in order to identify FMS and PTSD that may develop over a period of

time. If personnel are not correctly diagnosed by the time they reach the Veterans Affairs (VA) (given that one of the diagnoses does develop), appropriate treatment would not be provided, thus resulting in significant increases in medical costs. Second, further research on the pathophysiological mechanisms of FMS such as central sensitization and its potential impact on the limbic system would be important an important route and may potentially delineate the relationships among FMS symptoms (e.g., mood or mental health disorders, such as anxiety and depression, and cognitive or memory difficulties). Also, neuroimmune mechanisms are another promising research avenue, especially regarding physical trauma; major infection and autoimmune disorders. Identifying the mechanisms of FMS etiology would help with creating clinical lab signs of FMS; the lack of such measures being a major source of negative biases of providers toward FMS. Third, musculoskeletal pain, depression, and reduced quality of life are symptoms associated with mild traumatic brain injury (TBI); within the current war, TBI has been experienced at significant rates (e.g., 22% or more) (Okie, 2005). It is important to consider the possible role that war may play in the etiology of FMS symptoms, as preventative measures could potentially be identified. Finally, it may be relevant to study the extent (e.g., mild, moderate, or severe) to which personnel may experience particular diagnoses of interest, as this may help to highlight the diagnoses' relationships with FMS and PTSD. In closing, it is hoped that this study aided in characterizing FMS within a military cohort and clarified changes that could potentially be made on the clinical side by providers that may allow for more correct representations of FMS and PTSD diagnoses within military populations. This study may help in identifying potential future research directions regarding FMS within the military that may lead to further

knowledge and treatment options for FMS and prevent increased rates of FMS development within the general and military populations.

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