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## Behavioral Symptom Clusters, Inflammation, and Quality of Life in Chronic Low Back Pain Patients

Anitha Saravanan

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LOYOLA UNIVERSITY CHICAGO

BEHAVIORAL SYMPTOM CLUSTERS, INFLAMMATION AND QUALITY OF LIFE IN  
CHRONIC LOW BACK PAIN

A DISSERTATION SUBMITTED TO  
THE FACULTY OF THE GRADUATE SCHOOL  
IN CANDIDACY FOR THE DEGREE OF  
DOCTOR OF PHILOSOPHY

PROGRAM IN NURSING

BY

ANITHA SARAVANAN

CHICAGO, IL

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*Ad Majorem Dei Gloriam!*

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Once you start working on something, don't be afraid of failure and abandon it.  
People who work sincerely are the happiest.

– Chanakya

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## ABSTRACT

Chronic low back pain (CLBP) is a prevalent condition, often involving an inflammatory process. Those with CLBP frequently experience behavioral symptoms, including depressed mood, fatigue, and sleep disturbance, which may exacerbate pain and reduce quality of life (QOL). The purpose of this study was to identify behavioral symptom clusters (depressive mood, fatigue, poor sleep) in individuals with CLBP, and to determine whether there are differences in pain, QOL and inflammation (plasma IL-6) based on cluster membership. CLBP patients (N=69; age = 56±13 years) completed measures of pain, depressive mood, fatigue, sleep, and QOL. Blood was obtained for IL-6 measurement. Latent class analysis revealed a two-class model. Participants in Class 1 characterized by High Behavioral Symptoms (HBS) had more depressive mood, fatigue, and sleep disturbance (including less sleep per night) compared to participants in Class 2 characterized by Low Behavioral Symptoms (LBS). Univariate general linear models revealed HBS reported worse QOL and pain interference than those in LBS. Pain severity did not significantly differ between the classes. Exploratory analysis suggested this was due to a moderating effect of IL-6 on pain severity. Levels of IL-6 (controlling for BMI) were trending to significantly greater in HBS, compared to LBS, with higher levels of IL-6 correlating with greater pain severity and more sleep disturbance. Further, logistic regression revealed higher levels of IL-6 predicted HBS membership. In conclusion, behavioral symptoms cluster in individuals with CLBP and worsen QOL. Inflammation contributes to the complex relationship between behavioral symptoms and pain severity. Clinical recognition of behavioral symptom

clusters can foster more comprehensive pain assessment and tailored interventions for CLBP patients.

## CHAPTER ONE

### STATEMENT OF THE PROBLEM

Pain is a complex phenomenon and is listed as the chief complaint of more than 60% of all primary care patients and is the number one reason patients consult a healthcare provider in the United States (Gaskin & Richard, 2011). More than 250 million Americans and nearly 10% of the world's population are affected by chronic pain. As of 2010, at least 100 million adult Americans were estimated to suffer from chronic pain conditions (AAPM, 2010). Most people with chronic pain have multiple pain sites according to Center for Disease Control. The cost of unmanaged pain ranges from \$560 to \$635 billion annually in the United States (Gaskin & Richard, 2011).

Common causes of chronic pain include headache (16.1%), low back pain (28.1%), neck pain (15.1%), knee pain (19.5%), shoulder pain (9.0%) and hip pain (7.1%). In a 2006 survey, 59% reported that pain impacts their overall enjoyment of life, with 77% reporting feeling depressed, 70% having trouble concentrating, 79% having low energy levels and 86% having inability to sleep well (AAPM, 2010).

#### **Prevalence of Chronic Low Back Pain (CLBP)**

An epidemiological review reported that 55% of adults in the United States had CLBP extending beyond one year (Lawrence et al 2008). It is a leading cause of disability world-wide and CLBP management is only moderately effective (Murray et al., 2013). CLBP is one of the highly prevalent and expensive musculoskeletal conditions (Buchbinder et al., 2013; Dagenais et

al, 2008). According to the United State Bone and Joint Initiative, back pain accounts for more than 264 million lost work days in one year—that's two work days for every full-time worker in the country (2018). In specific, CLBP has a lifetime prevalence of 40% and point prevalence (at any point in time) of 20% (Hoy et al., 2012). Freburger et al (2009) administered a cross sectional survey to investigate the prevalence of CLBP in Northern California over a 14-year period (1992-2006). Of the 4437 households that were contacted, CLBP (that limited daily activities) increased significantly over the 14-year interval from 3.9% in 1992 to 10.2% in 2006. This increase occurred across all age groups, both genders, and black and white races. The proportion of subjects who sought healthcare for CLBP had also increased from 73% to 84% over the 14 year interval (Freburger et al., 2009).

CLBP patients suffer high economic burden and comorbidity (Gore et al, 2012). Direct cost includes health care resources (Physician visits), pharmacological, non-pharmacological and invasive therapies (Luo et al, 2004). In the United States, the economic burden including direct and indirect costs range from \$84% billion to \$624.8 billion and out of this, lost work productivity is the key contributor of indirect costs (\$7.4 to \$28 million) (Dagenais et al, 2008). Moreover, CLBP is associated with psychological symptoms (i.e., anxiety & depression), and these symptoms complicate management (Manchikanit, L et al. 2009). CLBP patients have greater burden of comorbidity including depression, anxiety and frequency of musculoskeletal and neuropathic pain compared to non –CLBP controls (Gore et al, 2012).

### **Definition of CLBP**

CLBP for this study is defined based on the recommendations by the Research Task Force (RTF). According to the RTF, CLBP is defined as pain that exists in the space between the



lower posterior margin of the posterior rib cage and the horizontal gluteal fold. Additionally, the pain had existed beyond three months and for at least half days in the past six months.

Recommendations by the RTF also include asking two questions to define chronicity. (1) “How long has back pain has been an ongoing problem for you?” (2) “How often has low-back pain been an ongoing problem for you over the past 6 months?” (Deyo et al., 2015).

### **Scope of the CLBP Problem**

CLBP can cause physical, emotional, and psychosocial problems that impact all aspects of daily living. When patients perceive that their contribution to themselves, and their families and community are diminished, there can be additional stress and depressed mood that can further intensify their pain levels. Additionally, loss of financial status, change in or loss of employment or other losses due to CLBP can also increase risk for depressed mood and sleep disturbances, thereby affecting quality of life. Few resources are available to address the multitude of psychosocial problems and life challenges faced by CLBP patients.

Findings from studies show that when physical symptoms increase, psychological symptoms also increase; with a correlation of 0.5 between physical symptom checklists and psychological distress scales (Watson & Pennebaker, 1989). Further, regardless of symptoms with or without a diagnosed cause, patients who reported a greater number of physical symptoms, also reported greater anxiety or depression and vice versa (Kroenke et al., 1994).

There are limited pharmacological and non-pharmacological interventions currently available to address the complex combination of symptoms experienced by CLBP patients. For instance, if a patient complains of CLBP and sleep disturbances, it is not unusual for practitioners to prescribe analgesics that might also have some benefits for improving sleep

quality. The anticonvulsants (Pregabalin) and SNRI (Duloxetine) classes of drugs have shown to be effective in improving sleep and reducing pain in neuropathic pain (Sabatowski et al., 2004 & Boyle et al., 2012). These medications provide symptom relief but not all patients benefit from pharmacological interventions. Further opioids are used widely to manage chronic pain; yet, increasingly opioid use is associated with serious health risks. Although there are no placebo-controlled randomized clinical trials to support use of long-term opioid therapy for chronic non-cancer pain (Noble, 2008; Eriksen et al., 2006 & Portenoy et al., 2007, the volume of prescribed opioids in the United States has increased to 600% from 1997 to 2007 (CDC, 2012). Several studies have identified the potentials risks that can affect individuals, patients, families and communities at large. In the year 2012, health care providers wrote 259 million prescriptions for painkillers, enough for every adult American to have a bottle of pills per the National Vital Statistics System Mortality Data (CDC, 2012).

### **Scope of Behavioral Symptoms**

#### **Depressive Mood in CLBP**

Depression coexists with chronic pain (Krishnan et al., 1985) and is estimated to cost \$83 billion annually in the United States (Greenberg et al., 2003). Some studies show a 30% to 60% co-occurrence rate of pain and depression (Baer, 2003). Others show as much as 31% to 100% (Miller & Cano, 2009). Meta-analysis has confirmed that depression is a consequence of chronic pain and not a predisposing factor (Dworkin & Gitlin, 1991). Further, studies have also confirmed that anti-depressants act in chronic pain through analgesic effect rather than through effect to improve undiagnosed depression (Blackburn-Munro, 2001).

Although depression is known to accompany chronic pain, the nature and extent of the relationships between these symptoms is still unclear. Banks and Kerns (1996) argue that depression appears to be highest among chronic pain patients as compared to other chronic medical conditions. Findings from current studies suggest that there is a bidirectional relationship between the chronic pain and depression, but there is lack of evidence on the effect of intensity and/or severity of one symptom on the other. Additionally, there is lack of conclusive evidence on the predisposition of other conditions that might be a risk for developing CLBP. Because symptoms of CLBP and depressive mood present challenges in symptom management, and in order to help clinicians to identify and address the psychological distress symptoms, it is essential to clarify the relationship between these two symptoms.

### **Sleep Disturbances in CLBP**

The impact of CBP on sleep disturbances is recognized worldwide. Sleep disturbance in CLBP patients is reported to affect about 50–60% of individuals (Martin, R et al., 2006; Alaadi, SM et al. 2012); but others report upwards of 88% of patients with CLBP with sleep disturbance (Smith et al, 2000 and Pilowski et al, 1985). Conversely, more than 40% of patients with insomnia also report chronic pain and insomnia has been independently linked to significant decrease in quality of life (Zammit et al, 1999; Skevengton et al; 2001; Smith et al; 2000).

In combination, CLBP and sleep disturbance can cause devastating effects on the well-being of patients and their families. For example, sleep disturbance is known to increase the severity and intensity of CLBP, and vice versa (i.e., the relationship is reciprocal) (Moldofsky, 1975; 1976). There is lack of evidence, however, to show the extent of the effect of sleep disturbance on pain intensity, quality, duration and severity in CLBP patients. There is also a

lack of evidence on the extent of the effect of CLBP on specific components of sleep, in particular the sleep latency, total sleep time and sleep efficiency. Further, there are limitations in the measurement of sleep, with some studies using subjective and others using objective measures of sleep in CLBP. Moreover, there is lack of evidence on the mechanisms underlying the relation between these disorders.

### **Fatigue in CLBP**

Fatigue is a subjective experience, which includes physical and psychological attributes (Aaronson et al., 1999). It is defined as tiredness that is extreme and persistent; exhaustion; or weakness that can be either mental or physical or a combination of both (Dittner et al., 2004). When a symptom of fatigue exists for a long duration (more than six months) without a known cause, it is classified as chronic fatigue (Piper, 1989). It is estimated that about 55% of persons with chronic pain may experience fatigue but this is the symptom that often receives the least attention in clinical practice (Mota & Pimenta, 2006). Studies are focusing on not only identifying the relationship between types of pain (musculoskeletal pain versus neuropathic pain) and fatigue, and location of pain and fatigue, but also relationships among fatigue, pain, depression and sleep disturbances (Lentz et al., 1999; Kwekkebom et al., 2010; Starkweather et al., 2013 & Jaremka et al., 2014).

### **Anxiety in CLBP**

Previous research in CLBP and behavioral symptoms has primarily been on depression, but recent findings emphasize the importance of anxiety in this population (Reme et al., 2011; Newcomer et al., 2010 & Moix et al., 2011). Reme et al., 2010 studied the prevalence of psychiatric disorders in 565 patients and assessed with the Mini-International Neuropsychiatric

Interview (MINI), a short structured diagnostic interview for DSM-IV and ICD-10 psychiatric disorders. The prevalence of psychiatric disorders was 31% and the most common were somatoform disorders (18%), anxiety disorders (12%) and major depressive disorders (4%). Based on this, the researchers recommended screening CLBP patients for psychiatric comorbidity in secondary care due to the serious consequences for prognosis, outcome and health care utilization.

### **Role of Inflammation as a Potential Common Pathway Linking Pain and Depressive Mood**

Findings from studies demonstrate that depression may increase vulnerability to pain and increase circulating levels of inflammatory markers, such as IL-6. For example, higher IL-6 levels have been linked with both greater pain and greater chronic medical comorbidity in patients with greater depressive symptoms (Poleshuck et al., 2013). Several mechanisms underlie the coexistence of pain and depression due to inflammation. They include direct effects of proinflammatory cytokines, increased levels of brain extracellular glutamate, and the switching of GABA neurotransmission from inhibition to excitation (Jaremka et al., 2014). Understanding neuro-immune mechanisms that underlie depression and pain comorbidity may result in interventions that can treat both conditions simultaneously with more than just analgesics and antidepressants (Walker et al., 2014). Earlier studies in the past few decades had focused on understanding the chronic pain mechanisms in relation to processes of hyperalgesia. Now, it is having been recognized that inflammatory mediators can influence both inflammatory pain and nerve related pain caused by damage to peripheral nerves or to the CNS (Jaremka et al., 2014).

### **Symptom Clusters in Various Populations**

The study of symptoms clusters has been limited to certain patient populations. For example, in cancer patients, an extensive literature demonstrates the occurrence of symptom clusters in a variety of cancer types (Kwekkeboom et al., 2010). However, most studies have focused predominately in lung and breast cancer populations (Liu et al., 2009; Lengacher et al., 2012; Ho et al., 2015). The identified clusters have been grouped into either a general category or specific categories. General category symptom clusters include pain, fatigue, disturbed sleep, shortness of breath, drowsiness, dry mouth, difficulty remembering, and numbness or tingling (Ho et al., 2015; Lengacher et al., 2012; Kwekkeboom et al., 2010)). Whereas, gastrointestinal symptom clusters include nausea and vomiting and clusters under mood problems included anxiety and depression (Kim et al., 2005; Liu et al., 2009; Miakowski & Dodd, 2004).

There is also an extensive literature on symptom clusters in heart failure patients. Those studies identify a correlation between depression and fatigue, depression and anxiety, depression and sleep, depression and pain, anxiety and fatigue, and dyspnea and fatigue (Yu et al., 2016; Moser et al., 2014; Jurgens et al., 2009). Most researchers' grouped symptoms in clusters of two or three based on physical distress, emotional/cognitive distress, and discomfort (Herr et al., 2014; Kabban et al., 2015). A cluster placed under physical symptoms included fatigue, pain, drowsiness, nausea and reduced appetite. Emotional/ cognitive symptom clusters have been identified as anxiety, and depression.

It is expected that symptom clusters will exist in other chronic conditions; however, there is not adequate investigation of symptom clusters across various conditions. It is possible that greater understanding of the presence and type of symptom clusters that exist in other patients

with non-cancer chronic pain can lead to targeted interventions addressing more than one symptom.

### **Summary**

CLBP is a significant health issue that negatively impacts all aspects of quality of life. It is difficult to assess, diagnose and manage CLBP; in part, due to the complexity of other accompanying symptoms (fatigue, sleep disturbances, anxiety and depression) that co-occur with pain. Further, there is lack of conclusive evidence as to whether some symptoms relate to, or cluster with, each other more than other symptoms. There is also deficit in knowledge on the role of inflammation in the etiology and persistence of these symptoms.

Despite the urgent need to identify the symptoms that might affect health outcomes, there has been little inquiry on the symptoms that might coexist with CLBP and thereby affect health outcomes. In order to be able to understand the complexities of CLBP and symptoms that coexist with CLBP, it is important to determine if symptoms appear in clusters in CLBP and further examine the underlying inflammatory process. Identification of phenotypic differences based on behavioral symptom clusters might explain some of the variance in pain symptoms and treatment response. Such knowledge can be used to tailor an individualized management plan for patients in the future.

### **Significance**

CLBP is one of the most highly prevalent and expensive musculoskeletal conditions (Woolf & Pledger, 2003) (Dagenais et al., 2008). While experts estimate 80% of the population will experience back pain at some time in their lives (Rubin, 2007), an epidemiological review reported that 55% of adults in the United States had CLBP extending beyond one year

(Lawrence et al 2008). CLBP patients incur increased economic burden and comorbidity (Gore et al, 2012). In the United States, the economic burden including direct and indirect costs range from \$84 billion to \$624.8 billion and out of this, lost work productivity is the key contributor of indirect costs (\$7.4 to \$28 million) (Dagenais et al., 2008). Although CLBP is a leading cause of disability world-wide, clinical management of CLBP is only moderately effective (Henschke et al., 2010).

This project will evaluate behavioral symptoms as a cluster (both presence and intensity) to determine the extent to which identified symptom clusters influence pain and quality of life. Additionally, levels of circulating proinflammatory cytokines will be evaluated to determine the extent to which inflammation may serve as a common mechanism underlying the associations among behavioral symptoms and pain in CLBP patients. Behavioral symptoms (depressive mood, sleep disturbance, anxiety and fatigue) commonly accompany CLBP and are a significant problem for both patients and caregivers because they assume responsibility to manage these symptoms, in addition to dealing with their pain. The literature demonstrates that chronic behavioral symptoms negatively impact patient outcomes, including mental and physical functional status and overall quality of life (Borsbo et al., 2010; Gormsen et al., 2010; Kroenke et al., 2013; Sahin et al., 2017). For the most part, the prevalence and intensity of behavioral symptoms are not routinely assessed, nor are they adequately considered as part of the pain management plan. Also, research on behavioral symptoms typically takes a reductionist approach, focusing on one symptom; while ignoring the possibility that these symptoms co-occur in clusters, interact with each other, and often intensify each other.



Although research using a focused approach on individual behavior symptoms in CLBP has increased knowledge of the prevalence of fatigue, sleep disturbance, and depressive mood in CLBP patients, and has also added insight as to the importance of assessing these symptoms, a new approach is needed to meet the challenges in managing multiple symptoms in this patient population. Most clinicians would agree that symptoms do not present in isolation; rather multiple symptoms are experienced simultaneously. Such co-occurrence of symptoms or symptom clusters has been investigated in cancer populations, and the findings have led to advances in symptom management for cancer care (Garland et al., 2014; Kwekkeboom et al., 2010; Lengacher et al., 2012; Liu et al., 2009; Miaskowski et al., 2004). Yet in CLBP patients, few, if any, studies have investigated behavioral symptoms as a cluster, including how such clusters influence the pain experience and quality of life of these patients. Given this, there is a critical need to identify which symptoms cluster together and how these symptoms affect the pain experience and overall quality of life in CLBP patients. Such an approach is consistent with the holistic view of nursing, and with the National Institute of Nursing's emphasis on symptom management (The NINR Strategic Plan, 2016).

Ultimately, application of knowledge of symptom clusters in CLBP patients' can lead to improved ways of patient assessment and management. Furthermore, this project is significant in that it will examine inflammatory mechanisms posited to underlie behavioral symptom clusters in patients with CLBP. Given that inflammatory processes are implicated in certain types of back pain, and that inflammation is associated with each of the behavioral symptoms to be addressed (i.e., depressive mood, sleep disturbance, and fatigue); it is possible that increased circulating levels of proinflammatory cytokines may be a common underlying mechanistic

pathway linking these symptoms to pain. Understanding potential inflammatory mechanisms in CLBP pain has implications for the development of new approaches to manage pain. This concept is supported by work in other patient populations, which demonstrate that both pharmacologic and behavioral approaches reduce levels of proinflammatory cytokines (Bower et al., 2016; Gallegos et al., 2015; Janusek et al., 2006; Janusek et al., 2008; Reich et al., 2017; Rosenkranz et al., 2013).

### **Clinical Implications**

Current practice predominately involves assessing and managing a patient with CLBP by focusing on a single symptom; that is, chronic pain. The results from this project will allow for an appraisal of CLBP not as a unitary symptom, but as a constellation of several interacting symptoms with bidirectional linkages to the pain experience. Further, viewing symptoms as clusters in CLBP can guide the development of more comprehensive interventions that target more than pain per se, but other symptoms that intensify and perpetuate pain. In the end, the findings from the proposed study will identify the extent to which clusters of symptoms impact the pain experience and quality of life in CLBP and, secondly the extent to which inflammatory processes underlie the complex relationships among pain, depressive mood, and poor sleep.

It is important to examine the various pain profiles that include behavioral symptoms. Understanding differences in pain profiles and their relationship to other symptoms can widen the scope of managing pain to be more holistic, which is the essence of nursing. Moreover, knowledge of symptom clusters in CLBP can help identify if there is a sentinel symptom or groups of symptoms that can be classified as sentinel symptom cluster. Evidence for the existence of symptom clusters can help shape new ways to identify and manage symptom

clusters and to prevent the vicious cycle among these symptoms that amplifies pain and erodes quality of life. For instance, this may include more comprehensive assessment tools that allow mapping of symptom clusters based on type, quality and intensity; which can inform the clinician to more efficiently and effectively manage the symptoms in those with CLBP.

### **Implications for Nursing**

Currently, when a CLBP patient is seen in the health care setting, pharmacological approaches and nonpharmacological approaches, including pain rehabilitation programs are recommended. However, these approaches have not benefited CLBP patients as expected. As a result, the pain and suffering caused by this condition continues to challenge not only patients but the health care provider as well. The metaparadigm of nursing consists of health, person and environment and we nurse are in the forefront when it comes to addressing pain and suffering in individuals. The American Nurses Association's (ANA) (2004) scope and standards of practice requires that nurses possess and maintain adequate knowledge and competency in nursing practice that obligates knowledge about pain management. Further, the Nursing Social Policy statement (2010) and the social responsibility and the Code of Ethics statement (2001) indicate that nurses have a moral obligation to advocate on behalf of the patient in managing pain and other distressing symptoms. Hence it is essential for nursing to understand the implications of CLBP and its impact on patients and the society. Historically, CLBP has caused loss of health, decreased functional status, disability, loss of job status and financial losses.

Although there is evidence on the effectiveness of the non-pharmacological interventions, not all patients have access to these modalities. An innovative approach to address the challenges of symptom management in CLBP might be to look at the symptom clusters, such as the

approach used in cancer patients. In cancer patients, significant advances have been made in addressing the interventions that help to improve the three cancer-related symptoms (pain, fatigue and sleep disturbance).

### **Conceptual Framework**

The central hypothesis for the proposed study is that behavioral symptoms will exist in clusters to influence the pain experience and quality of life in adults with CLBP. It is further hypothesized that increased inflammation serves as a common pathway linking behavioral symptom clusters with pain. Individuals with CLBP who have certain clusters will experience less pain, have lower levels of circulating proinflammatory cytokines, and report better quality of life, than other clusters.

Several theories have been developed to conceptualize the symptom experience in humans (Lenz and Pugh 2008; Humphreys et al. 2008; Kim et al. 2005; Goodell and Nail 2005; Parker et al. 2005; Armstrong 2003; Haworth and Dluhy 2001; Dodd et al. 2001a; Lenz et al. 1997; McClement et al. 1997; Teel et al. 1997; Lenz et al. 1995; McDaniel and Rhodes 1995; Larson et al. 1994; Rhodes and Watson 1987). These theories have focused upon the complexity of the symptom experience itself, how the symptoms manifest, and the outcome of symptoms. Some theories have attempted to accommodate the concept of symptom clusters: The Theory of Unpleasant Symptoms (Lenz and Pugh 2008), The Theory of Symptom Management (Humphreys et al. 2008) and The Symptoms Experience Model (Armstrong 2003). However none of the theories have focused on conceptualizing symptom clusters in those with chronic pain. Some challenges that arise in developing theories to explain symptom clusters could be attributed to: 1) the study of symptom clusters is relatively new, 2) the subjective nature of the

symptoms itself, and 3) the complexity in measuring the symptom experiences from an individual's perspective. Hence, this study will be guided by the Theory of Unpleasant Symptoms (TOUS), as well as a conceptual model that explicates the relationships among the study variables. See **Figure 1**.

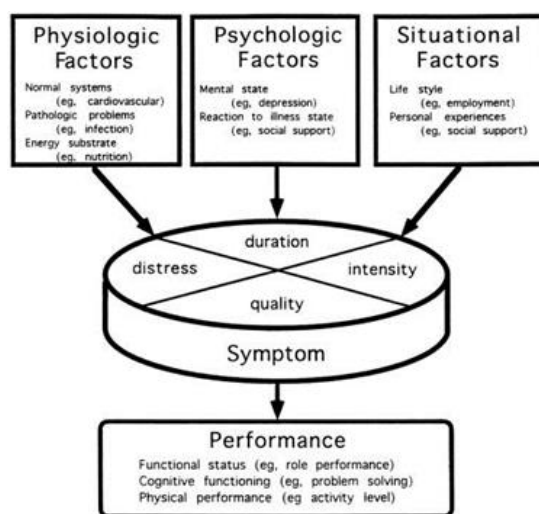
### **Theory of Unpleasant Symptoms (TOUS)**

TOUS, is a middle range theory, developed by Lenz and colleagues, and will provide a theoretical foundation for the proposed study. The TOUS allows for a different perspective of viewing symptoms. It provides researchers with a newer approach to view symptoms as clusters and to understand how the symptoms and influencing factors can intensify each other and impact an individual's functional outcomes and quality of life. The TOUS has been used as framework to guide studies of symptoms clusters in patients with cancer and in cancer survivors (Chen & Tseng, 2005; Fox & Lyon, 2007; Myer, 2009; Lee, 2005); to predict physical activity based on symptom cluster in multiple sclerosis (Motl & McAuley, 2009); to measure outcomes in post-operative tonsillectomy pediatric patients (Huth & Broome, 2007); and to diagnose CHF symptoms as a group (Jurgens et al., 2009). Further, studies have been conducted to identify the cluster of symptoms and hence accordingly manage treatment options in practice, such as has been accomplished with Alzheimer's patients (Hutchinson & Wilson, 1998).

Initially, Lenz and colleagues studied three single concepts (fatigue during postpartum, fatigue during intrapartum, dyspnea in COPD and asthma) in different clinical populations and integrated their findings to identify commonalities across phases and concepts. This work formed the basis for the TOUS theory (Lenz et al, 1995). The two activities a) generating frame for the study of fatigue during phases of child bearing and b) identifying similarities between the

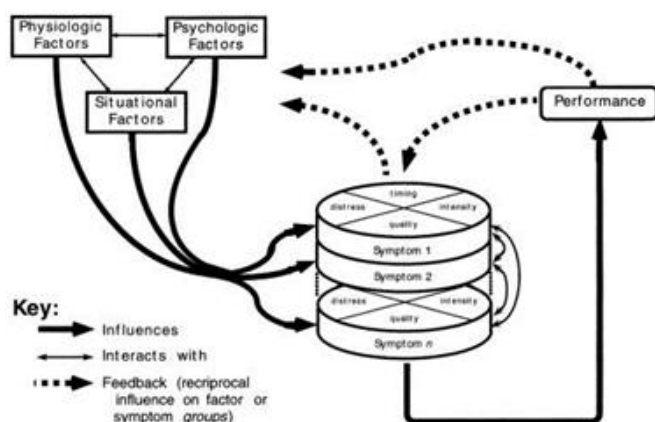
concepts of fatigue and dyspnea provided the basis of the TOUS theory, as depicted in Figure 1. Later, Lenz et al (1997) studied the potential for interaction among the influencing factors and generated a new model of the theory as shown in Figure 2. To facilitate identification of similarities in their conceptualizations of two of the three symptoms (dyspnea and fatigue) they identified similarities as: a) both are subjective symptoms, b) both can be acute or chronic, c) both occur due to anxiety or depression, d) both can occur under normal or illness conditions, and e) both can affect function including activities of daily living, and social interaction (Lenz et al, 1995).

Figure 1. Original illustration of the TOUS



*Note.* Adapted from “The middle-range theory of unpleasant symptoms: An update,” by Lenz, E. R., Pugh, L. C., Milligan, R. A., Gift, A., & Suppe, F., 1997, *Advances in Nursing Science*, 19(3), 14-27. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9055027>

Figure 2. The updated TOUS.

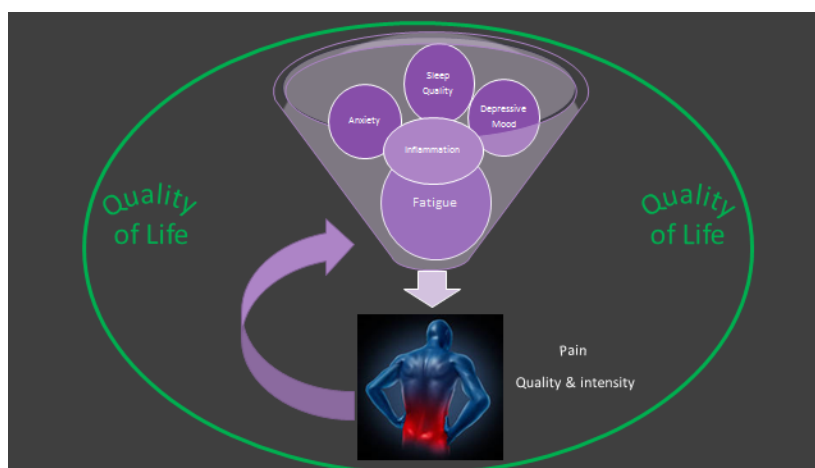


*Note.* Adapted from “The middle-range theory of unpleasant symptoms: An update,” by Lenz, E. R., Pugh, L. C., Milligan, R. A., Gift, A., & Suppe, F., 1997, *Advances in Nursing Science*, 19(3), 14-27. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9055027>

For this study, a framework that integrates existentialism and the TOUS paradigm will be used to explore symptom clusters in adult CLBP patients. Within the TOUS, symptoms are viewed as occurring in concurrence, affecting ones’ normal functioning and resulting in a multiplying effect based on the physiological, psychological and situational factors (Lenz, et al., 1997). The TOUS incorporates the major concepts of symptoms and performance outcomes, along with the interrelated categories of psychological, physiological, and situational factors and provide a framework for the metaparadigms of the TOUS (Lenz & Pugh, 2003). Soren Kierkegaard in his words on existentialism raised searching questions of the self; since all aspects of life and existence are subjective and ambiguous (Audi, 1999). His quote, “The greatest hazard of all, losing one’s self can occur very quietly in the world, as if it were nothing at all. No other loss can occur so quietly: any other loss- an arm, a leg, five dollars, a wife etc.- is sure to be noticed” (Kierkegaard, 2010). This philosophy can be aptly applied to the patient with CLBP. The sufferings faced by CLBP include grief, pain and psychological distress can challenge the

existence of the self. In the clinical populations that include symptoms of sleep disorders, chronic pain and psychological disorders, there are fewer interventions to alleviate human suffering. It is essential for nursing to focus on issues that affect the welfare of CLBP patients in improving individual and community health.

Figure 3. Conceptual Model for proposed study.



The Conceptual Model for this study is illustrated in Figure 3. The model proposes interactive relationships among depressive mood, sleep quality, and fatigue; which through inflammation impacts the pain experience and quality of life of the person with CLBP. The model explicates the potential linkages and clusters of different combination of symptoms among sleep disturbance, depressive mood, anxiety, fatigue, and inflammation in the person with CLBP; which ultimately impacts the person's pain experience and quality of life. It is hypothesized that behavioral symptoms (anxiety, fatigue, poor sleep quality, and depressive mood) exist in individuals with CLBP as clusters; which synergistically contribute to worse pain and poorer quality of life. This view is consistent with TOUS, which theorizes that symptoms occur in concurrence, affecting a person's normal functioning and resulting in a multiplying effect on outcomes (i.e., physiological, psychological and situational factors (Lenz et al., 1997)).



Moreover, inflammation is proposed as a common pathway that links symptoms with pain outcomes. This is based upon the literature that finds CLBP to be associated with elevated levels of proinflammatory cytokines (Risbud & Shapiro, 2014). A Systematic review of articles done to assess the magnitude and direction of depression with inflammatory markers published for the period between January 1967 and January 2008 identified that the inflammatory markers CRP, IL-6, IL-1, and IL-1ra were positively associated with depression (Howren et al., 2009). Thus, inflammation may serve as a common biological pathway that links behavioral symptoms to the pain experienced by those with CLBP. Lastly, the model posits that the relationship between behavioral symptom clusters and pain is bidirectional.

### **Rationale for the Conceptual Model**

Chronic low back pain (CLBP) is a significant and common health issue and is a leading cause of disability worldwide (Buchbinder et al., 2013). The reported estimate of lifetime prevalence of CLBP is 40%, and point prevalence (at any point in time) is 20% (Hoy, DG et al., 2012). Management of CLBP is only moderately effective (Hoy et al., 2014; Henschke, et al, 2010). Moreover, individuals with CLBP experience burdensome behavioral symptoms (i.e., depression, fatigue, and poor sleep quality); all of which complicate clinical management (Manchikanit, L et al. 2009).

### **Depression**

Numerous studies suggest that depression worsens both the severity of pain and disability caused by chronic LBP (Carley et al, 2015). A large survey of community dwelling adults found that mild to severe depressive symptoms increased the odds of disabling LBP over a period of two years by 30–60%. Similarly, baseline disabling low back pain ranging from a little of the

time to all of the time increased the odds of depressive symptoms by 27.9–84.2%, respectively. Moreover, there is also a bidirectional relationship between depressive mood and LBP intensity; and inflammation may mediate such a relationship. For example, higher IL-6 levels have been linked with both greater pain and greater chronic medical comorbidity in patients with greater depressive symptoms (Poleshuck et al., 2013). This was confirmed in a systematic review which concluded that inflammatory markers (CRP, IL-6, IL-1, and IL-1ra) are positively associated with depression. Moreover, a dose-response relationship between depression and inflammatory markers was identified, which was consistent with three causal pathways: depression to inflammation, inflammation to depression, and bidirectional relationships (Howren et al., 2009).

### **Sleep Disturbance**

It is reported that 50–60% of LBP patients report sleep disturbance (Martin et al., 2006; Alaadi et al. 2012). CLBP patients report increased duration to sleep onset, reduced total sleep time, and lower sleep efficiency (Kelly et al., 2011). Moreover, sleep disturbance is associated with psychological distress, physical disability (Van de Water et al., 2011), fatigue and day-time sleepiness (McCracken et al., 2002), more severe pain (Alaadi et al., 2012), and more hospitalization for their back pain than those without sleep problems (Kaila-Kangas et al., 2006). Similar to the relationship between depression and pain, the literature suggests a bidirectional relationship between disturbed sleep and pain intensity (i.e., pain may lead to sleep disturbance & poor sleep may cause or exacerbate the pain) (O'Brien et al., 2011). This is confirmed in longitudinal studies which have identified a bidirectional relationship between sleep and pain, such that a night of poor sleep quality was followed by a day with more severe pain; which worsened sleep quality during the subsequent night (Alaadi et al., 2014 ; Jaussent et al., 2017).

## **Anxiety**

The two most common psychological conditions are anxiety and depression (Anseau et al., 2004). In chronic pain, the pain–depression–anxiety relationship is well established. Most research has studied the comorbidity of pain with depression than with anxiety (Kroenke et al., 2013). Anxiety is as prevalent as depression and adversely affects patients functional ability and health care costs (Stein et al., 2015). anxiety is also another key behavioral symptoms for which there is substantial evidence that there is a bidirectional relationship between CLBP and anxiety.

## **Fatigue**

Fatigue is prevalent and problematic for individuals with CLBP (Fishbain et al., 2004; Starkweather, 2013; Snekkevik et al., 2014), and fatigue may exacerbate symptoms and functional outcomes. For example, CLBP patients found who have substantial fatigue have more pain and depressive symptoms and are at risk for greater disability (Snekkevik et al., 2014). Fatigue is related to greater inflammation in those with back pain. Individuals with persistent radiculopathy who reported moderate to high fatigue levels, also reported greater psychological distress, depressive symptoms and had higher circulating levels of IL-6 and sIL-6R, compared to those with low levels of fatigue (Starkweather, 2013). These findings suggest that inflammatory cytokines may influence the manifestation of fatigue and other behavioral symptoms (distress and depressive symptoms) in individuals with back pain.

## **Inflammation and CLBP**

Chronic LBP is strongly associated with disc degeneration and degenerated discs exhibit high tissue levels of proinflammatory cytokines (i.e., inflammation within the disc microenvironment) (Risbud & Shapiro, 2014). Recently, CLBP was shown to be associated with

persistent elevations of proinflammatory cytokines in the serum (Pedersen et al., 2015). That study prospectively evaluated serum levels of the proinflammatory interleukins (IL-6 and IL-8) in patients with lumbar radicular pain due to disc herniation. The findings revealed that chronic lumbar radicular pain was positively associated with a persistent increase of both IL-6 and IL-8.

In summary, behavioral symptoms (depression, poor sleep, and fatigue) are associated with greater inflammation (Gorth et al., 2015), and worse pain in CLBP (Pegram et al., 2017). It is possible that behavioral symptoms may establish and maintain their co-occurrence with pain by increasing inflammation. Moreover, these symptoms may occur in clusters; however, the existence of behavioral symptom clusters in CLBP, and whether they alter the experience of pain and quality of life is unexplored. Such an understanding is significant, as behavioral symptoms adversely impact the clinical management of CLBP. These symptoms not only intensify the pain experience, but are likely to hinder exercise performance (part of pain management) and consequently lead to poorer treatment outcomes. In addition, symptoms like poor sleep and depressed mood may contribute to progression from acute to chronic pain. Thus, increasing knowledge of the relationship between sleep disturbance, depressive mood and inflammation in patients with LBP is an important clinical and research question.

Thus, the present study will use a cross sectional design to identify the presence of symptom clusters of fatigue, sleep disturbance, and depressive mood, in CLBP; and to determine the extent to which identified clusters predict the pain experience and quality of life. Further, this study will also evaluate the role of proinflammatory cytokines as a common pathway linking behavioral symptoms to pain.

## CHAPTER TWO

### REVIEW OF THE LITERATURE

#### **Symptoms and Symptom Clusters**

The meaning of the word “symptom” has evolved over the past few centuries. Per the Oxford Dictionary, in the Middle Ages until the mid-19<sup>th</sup> century, symptoms were considered as physical or mental phenomena that originated from or accompanied an illness. By the end of the 19<sup>th</sup> century, the word had taken on different meanings. Symptoms were considered subjective and different from signs, which were considered objective and sensed by the observers (Oxford Dictionary, 1992). According to Komaroff, contemporary medical science in the 20<sup>th</sup> century has placed great emphasis on identifying the objective experience using objective pathology which has transformed the ability to cure diseases (Komaroff et al., 2001). This transition has benefited patients and providers but has come with a price. Sharpe and Carson (2001) and Aronowitz et al., 2001 contend that there is less emphasis placed on taking a history to assess symptoms and there is skepticism when objective methods are used.

Nurses will agree that the heart of nursing lies in managing pain and discomfort. This is consistent with the philosophical approach of Florence Nightingale who emphasized that the focus of nursing was to relieve pain and discomfort (Nightingale, 1946). Nurse scientists have more recently focused on symptom management to improve approaches to relieve pain and discomfort in patients. Furthermore, the concept of symptom clusters has gained attention in the past few decades. For example, the National Institute of Nursing Research (NINR) has placed

symptom management and symptom clusters in the top list of goals under the NINR mission and strategic plan.

The concept of symptom cluster is not new to nursing. In oncology nursing, symptom clusters have been extensively investigated as a way to improve symptom management. In order to define symptom cluster, Kim et al., 2005, conducted a concept analysis of symptom clusters and identified them as a stable group of two or more symptoms that are concurrent and related to one another but are not dependent on other symptom clusters. Further, symptom clusters do not necessarily share etiologies (Dodd et al., 2004 & Miaskowski et al., 2004).

Using the Rodgers' evolutionary method of concept analysis, Kim et al., 2005 identified attributes of symptom clusters as relationships of symptoms and relationships of clusters, underlying dimensions, stability, occurrence, and common etiology. They defined symptom clusters as two or more symptoms related to each other and which occur together. Symptom clusters should also have a stronger relationship among symptoms across different clusters. Although symptoms within in cluster might not share the same etiology, they should include both subjective (self – reported) symptoms and objective (observed) signs. They further identified the consequences of symptom clusters to be emotional distress, increased financial burden, poorer health status and interference with activities of daily living (Kim et al., 2005).

Despite the recognition of the potential importance of viewing symptoms as clusters, the complex relationships between symptoms have not been well described in the literature, and the available research on symptom clusters is limited to a few patient populations. While there is need for conceptualization, there is also a need for design, measurement and analysis of the symptom clusters across a variety of patient populations.

## **Symptom Clusters in Cancer**

Symptom clusters have been explored most frequently in cancer populations. Over the past decade, an abundance of literature has provided level-one evidence supporting the value of assessing symptom clusters in cancer patients. These studies can provide direction and depth to future studies investigating symptom clusters in non-cancer patients. It is likely that like what has been learned in cancer patients; symptom cluster analysis in individuals with non-cancer pain will increase understanding of the multi-dimensional nature of pain, as well as predict health outcomes, including quality of life.

In an early review of the literature regarding symptoms in cancer patients, Fan et al (2007) identified seven studies which validated the M.D Anderson Symptom Inventory in three types of cancer (breast, lung and gastrointestinal). Findings, however, did not support common clusters in those with lung and breast cancer. This may relate to disparity in assessment tools, statistical analyses and unique differences based on type of cancer. However, the authors concluded that multiple symptoms affect prognosis, functional status and quality of life in cancer patients. Since this review, several studies have provided new evidence supporting the existence and importance of symptom clusters in cancer patients; and at least three more recent systematic reviews have been published and are described below.

Harrington et al (2010) conducted a systematic review of studies (2000-2008) examining late effects and long-term symptoms grouped as physical limitations, cognitive limitations, depression/anxiety, sleep problems, fatigue, pain, and sexual dysfunctions. The authors concluded that symptom burden in cancer survivorship was consistent in all the four cancers (prostate, breast, gynecological and colorectal) despite different treatment exposure. Also, the

four most common symptoms were depressive symptoms, pain, and fatigue. In another systematic review, Dong et al (2014) examined the composition, consistency and longitudinal stability of symptom clusters in advanced cancer patients. These authors identified 33 studies that used various statistical methods (principal component analysis, exploratory factor analysis, and hierarchical cluster analysis) to analyze symptom clusters. The four symptom clusters identified were: anxiety-depression, nausea-vomiting, nausea-appetite loss, and fatigue-dyspnea-drowsiness-pain. From a methodological perspective, it is important to note that all four statistical methods tended to reveal different symptom clusters. Hence the authors concluded that there was a lack of consistency in identifying symptom clusters and associated variables and recommended using the patient's subjective experience of symptom clusters in future studies.

A recent literature synthesis (Reilly et al., 2013) of symptoms experienced by cancer patients receiving active treatment evaluated 21 multinational studies representing a pooled sample of 4067 cancer patients. Across these studies patients reported severity and prevalence of individual symptoms based on eighteen instruments that included measuring single symptoms, multiple- symptom inventories, from HRQOL or health status measures. Most studies used the MD Anderson Inventory. Forty-seven symptoms were identified, which categorized into 17 groupings. The researchers concluded that a discrete set of symptoms are common across cancer types and may serve as basis for describing a core set of symptoms in cancer.

Since the publication of the above reviews, Ho et al (2015) published findings from a longitudinal study which examined the relationship among depression, fatigue and sleep disturbances in premenopausal breast cancer patients compared to postmenopausal women



across three-time points. T1 (i.e., at least two weeks after breast surgery but prior to beginning CT), T2 (i.e., within one month after completing a three- to six-month CT regimen, or approximately six months after T1 for patients who did not receive CT in Study 1), and T3 (i.e., six to eight months after T2). Results revealed that fatigue, depression and sleep disturbances manifest as a symptom cluster. Additionally, path analysis within and across-symptom paths indicated that all three symptoms correlated within the three-time points. Such a correlation between symptoms is important since it can denote that the symptoms manifest as clusters. Further, it might also help to identify if one symptom precedes another.

In summary, within the cancer literature, studies of symptom clusters have included mixed-cancer samples; however, some studies have focused on specific cancer types (lung and breast predominantly). These studies evaluated symptoms in cancer patients undergoing chemotherapy, as well as cancer survivors who had completed treatment. In general, the findings identified the symptoms that most commonly make up clusters to be pain, fatigue, and disturbed sleep, emotional distress, shortness of breath, drowsiness, dry mouth, sadness, difficulty remembering, numbness or tingling during treatment. It is interesting to note that certainly some of these symptoms associate more with active cancer treatment; thus, it is important to differentiate symptom clusters with respect to timing of treatment. Also, the symptom clusters identified were labeled as general, gastrointestinal or mood problems. Clusters placed within the general category included pain, fatigue, disturbed sleep, shortness of breath, drowsiness, dry mouth, difficulty remembering, and numbness or tingling. Clusters placed under gastrointestinal category mostly included nausea and vomiting and clusters under mood problems included anxiety and depression. The above studies provide evidence for the existence of distinct

symptoms clusters which can be identified, some of which may be common across cancer types and the cancer trajectory. Collectively, these findings can guide testing of interventions to address multiple symptoms across cancer types and across the cancer trajectory.

### **Symptom Clusters in Heart Failure**

Heart failure patients experience anywhere from about two to nine symptoms (Herr et al., 2014). Studies have begun to examine the relationships among heart failure symptoms with the purpose of determining if such examination can inform clinicians to improve management and, thus, benefit these patients' A recent systematic review conducted by Herr et al., addressed the relationships among heart failure symptoms. Out of 1316 studies identified 34 met criteria to be included in the systematic review. Results yielded a correlation at moderate level between depression and fatigue, depression and anxiety, depression and sleep, depression and pain, anxiety and fatigue, and dyspnea and fatigue. The researchers concluded that there is adequate support for the presence of heart failure symptom clusters. They also suggested that studies defining the phenotype of individual heart failure symptoms might benefit this group of patients (Herr et al., 2014).

A cross sectional study was conducted to identify symptom clusters in individuals with heart failure and to identify the relationship between clusters and functional status. That study enrolled a convenience sample of 117 heart failure patients. Symptom clusters were analyzed using factor analysis (principal components method). Additional analysis using regression analysis (a backward stepwise model-building approach) to examine the effects of the symptom clusters; age and co-morbidity on functional limitations and mobility were conducted. Findings

revealed three symptom clusters: sickness behavior, discomfort of illness and gastrointestinal distress (Herr et al., 2015).

In yet another interesting cross-sectional study conducted in three different regions of the world (USA, Asia and Europe), investigators sought to identify and compare symptom clusters in heart failure patients across cultures. Patients with confirmed heart failure (N=720) were classified using New York Heart Failure Association Classification. Cluster analysis used hierarchical cluster approach and Ward's method. Findings revealed a core group of symptoms that formed two clusters: physical capacity symptom cluster and emotional/ cognitive symptom cluster. These symptoms clustered similarly among the cultural groups despite the cultural diversity (Moser et al., 2014).

Yu et al., 2016 conducted a secondary data analysis of a cross sectional study which interviewed 119 advanced HF patients. The purpose of that study was to identify symptom clusters in heart failure patients and their relationship with quality of life. Exploratory factor analysis was used to identify symptom clusters and hierarchical regression analysis was used to identify the relationship with quality of life. After adjusting for age, gender and comorbidities three distinct symptom clusters were identified. The clusters were distress (shortness of breath, anxiety, and depression), decondition (fatigue, drowsiness, nausea, and reduced appetite), and discomfort (pain, and sense of generalized discomfort). Based on these findings the researchers recommended a need to develop palliative care interventions for symptom cluster control for individuals with advanced congestive HF (Yu et al., 2016).

To summarize, more than one investigator found that there is a correlation between depression and fatigue, depression and anxiety, depression and sleep, depression and pain,

anxiety and fatigue, and dyspnea and fatigue in HF patients. Most researchers grouped symptoms in clusters of two or three based on physical distress, emotional/cognitive distress, and discomfort. Clusters placed under physical symptoms include fatigue, pain, drowsiness, nausea and reduced appetite. Emotional/ cognitive symptom clusters have been identified as anxiety, and depression. There appears to be emerging trends to continue to investigate symptom clusters in HF. Collectively these findings provide clear indications that symptom clusters can be identified in HF patients, and that this knowledge has potential to improve symptom management in HF patients

### **Symptom Clusters in Spinal Cord Injury**

Studies on presence of symptom clusters in spinal cord injury (SCI) have gained momentum since the early twenty first century. Researchers noted the presence of certain symptoms more commonly than the others and with more intensity and severity. The most commonly and frequently occurring symptoms in individuals with SCI include chronic pain, spasticity and depression. Many studies in the SCI population have revealed the occurrence of chronic pain and its effect on functional ability and quality of life. A link between chronic pain and depression has also been identified, such that increased pain related to increased depressive symptoms (Barrett et al., 2003; Rintala et al., 1998; Ulrich et al., 2007; Jensen et al., 2007; Widerstrom-Noga, Felix, Cruz-Almeida, & Turk, 2007).

Four studies (Hitzig et al., 2008; Johnson et al., 1998; Noonan et al., 2008) evaluated the symptoms of chronic pain, spasticity and depression in SCI patients. Noonan et al. (2008) enrolled 70 individuals who experienced traumatic central cord syndrome; the purpose was to study the impact of spasticity, neuropathic pain and sexual dysfunction on quality of life and

satisfaction. Findings revealed spasticity to be reported most often (59%), followed by chronic neuropathic pain (39%). Spasticity was not significantly associated with the mental component of general health status measure as compared to the physical component score. In a sample of 216 patients with SCI, Ravenscroft et al (2000) studied the severity and impact of chronic pain in spinal cord injury. Results demonstrated that participants with chronic pain had significant impairment of daily activities. Muscle spasms were reported in 25% of participants which exacerbated pain. Further, pain and depression was reported by 39% of the participants who also identified pain as a contributing cause of depression.

Other studies which examined symptom clusters in SCI individuals, explored the experiences of these individuals with respect to chronic neuropathic pain. Those findings identified physical factors including constipation, infections, spasticity and emotional factors (anxiety, depression and stress) as contributing to worsening of their pain (Henwood & Ellis., 2004). Barrett et al. (2003) studied SCI injury patients admitted to the hospital due to post injury complications. They found that patients with pain had significantly greater levels of psychological distress than patients without pain. A recent meta-analysis found 22.2% of individuals had a diagnosis of depression after spinal cord injury, which is greater than the prevalence of depression in the general medical population (Williams & Murray 2017).

### **Summary**

The review of literature thus far examined symptom clusters in the most commonly studied disease conditions. Many conditions such as myocardial infarction, chronic venous diseases, and certain respiratory conditions are being studied as well, but are beyond the scope of this proposal and will not be considered. However, it is valuable to review the literature and learn

how symptom clusters are being studied in various conditions, as these findings can guide research of symptom clusters in other health conditions. Researchers continue to investigate the existence of symptom clusters and the possible interventions that might benefit individuals who have various symptom clusters in different disease conditions. While symptom clusters seem to a promising approach to relieve pain and suffering in cancer populations, studies are needed to assess the effectiveness of using a symptom cluster approach in non-cancer pain conditions. It is not unusual to for patients in many chronic conditions to have more than a few symptoms. The limited investigation of symptom clusters across disease conditions is likely since the concept of symptom cluster is still relatively new. The next section will review the findings from those studies that have examined the relationships between two or more symptoms in individuals with CLBP.

### **Chronic Pain and Sleep**

Sleep is important for growth, tissue restoration and conservation of energy (Adam & Oswald, 1977; Adam & Oswald, 1983). While various sleep disorders including narcolepsy, insomnia, and sleep apnea, are described in the pain literature, sleep disturbances and insomnia have been most often studied. Insomnia is defined as a sleep disorder in which a person's mental health and ability to function are reduced by the chronic inability to sleep. About 25% of the United States population complain of insomnia (Wittig et al, 1982) and persistent insomnia (i.e., greater than 3 years) is present in nearly 50% of this population (Arnett, 1988). The CDC has identified insufficient sleep as a public health epidemic ([cdc.gov](http://cdc.gov)). Insomnia is associated with diminished psychological well-being, including feelings of depression. Moreover, the co-existence of insomnia with chronic pain makes it more challenging to manage both symptoms.

In contrast to insomnia and sleep deprivation, the term ‘sleep disturbance’ in the chronic pain population is characterized by delayed sleep onset, poor sleep quality, reduced sleep efficiency and duration, increased activity or movement during sleep, fragmentation of sleep architecture and non-restorative sleep (Landis et al, 2004; Lautenbacher et al, 2006). For many healthy individuals, sleep disturbance occurs occasionally, such as when one has trouble falling asleep or going to back to sleep after waking up during the night. It is natural to expect persistent pain will affect sleep, and researchers continue to be intrigued by the relationship between pain and sleep.

There is clear evidence that lack of sleep affects pain in a variety of ways. Early evidence found a clear effect of sleep deprivation on pain perception in animals, but data in humans at this time was inconclusive (Lautenbacher et al., 2006). However, there is now evidence of the hyperalgesia effect of sleep deprivation in both animals and humans (Ancoli, 2006). A recent study using a mouse model, demonstrated that sleep deprivation exacerbated the physiological and behavioral response to musculoskeletal sensitization (Sutton & Opp, 2015). Further studies of experimental sleep deprivation in human subjects demonstrated that sleep deprivation enhances pain (Daya & Bentley, 2010; Smith et al, 2007; Kundermann et al., 2004; Lentz et al, 1999; Onen et al., 2001; Hicks et al, 1978) and sleep loss reduces the threshold for pain perception in adult human subjects (Nascimento et al., 2007). Recent meta-analysis to quantify the effect of sleep deprivation in healthy human subjects on pain perception revealed a medium effect size (SMD =0.62) (Schrimpf et el., 2015). A population based found poor sleep preceded new onset of chronic widespread pain (CWP) (Gupta et al., 2006). In another study, sleep loss and REM sleep loss were reported to have hyperalgesia effects (Roehrs et al., 2006). A

systematic review conducted in 2014 found evidence on the effect of sleep deprivation in animal and human models (Karman et al., 2014). Additionally, another review focusing only on controlled trials reported conclusive evidence on the increase in bodily complaints or decrease of pain thresholds subsequent to sleep deprivation (Finan et al., 2013). Collectively, these findings suggest that lack of sleep results in greater sensitization of pain pathways, as well as greater perception of pain; yet the precise mechanism remains unclear.

There is burgeoning research demonstrating a bidirectional relationship between disturbed sleep and pain intensity. That is, pain may lead to sleep disturbances and poor sleep may cause or exacerbate pain (O'Brien et al., 2011). Longitudinal studies demonstrated that a night of poor sleep quality was followed by a day with more severe pain, which consequently worsened sleep quality during the subsequent night (Flume et al., 2009). Also, cross sectional studies of healthy subjects suggest that pain disturbs sleep quality /continuity and poor sleep further exacerbates pain (Smith & Haythornthwaite, 2004). The bidirectional relationship between sleep and pain is confirmed by pharmaceutical studies showing that medications used to treat insomnia (eszopiclone, triazolam) result in both an improvement in sleep as well as reduction of pain (Roth et al., 2009, Walsh, 1996). Also, clinical trials show improvement in pain sensitivity in patients with effective treatment of sleep disorders like restless leg syndrome (RLS) and obstructive sleep apnea syndrome (OSAS) (Khalid et al, 2011; Stiasny – Kolster et al, 2013).

Several studies have highlighted the effect of sleep disturbance on different bodily functions, including cognition, metabolism, emotion and pain regulation, cardiovascular and immune function. (MMWR, 2011; Brown et al., 2012, Hanlon et al., Imeri & Opp 2009). Sleep



disturbance is strongly associated with psychological distress, physical disability (van de Water, AT 2011), fatigue and day-time sleepiness (McCracken LM et al., 2002), more severe pain (Alsaadi, SM 2012), more hospitalization for low back pain than those without sleep problems (Kaila-Kangas, L et al., 2006). Moreover, sleep disturbance in chronic pain may be attributable to pain itself. In contrast to the traditional belief that pain severity can predict severity of sleep disturbance, studies show that enhanced pain perception can also be due to sleep disturbance; hence, resulting in a vicious cycle. This is substantial; as 50-88% of patients with chronic pain also suffer from sleep disorders (Smith et al, 2000; Gislason & Almquist, 2015; Pilowsky, 1985) and more than 40% patients with insomnia also have a diagnosis of chronic pain (Ohayon, 2005).

Chronic musculoskeletal pain, including that due to arthritis, low back pain and fibromyalgia, are often associated with insomnia (Siversten et al, 2009; Ancoli, 2006; Gureje et al, 2009). Epidemiological studies highlight poor sleep quality as an independent risk factor for developing chronic pain, especially musculoskeletal pain (Mork & Nilsen, 2011). A few studies identified the effects of sleep deprivation (total, selective, slow wave and delta wave interruption) in healthy subjects on musculoskeletal pain. Those studies found relationship between slow wave sleep (SWS) and sensitivity to pain (Older et al, 1998; Onen et al; 2001 & Lentz et al; 1999). For example, Lentz et al disrupted SWS for 3 consecutive nights in healthy middle aged women and assessed musculoskeletal pain with dolorimetry. They found decreased pain sensitivity in those with disrupted SWS (Lentz et al; 1999). Arima and colleagues investigated the effects of SWS deprivation for 3 continuous nights on jaw-muscle activity in men without temporomandibular disorders. They reported that out of 10 a subgroup (5 subjects)

who showed reduction in SWS during all 3 nights demonstrated a significant trend ( $p=0.06$ ) for decreased pain threshold (Arima et al., 2001).

Alsaadi et al (2014) evaluated the relationship between intensity of LBP and sleep disturbance. Eighty patients completed a sleep diary and also used an arm band to measure sleep. Findings revealed that a night of poor sleep, difficulty falling asleep, waking after sleep onset and low sleep efficiency were followed by a day of higher pain intensity. Additionally, a day with higher pain intensity was associated with a decrease in subsequent night's sleep quality, an increase in sleep latency, waking after sleep onset and low sleep efficiency. Similar to the findings of Alsaadi and colleagues, Koffel et al (2016) examined changes in pain that might predict sleep complaints, in 250 veterans. They identified that changes in sleep complaints at 3 months predicted changes in pain at 12 months ( $p < 0,001$ ); and to a lesser extent changes in pain predicted changes in sleep ( $p < 0.05$ ). Other studies have shown that impaired sleep led to new onset or worsening of pain (Haack & Mullington, 2005 & Edwards et al; 2008).

In summary, most studies that researched pain and sleep studied individuals with sleep disturbance, as opposed to sleep disorders, such as insomnia. Further, patients with chronic pain more often present with symptoms of sleep disturbance, rather than insomnia. Hence for purpose of this study, sleep disturbance will be studied in relation to CLBP.

### **CLBP and Sleep Disturbance**

In a systematic review, CLBP was reported to contribute to increased duration of sleep onset, reduced total sleep time, and lower sleep efficiency (Kelly et al., 2011). These findings are confirmed internationally. For example, a study in France investigated subjective sleep quality in 101 CLBP patients, and found significant alterations in sleep in those with CLBP compared to

healthy controls matched for age, sex and height (Marty et al., 2008). Another study conducted in Norway on 457 CLBP patients also identified significant sleep problems as compared to controls (Hagen et al, 2006). Similarly in the UK a study of 70 CLBP patients found significant changes in sleep onset and maintenance when compared to control group matched for age and sex (Tang et al, 2007).

Axen (2015) conducted a case control study to investigate the correlation between pain and sleep disturbance and the effect of back pain on sleep disturbance. Among 233 patients with acute and persistent LBP, 67% of the sample reported sleep disturbance, which was significantly correlated with greater pain. Also, there was a greater risk of reporting sleep disturbance after experiencing pain the previous week (relative risk = 2.1 to 5.8) and a dose response between the number of days with pain and the risk of sleep disturbance. Similarly, another study (O'Donoghue et al., 2009) found that people with CLBP reported poor sleep quality, clinical insomnia, longer sleep onset latency, lower sleep efficiency and more awakenings during sleep ( $p < 0.05$ ), compared to age and gender matched individuals with chronic pain.

A prospective cross sectional evaluation of 268 patients with LBP undergoing rehabilitation identified a significant relationship between pain and sleep. Pain was measured using the Brief Pain Inventory (BPI), while sleep was measured using the Pittsburgh Sleep Quality Index (PSQI). Findings revealed a 55% increase in the proportion of subjects reporting restless/light sleep after pain onset. Significant direct correlations between SF-MPQ and PSQI; between PSQI and VAS; and between overall quality of sleep and VAS were observed. The researchers concluded that CLBP significantly reduces quality of sleep (Marin et al, 2006).

O'Donoghue and colleagues (2009) compared the sleep quality of 15 CLBP participants with healthy age and gender matched controls using subjective and objective measures. That study found that CLBP participants demonstrated significantly poorer overall sleep, as measured objectively and subjectively. They also demonstrated lower actigraphy sleep efficiency and increased awakenings after sleep onset. Subjectively, they reported increased insomnia, lower sleep efficiency ( $p < .001$ ) and increased sleep time. Additionally their findings demonstrated a significant association between low back pain and physical health, disability levels, and subjective sleep quality in the CLBP participants.

While the above studies detected alterations in sleep onset, quality and efficiency, some studies used polysomnography as an additional measure to address sleep disturbance in CLBP. For example, a study of CLBP patients (N=51), who completed a self-inventory of sleep performance found that half of the participants reported poor sleep, and those with high sleep intensity reported less sleep time, more delayed sleep onset, and more nighttime awakenings than patients with low intensity. Further, that study revealed decreased or absent stage three and stage 4 sleep, periodic leg movements and shortened time to onset of rapid eye movement (REM) sleep (Atkinson et al., 1988).

To summarize, evidence to date confirms that CLBP is associated with greater sleep disturbance; and that there is a bidirectional relationship between sleep and CLBP (i.e., pain can lead to sleep disturbance and sleep disturbance can exacerbate pain). Studies, however, differ widely in the measurement of sleep quality, and include a mix of subjective and objective measures, making it difficult to compare findings across studies. Most studies were saturated with self-report subjective measures of sleep, and discrepancies between subjective and objective

measures were identified in three studies (Atkinson et al., 1988; Bulthuis et al, 2004 & Lavie et al, 1992).

It is recognized that there is value in using a combination of subjective and objective measures of sleep quality; however, there is a need for more standardization of sleep measurement, as well as a need for feasible and valid approaches to measure sleep quality in those with CLBP. In addition, the current literature is unclear as to the influence of ‘sleep disturbance’ versus ‘insomnia’ in the CLBP population. The field is also limited in that most studies evaluated Caucasian populations. Hence, there is a need to enroll more diverse populations with CLBP to understand the influence of various socio-demographic and cultural factors, which can lead to more tailored approaches to manage the challenge of co-occurrence of pain with sleep disturbance. Lastly, there is a need to understand the underlying mechanisms linking sleep disturbance to the pain experienced in those burdened by CLBP.

### **Mechanisms Linking Sleep to Pain**

The biological mechanism(s) linking sleep and pain are likely complex and remain unclear. Yet, scientists are exploring several hypotheses to clarify potential mechanisms that might explicate biological processes that underlie the relationship between sleep and pain. For example, the neurological hypothesis theorizes that pain and sleep are linked by alpha wave intrusion into Non Rapid Eye Movement (NREM) phase of sleep. (Moldofsky, 1975; 1976). Other theories invoke dysregulation of neurotransmitter systems, such as the serotonin system (Foo and Mason, 2003), the dopaminergic system (Argoff, 2011; Carver et al, 2008; Ursin 2002), and the endogenous opioid systems (Sutton & Opp, 2014) (Basbaum & Fields, 1984). Animal data demonstrate opioid injections placed in the nucleus of the solitary tract (NST) (an area that

contains the highest concentration of opioid receptors) (Reinoso & Andres 1995) enhanced slow wave sleep. More recently, a psychoneuroimmunology approach suggests a role for inflammation as one possible mechanism for worsening of chronic pain in those with sleep disturbance. Data supporting a role for inflammation is described below.

### **Sleep and Inflammation**

A recent meta-analysis concluded that sleep deprivation is accompanied by increases in systemic inflammation (Irwin et al, 2015). Moreover, systemic inflammation has been found to decrease pain threshold in humans who are sleep deprived (De Godin et al, 2013). It is likely that sleep and pain are linked through elevations in levels of proinflammatory cytokines (i.e., tumor necrosis factor (TNF) and regulation of the hypothalamic-pituitary-adrenocortical (HPA) axis (Floam et al, 2015). However, data is limited in humans who have chronic pain conditions. Further, there remains difficulties in arriving at conclusions on the effects of sleep on pain and inflammation due to methodological issues related to measuring sleep disturbance and differences in characteristics of sleep disturbance).

Based on evidence to date, insufficient sleep may facilitate and/or exacerbate pain through elevations of pro-inflammatory cytokines, like IL-6. Reductions in sleep quality and quantity have each been associated with higher circulating levels of IL-6 during the day (Heffner et al., 2012). In another study, patients with temporomandibular pain disorders (40 females) who were classified as having high disability (Graded Chronic Pain Scale) also had the highest PSQI. Moreover, plasma levels of IL-1 $\beta$ , IL-6, IL-10, and TNF- $\alpha$  were significant in the high-disability group. Further, the plasma cytokine levels were significantly correlated with increased sleepiness (Epworth Sleepiness Scale) and PSQI scores suggestive of sleep disturbance (Park, J. W., &

Chung, J. W, 2016). Further, insufficient sleep may establish and maintain its co-occurrence with pain and increased inflammation. Additionally, inflammation can signal the brain to engender depressive mood (Inflammatory Theory of Depression) and depressive mood can lead to increased pain perception (Tang et al., 2008).

### **Chronic Pain and Depression**

Depression coexists with chronic pain (Krishnan et al., 1985) and is estimated to cost \$83 billion annually in the United States (Greenberg et al., 2003). Some studies show 30% to 60% co-occurrence rate between chronic pain and depression (Baer, 2003). Others show as much as 31% to 100% (Miller & Cano, 2009). Depression is commonly associated with chronic back pain and can also be a risk factor for both low back pain and sciatica (Parreira, P et al., 2018). While there is a growing body of literature supporting the link between CLBP and depression, how depression relates to other behavioral symptoms, and whether a common biological mechanism links these symptoms with pain remains unclear. This section will summarize the evidence on the relationship between pain and depression, with emphasis on CLBP.

Numerous studies suggest that depression worsens both the severity of pain and disability caused by pain. A National survey found that subjects with chronic pain due to musculoskeletal conditions scored significantly higher than normal on the CES-D. That study also found that 18% of the population with chronic pain suffers from depression, as compared to 8% of the population who did not have chronic pain (Magni et al, 1990). A Canadian Community Health Survey (N=118,533) revealed that rates of major depression were at 19.8% for individuals with chronic back pain, as compared to 5.9% for pain-free individuals. Moreover, greater pain

severity not only predicts greater disability but also is associated with greater severity of depression (Currie & Wang, 2004).

### **CLBP and Depression**

CLBP can be debilitating due to the pain itself and also due to its impact on psychosocial well-being. For example, depression may reduce functional activity in chronic pain by distorting one's perception of their ability to carry out activities. This was demonstrated by Huanan, et al., 2010 who found that individuals with chronic pain and depression do not have lower objective activity levels (measured by accelerometer) but had lower perception of their ability to carry out activities. Acute back pain may differ from chronic back pain, as a recent study found that depression in persons with acute back pain was not significantly associated with perceived disability (Salt, E et al., 2018).

Mood disorders, such as anxiety and depression, which accompany CLBP, can complicate clinical management. In a large survey of community dwelling adults it was found that mild to severe depressive symptoms increased the odds of disabling LBP over a period of 2 years by 30–60% (Baer, 2003). A systematic review evaluated the effect of depression on acute and sub-acute chronic back pain. That review focused on depression or symptoms of depression as a prognostic factor on pain-related outcomes, including pain intensity, chronicity (non-recovery from low back pain), disability, return to work, health-related quality of life, and overall patient satisfaction. Eleven of the 17 articles reviewed found that symptoms of depression at baseline were related to worse low back pain outcomes at follow-up (effect size ranged from 1.04 to 2.47). All studies regardless of statistical significance showed that there was a relationship between depressive symptoms and low back pain outcomes (Pineiro et al., 2016).



Mood disturbance may also lower pain threshold. For example, a cross-sectional two-phase population based study (N= 424), revealed that high levels of psychological distress, disturbed sleep and depression were all associated with having a low pain threshold (Chiu et al., 2005). depression is a significant mediator of the relationship between pain and self-perceived disability in people with CLBP (Marshall et al., 2017), emphasizing the importance of addressing symptoms of depression in those with CLBP. Further, persons with CLBP who had both anxiety and depression had higher pain severity, higher pain-related disability. Further, the interaction between anxiety and depression predicted changes in pain interference at one-year follow up (Oliviera et al., 2018).

The relationship between depression and pain is likely bidirectional. Findings from a study of individuals with disabling low back pain showed that pain, ranging from a little of the time to all of the time, increased the odds of depressive symptoms by 27.9–84.2%, respectively. In contrast, depression may precede the development of CLBP. Polatin et al were interested in studying the psychiatric syndromes in 200 CLBP patients who entered a functional restoration program. They found the common diagnoses were major depression, substance abuse, personality disorder, and anxiety disorders; with prevalence rates significantly greater than the general population. Most interestingly, the study revealed that 54% of those who reported depression, 94% of those with substance abuse, and 94% of those with anxiety disorders experienced these conditions before the onset of their CLBP (Polatin et al., 1993).

In another study conducted to identify if depression is an independent risk factor for onset of neck and low back pain, a population-based random sample of adults was surveyed and followed at 6 and 12 months to measure the time-varying effects of depressive symptoms on two

types of pain. After considering possible confounding effects of demographics, socio-economic status, health, medical conditions and injuries, it was found that there was an independent and robust relationship between depressive symptoms and episode of pain. The authors concluded that depression is a strong and independent predictor for onset of neck pain and low back pain (Carroll, 2004).

To summarize, the existing evidence identifies that depression often co-occurs with CLBP, and there is a bidirectional relationship between depressive mood and CLBP intensity. However, there is insufficient evidence on the nature and severity of the effect of one condition on the other. Further knowledge is needed to understand the predisposition of other conditions that lead to CLBP and the underlying processes that could attenuate or ameliorate CLBP. Future studies are needed to help clinicians address the high rates of emotional distress syndromes in CLBP.

### **Depression, Inflammation, and Chronic Pain**

Both depression (Howren et al., 2009) and chronic pain are associated with inflammation independent of depression (Fasick et al., 2015), suggesting that inflammation may be a common pathway whereby these symptoms interact. The following will summarize evidence that supports a role for inflammation in depression.

A large body of work has evaluated levels of inflammatory markers in clinically depressed patients. Overall those studies reveal that depressed patients have activated inflammatory pathways, including increased expression of chemokine, adhesion molecules and cytokines as compared to individuals without depression (Musselman et al., 2001; Bouhuys et al., 2004). Other studies have shown that patients with major depression have increased serum

and/or plasma concentrations of C-reactive protein (Danner et al., 2003; Ford et al., 2004) IL-6 (Alesci et al., 2005; Sluzewska et al., 1995) and proinflammatory TNF- $\alpha$  (Konsman et al., 2002; Mikova et al., 2001). These markers exist in both serum and cerebrospinal fluid in depressed patients (Maes, 1999; Irwin, 2002). Experimental studies in humans have demonstrated development of depressive symptoms following infusions of cytokines, such as IFN- $\alpha$  (Musselman et al., 2001; Capuron et al., 2004). Further, elevated levels of cytokines such as IL-6 and TNF- $\alpha$  predict non-response to treatment for depressive symptoms; and that depressed patients with increased inflammatory biomarkers are less likely to respond to conventional antidepressant treatments (Lanquillon, 2000).

To synthesize the literature regarding depression and inflammation, a systematic review was conducted to assess the magnitude and direction of depression with inflammatory markers; studies published between January 1967 and January 2008 were included. That review concluded that inflammatory markers (CRP, IL-6, IL-1, and IL-1ra) are positively associated with depression. Associations were strongest in clinically depressed patient samples, but significant associations were also identified in community-based samples. Moreover, a dose-response relationship between depression and inflammatory markers was identified, which was consistent with three causal pathways: depression to inflammation, inflammation to depression, and bidirectional relationships (Howren et al., 2009). Other more recent evidence also confirms that inflammation may serve as a common pathway linking depression to chronic pain. For example, higher IL-6 levels have been linked with both greater pain and greater chronic medical comorbidity in patients with greater depressive symptoms (Poleshuck et al., 2013). IL-6 was unrelated to pain or chronic medical comorbidity among patients without clinically

significant depressive symptoms. Hence, the authors concluded that depression may increase primary care patients' vulnerability to pain, resulting in elevated levels of inflammatory markers such as IL-6 (Poleshuck, 2013).

A study of 218 outpatients with rheumatoid arthritis identified depression scores to be positively correlated with CRP level; and that. Both the depression score and the CRP level were significantly associated with pain, even after adjustment for clinical covariates. Further, logistic analysis revealed that the combined effects on the risk of severe pain linearly increased with both depression scores and CRP levels. The authors noted that prior studies focused on understanding chronic pain mechanisms in relation to processes of hyperalgesia. Now, it has been recognized that inflammatory mediators can influence both inflammatory pain and nerve related pain caused by damage to peripheral nerves or to the CNS (Marchand et al., 2005).

Klyne et al., evaluated circulating pro-inflammatory cytokines and C-reactive protein (CRP) to explore the relationship of these inflammatory markers with pain severity and other symptoms in acute low back pain (LBP). That study enrolled ninety-nine individuals who were evaluated within two weeks of onset of acute LBP and compared to fifty-five pain-free controls. Findings revealed that CRP was higher in LBP patients compared to controls and in those with high- than low-pain. In addition, IL-6 was higher in those with high- than low-pain ( $p < 0.05$ ), but not controls. The investigators concluded that systemic CRP and IL-6 are important contributors to inflammation in the early post-onset phase of LBP and that various factors such as sleep quality and psychological status can shape these responses (Klyne et al., 2017).

Recent findings suggest the possibility of aberrant glial activation in the establishment and/or maintenance of central sensitization to pain. Nijs et al. reviewed preclinical

neurobiochemistry of animals and found high levels of BDNF, IL-1 $\beta$ , TNF- $\alpha$ , which increase the excitability of the central nervous system neurons. The authors discussed the possibility that glial activity in chronic pain may have been triggered by severe stress exposure, and/or sleeping disturbances, each of which are established initiating factors for chronic pain development (Nijs et al.,2017).

Currently, studies on the role of inflammation in CLBP are limited. One study, however, evaluated 127 patients with disc herniation to determine the association of two cytokines, IL-6 and IL-8, with long-lasting lumbar radicular pain (N=127). Findings revealed significantly higher levels of serum IL-6 and IL-8 in serum in patients with visual analogue scale (VAS) scores >3 at 12 months, than in patients with VAS <3 at 12 months (Weber et al., 2015). The authors concluded that their results were the first to show that chronic lumbar radicular pain may be associated with a persistent increase of proinflammatory cytokines after disc herniation.

Given that individuals with CLBP, experience co-occurring behavioral symptoms that are also independently associated with inflammation, clusters of these symptoms may underlie different pain profiles. The next section describes the extent to which fatigue might act on the intensity of the pain experience.

### **CLBP and Anxiety**

Several studies have identified a relationship between CLBP and anxiety. Similar to other symptoms, there is not enough evidence to support if anxiety worsens in CLBP or if underlying anxiety could be a predictor for CLBP. Earlier studies identified preexisting anxiety in patients developing CLBP. Polatin et al (1993) assessed 200 CLBP patients in a functional restoration program for current and lifetime psychiatric syndromes using a structured psychiatric interview

to make DSM-III-R diagnoses. Out of the patients with a positive lifetime history for psychiatric syndromes, 54% of those with depression, 94% of those with substance abuse, and 95% of those with anxiety disorders had experienced these syndromes before the onset of their back pain.

Hence it was concluded that that certain psychiatric syndromes appear to precede CLBP (substance abuse and anxiety disorders), whereas others (specifically, major depression) develop either before or after the onset of chronic low-back pain.

Kroenke et al examined the association between anxiety, health-related quality of life (HRQL) and functional impairment in primary care patients with chronic musculoskeletal pain. Interviews were conducted on 250 primary care patients enrolled in the Stepped Care to Optimize Pain care Effectiveness trial. Using validated measures to determine the proportion of patients screening positive for five common anxiety disorders: generalized anxiety, panic, social anxiety, posttraumatic stress and obsessive-compulsive disorder, it was found that 45% patients screened positive for at least one anxiety disorder and hence concluded that nearly half of primary care patients with chronic pain screen positive for one or more anxiety disorders, which in turn are adversely associated with impairment across multiple domains of HRQL.

Von Kroff et al., 2005 investigated comorbidity between chronic back and neck pain and other physical and mental disorders in the US population. They interviewed a probability sample of US adults (n=5692) with chronic spinal pain, other chronic pain conditions and also assessed mood, anxiety, and substance use disorders using Composite International Diagnostic Interview (CIDI). Results showed that the majority (87.1%) of people with chronic spinal pain reported at least one other comorbid condition, including other chronic pain conditions (68.6%), chronic

physical conditions (55.3%), and mental disorders (35.0%). Anxiety disorders and mood disorders showed a strong association with chronic spinal pain.

In a controlled trial in an interventional pain setting, evaluating 40 individuals without pain or psychotherapeutic drug therapy, Group I, control group; and Group II, chronic low back pain group with 40 chronic low back pain patients, there was significant differences were found among various clinical syndromes with generalized anxiety disorder, somatoform disorder, and depression, with 0% vs 20%, 0% vs 20%, and 5% vs 30% in Group I and Group II consecutively (Manchikanti et al., 2002).

In a recent interesting longitudinal study on 1,269 adult twins (mean age of 53 years), investigators studied whether chronic low back pain (LBP) increases the risk of depression or anxiety symptoms, after adjusting for shared familial factors. They identified significant association between chronic LBP and the risk of depression or anxiety symptoms in the unadjusted total sample analysis (odds ratio [OR]: 1.81, 95% confidence interval [CI]: 1.34–2.44). The researchers concluded that relationship between chronic LBP and the future development of depression or anxiety symptoms is not causal and is likely to be explained by confounding from shared familial factors Fernandez et al (2017).

To summarize, anxiety is also another key behavioral symptoms for which there is substantial evidence that there is a bidirectional relationship between CLBP and anxiety.

### **CLBP and Fatigue**

Findings from several studies demonstrate that fatigue is prevalent and problematic for individuals with CLBP (Fishbain et al., 2004; Starkweather 2013; Snekkevik et al., 2014). For example, one study evaluated CLBP patients (N=569) to identify the associations among fatigue,

depression, and pain; and to determine if fatigue predicted long-term disability. Findings revealed that prevalence of substantial fatigue to be 69.7%; and those with substantial fatigue had higher pain intensity, more depressive symptoms, and more disability than those without substantial fatigue. Musculoskeletal pain and depression were independently associated with substantial fatigue and fatigue predicted long-term disability at 3, 6, and 12 months' follow-up. Further, after pain and depression were controlled for, fatigue remained a significant predictor of disability at 6 months' follow-up. Hence the researchers concluded that the majority of the sick-listed CLBP patients reported substantial fatigue and those who had substantial fatigue had more pain and depressive symptoms and a significant risk of reporting more disability at 3, 6, and 12 months (Snekkevik et al., 2014)

Starkweather (2013) conducted an exploratory study of subjects with persistent radiculopathy to determine 1) relationships among fatigue, pain, psychosocial factors, and selected biologic markers of immune activation (interleukin [IL] 6 and soluble IL-6 receptor [sIL-6R]); and 2) differences in these variables based on fatigue severity. Participants (n = 80) were classified according to their level of fatigue as low (27.5%), moderate (32.5%), or high (40%). Findings revealed that individuals with moderate to high fatigue levels had greater psychological distress, depressive symptoms, IL-6 and sIL-6R, compared to those with low levels of fatigue. This study suggests the possibility of immune activation affecting fatigue severity and behavioral responses in patients with persistent radiculopathy.

A prospective cohort study of 120 chronic widespread pain patients (CWP) participating in multidisciplinary rehabilitation treatment (baseline, 6 and 18 months of follow-up) revealed that higher levels of pain, interference of pain, depression, and negative emotional cognitions,



were associated with a higher level of fatigue; while improvement in depression was related to improvement in fatigue. The authors concluded that in CWP patients, worse clinical status, and dysfunctional pain-related cognitions are associated with a higher level of fatigue. It was suggested that improvement in depression might be a mechanism of improvement in fatigue and that improvement in fatigue was independent of improvement in pain related cognitions (De Rooij et al., 2014).

Fishbain et al., 2009 analyzed the data from clinical trials of duloxetine [a selective serotonin and norepinephrine reuptake inhibitor (SNRI)] to determine whether an association between pain, sleep, and vitality exists. Data from 3 double-blind, randomized, placebo-controlled, 12-week trials of patients without mood disorder (N = 1,139) was evaluated. Of the identified 697 patients, correlations between changes in daily and night pain, and sleep interference with vitality changes were -0.34, -0.32, and -0.28, respectively ( $P < 0.001$ ). The direct effect of treatment on change in vitality was statistically significant (68%,  $P = 0.010$ ). Path analyses suggested vitality improvement in patients with chronic pain may be secondary to improvement in pain by duloxetine. The researchers concluded that it could not be proved that pain causes fatigue; however, there was indication that treatment of pain can improve perception of improvement in fatigue.

The above studies indicate that fatigue is also closely related to pain and there are possible relationships between pain, fatigue, depression and sleep disturbances as well.

### **CLBP and Quality of Life**

From a clinical and community health perspective, quality of life is an important outcome for CLBP patients. Nurses focus on relieving pain and suffering in patients and one of the

desired outcomes is to help patients achieve and maintain an optimal quality of life. CLBP patients have consistently reported decreased quality of life and multidisciplinary pain rehabilitation programs have been shown to improve their quality of life (Waterschoot et al., 2014; Veehof et al., 2011 & Morley, 1999). In a systematic review and meta-analysis of 12 studies (N=2961), Lee et al. 2015 identified factors which mediate quality of life in patients with back and neck pain. The researchers considered disability as a key indicator of quality of life. Results showed that self-efficacy, psychological distress, and fear were significant mediators of quality of life. Moreover, path analysis revealed that self-efficacy, psychological distress, and fear mediated the relationship between pain and disability, but catastrophizing did not.

Analysis of factors that contribute to decreased quality of life and how CLBP can affect quality of life can help to identify the gaps in literature. Based on this, new strategies to improve quality of life can be discovered. For example, research has shown that multidisciplinary pain rehabilitation programs improve daily functioning in patients with chronic back pain. A systematic review of 10 RCTs reporting on 10 multidisciplinary Pain Rehabilitation Programs (PRPs) concluded that PRPs that offer more than 100 hours are superior to mono-disciplinary treatment and PRPs offering 30 hours of rehabilitation (Waterschoot et al., 2014). Further, studies have shown that integrative approaches for chronic pain improve physical, social, work related activities and reduce pain, emotional distress; disability and medication use (Veehof et al., 2011). For example, meta-analysis of 25 RCTs of cognitive Behavioral Therapy (CBT) and behavioral therapy concluded that these therapies provide greater changes for cognitive coping, pain experience domains and reduced behavioral expression of pain (Morley, 1999).

Psychological and social factors also are known to contribute to health related quality of life in patients with CLBP. Keeley et al (2006) conducted a prospective study of patients with CLBP (N=108) from an orthopedic outpatient clinic. That study assessed demographic characteristics, details of back pain and physical aspects of health-related quality of life (SF-36 PCS); and recorded the number of healthcare contacts at the 6 month follow up. Independent predictors of SF-36 PCS at 6-month follow-up were duration of pain and back pain related social difficulties. Number of healthcare contacts over the 6 months ranged from 1 to 29, and was independently predicted by perceived cause of pain, fear avoidance beliefs about work and back pain related social difficulties. Based on these results, the investigators concluded that anxiety, depression; fear avoidance beliefs relating to work and back pain related stresses predicted the impairment in subsequent physical health-related quality of life and number of healthcare contacts.

In a similar study, Horng and colleagues (2005) evaluated factors as predictors of health related quality of life (HRQL) in CLBP patients (N=232) enrolled from several ambulatory clinics (physical medicine and rehabilitation). Results indicated that there were significant correlations of HRQOL with pain intensity, disability scale and days of disability. Significant predictors of HRQOL included pain intensity, family income, physical and psychological factors. Other changes environmental predictors included disability days, educational level, herb medications and physiotherapy. Importantly, the findings from this study also indicated that HRQOL of CLBP patients depended on functional status and psychological factors rather than simply physical impairment.

To support this literature, multidisciplinary interventional programs that include cognitive

behavioral treatment and physical therapy have also been shown to improve quality of life in CLBP patients. For example, Morone and colleagues (2011) conducted a single blinded RCT study to the effect of the multidisciplinary back school program in a rehabilitative center on quality of life in 74 patients with chronic non-specific low back pain at three and six months follow up. Participants in the treatment group (N=41) received medical assistance, education and active back exercises while the control group (N=29) received medical assistance only. The treatment group showed significant improvement in quality of life (both physical and mental) and significant improvement in disability scores. Moreover, pain perception score (VAS) showed a reduction in both groups, but it was significantly lower in BSG at end of treatment and both follow-ups.

In another RCT ( n= 50), Morone et al., 2011 evaluated the effect of the ‘Back School Program’ on mental components of quality of life in patients with musculoskeletal pain , mostly of the spine with scale elevations of MMPI-II. The control group received medical assistance only. Results indicated that the treated group had significant improvements in quality of life, pain and disability. These findings demonstrate that the Back School Program can improve quality of life, possibly by reducing pain and disability; yet, no mediation analysis was performed.

A third RCT by Banth and Ardebil (2015), evaluated the effect of mindfulness based stress reductions (MBSR) on pain and quality of life of female patients (N=88) with CLBP. Participants were randomly assigned to MBSR plus usual medical care, while the control group received usual medical care only Findings revealed that MBSR was effective in reducing pain severity (McGill Pain Score) and improving physical and mental quality of life. Patients who

attended 8 sessions of MBSR reported significantly lower pain than patients who received usual medical care.

### **Gaps in Knowledge: Symptom Clusters and Inflammation in CLBP**

The above review of literature summarizes the evidence to date as to the most common behavioral symptoms (i.e., depressive symptoms, sleep disturbance, and fatigue) associated with the pain experience in individuals with CLBP. Further, inflammation levels predicted behavioral Class membership. Only a handful of studies have examined symptom clusters in individuals with CLBP. One such study identified three clusters of symptoms in a cohort of patients with chronic low back pain (n=294). These clusters were derived from multiple psychological questionnaires, with cluster 3 exhibiting the highest scores across cognitive (eg, kinesiophobia, pain catastrophizing, endurance behaviors, low acceptance, low pain self-efficacy) and higher scores in affective factors (e.g., depressed mood, anxiety, stress) and significantly greater lumbar pressure pain sensitivity, more undiagnosed comorbid symptoms, and more widespread pain than other clusters (Rabey et al.,2016).

There is sufficient evidence that each of these symptoms might coexist with one or more but there are also several gaps in knowledge. For instance, existing evidence identifies that depression often co-occurs with CLBP, and there is a bidirectional relationship between depressive mood and CLBP intensity. However, there is not sufficient evidence on the nature and severity of the effect of one condition on the other. Additionally, it is not clear if there are underlying processes in CLBP and depression that could attenuate or ameliorate CLBP. Secondly, evidence to date confirms that CLBP is associated with greater sleep disturbance; and that there is a bidirectional relationship between sleep and CLBP (i.e., pain can lead to sleep

disturbance and sleep disturbance can exacerbate pain). However studies differ widely in the measurement of sleep quality, and include a mix of subjective and objective measures, making it difficult to compare findings across studies to arrive at a definitive conclusion. There are also design issues that limit the validity and generalizability of prior studies in examining relationship of sleep to CLBP. The value of subjective measures is recognized; however, there is need for studies that measure both subjective and objective measures, as each type of measure can provide valuable insight.

Finally, although evidence on relationship between CLBP and behavioral symptoms fatigue is evolving, there is need for further studies that address clusters of symptoms. It is notable that there are several gaps in the area of symptom cluster research in non-cancer pain. Only three studies have thus far studied symptom clusters in non-cancer pain; however, these studies did not focus on CLBP. Rather, those studies focused on the relationship between symptoms, in heterogeneous pain populations (headache, neck pain, fibromyalgia) and very few focused on CLBP in particular. Henceforth there is not only a dearth in knowledge on relationship between symptoms in CLBP but also as to what symptoms could occur in clusters in this population.

Although there is burgeoning evidence as the existence of depressive symptoms, sleep disturbance, and fatigue in CLBP, no studies have evaluated these symptoms as clusters, and this remains a gap in knowledge. Evaluating these symptoms as a cluster will advance knowledge of interactions among co-occurring symptoms, which can support the development of interventions that target more than one symptom. It is clear that the co-occurrence of symptoms adversely impacts the pain experience and quality of life in individuals with CLBP. Hence, there is a need

for future investigations to advance knowledge of the relationships among these behavioral symptoms as a cluster and to determine how they influence pain and quality of life in CLBP patients. Further, it is possible that these co-occurring symptoms are mediated through a common psycho-biological mechanism. Hence, there is a need to understand potential mechanisms, such as inflammation, which may serve as a common pathway linking these distressing symptoms to pain.

### **Implications and Future Direction**

Findings from this study will increase understanding of the role of depressive mood, fatigue, and poor sleep, as a symptom cluster, on inflammatory biomarkers, pain, and quality of life in patients with CLBP. This knowledge can inform the development of specific symptom profiles to be used clinically to develop individualized and mechanism-oriented treatment strategies for CLBP patients in the future. Moreover, it is important to understand whether a common pathway mediates these symptoms. One such pathway is inflammation. Each of these symptoms (i.e., depressive mood, sleep disturbance and fatigue) has been associated with excess production of inflammatory mediators. For example, insufficient sleep may facilitate and/or exacerbate pain through elevations of pro-inflammatory cytokines, like IL-6. Both, reductions in sleep quality and quantity have each been associated with higher circulating levels of IL-6 during the day. Insufficient sleep may establish and maintain its co-occurrence with pain and increased inflammation. Similarly fatigue can cause increased inflammation. Inflammation can signal the brain to engender depressive mood (Inflammatory Theory of Depression); Depressive mood can lead to increased pain perception. Thus, an examination of key inflammatory molecules (e.g., IL-

6) as a common pathway linking these behavioral symptoms can provide initial mechanistic evidence.



## CHAPTER THREE

### DISCUSSION OF PROPOSED RESEARCH METHODOLOGY

#### **Examination of Symptom Clusters and Underlying Inflammation in Patients with CLBP**

Chronic low back pain (CLBP) has been identified as one of the most common complaints of patients with musculoskeletal disorders (Andersson, 1999). CLBP is defined as presence of pain in the lumbar region that lasts more than 7-12 weeks (Currie & Wang, 2004). Further, CLBP can cause restricted work capacity, social activities limitations, emotional problems, and reduced quality of life (Bentsen et al., 2008). The overall purpose of this proposal is to determine the extent to which behavioral symptoms, independently or as a cluster, predict pain quality and intensity and quality of life in patients with CLBP. Additionally, the relationship of these symptoms as clusters and underlying inflammation will be determined. Thus, the following specific aims and hypotheses will be addressed in individuals with CLBP:

#### **Specific Aims and Hypotheses**

Aim 1: To identify behavioral symptom clusters in individuals with CLBP.

Hypothesis 1: Behavioral symptom clusters will be identified in individuals with CLBP.

Aim 2: To determine differences in pain experience (pain severity and interference) and quality of life among identified clusters.

Hypothesis 2: Pain experience and quality of life will differ among identified clusters.

Aim 3: Determine differences in inflammatory biomarkers based on symptom clusters and pain experience.

Hypothesis 3: Inflammation will differ with the pain experience, quality of life, and symptom cluster.

Aim 4: Explore regression models to determine predictors of the pain experience and quality of life in individuals with CLBP.

## **Research Design and Methods**

**Overview of design.** This chapter delineates how the proposed conceptual model was verified. Overview of design, setting, samples, study procedures and variables used in the analysis for applying the Model among CLBP are also included.

This cross-sectional design identified behavioral symptom clusters and determined differences in pain profiles and quality of life among the identified symptom clusters. In addition, differences in key inflammatory proinflammatory cytokines (i.e., IL-6 ) among clusters were examined. Individuals (N=69) who had experienced low back pain for at least 6 months were recruited from the chronic pain clinic at Loyola University medical Center. Participants completed psychometric instruments measuring; pain quality and intensity, depressive mood, fatigue, sleep as well as demographic forms. Health history was obtained by self-report and review of medical records. Blood amount of 10 ml was obtained by venipuncture for measurement of pro-inflammatory cytokines known to be associated with CLBP. Latent class analysis was used to identify symptom clusters, and differences in pain and quality of life among symptom clusters by analysis of variance.

**Sample.** Eligible participants (N=86) were identified by providers (Physicians and Nurses). The subjects were selected from the outpatient clinics of the Loyola University Medical Center. Inclusion criteria for the study were: a convenience sample of men and women, who

have been diagnosed with CLBP and are between the ages of 21 to 70 years. In addition, participants were alert and oriented, able to write, read and speak English at the fifth-grade level, and were able to consent to participate in the study. Exclusion criteria included no history of spinal or orthopedic surgeries in past 6 months, no lower extremity weakness or neurological signs of brain or nerve injury (eg., seizures, cerebral palsy, spinal tumor/ trauma or infection), no steroid therapy, no immune altering drugs, no chronic illnesses with immunological complications (eg., rheumatoid Arthritis, cancer in the past 5 years), no psychiatric disorders, no major immune-based disease, no drug or alcohol abuse, no heavy smoking ( no more than 15 cigarettes a day).

**Sample size.** An *a priori* power analysis conducted using Dziak et al., approach (Dziak et al., 2014) (for Aim 1) and the G\*Power 3 (Faul, Erdfelder, Lang, & Buchner, 2007) software (for Aims 2 and 3) to estimate the number of participants. To avoid missing an effect and accepting the null hypothesis, a higher power and alpha is the recommendation in pilot studies than in traditional studies (Schoenfeld, 1980). Therefore, instead of using an alpha of 5% (i.e. a two-tailed 5% type 1 error rate) and power of 80%, an  $\alpha=10\%$  and power of 85% were used in the subsequent calculations of the sample size. For Latent Class Analysis, a sample size of 98 would be able to detect an effect size of 0.45 with a 3-class LCA model (Dziak, Lanza, & Tan, 2014).

For Aims 2 and 3, the effect size was derived from three meta-analysis articles by Hoffman et al (34 articles) and Morley et al., 1999 (33 articles), Astin et al (25 articles). The effect size for depression in the above studies was large at 0.81 and effect size of pro-inflammatory markers derived from meta-analysis article by Howren et al (2009) (51 articles)

was 0.35. G\*Power calculations for F-tests, indicated that a sample of 98 were adequately detect an effect size of  $f^2=0.45$  using 3 classes and alpha level of 0.10 two-sided level of significance.

To preserve statistical power, multiple imputations were used for data missing at random.

*Study procedure.* Once IRB approval was granted, the principle investigator (PI) communicated with the Physician at the pain clinic and research committee team members to understand the detailed recruitment process, findings, and difficulties while conducting the study. Potential CLBP participants were then identified by the nurses and the physician and then approached by the principal investigator in the pain clinic. Potential participants were given a description of the purpose and nature of the study and their role, including risks and benefits before enrollment. Participants were screened and consents obtained. Eligible participants who met the inclusion criteria were enrolled and blood samples drawn. Study participants were provided with questionnaires and ACTi watch to take home. The study consisted of one-time point for data collection. After completion of the informed consent document, the participants were provided a packet of self-report questionnaires. They also were requested to provide blood sample of 10 ml during venipuncture. Participants completed the following self-reported measures: The Center for Epidemiologic Studies Depression Scale (CES-D), Pittsburgh Sleep Quality Index (PSQI), Brief Pain Inventory (BPI), Brief Fatigue Inventory (BFI), Quality of life (Carol Ferrans HRQoL), Social Provisions Scale analgesic use, demographics form, and survey of health behaviors. Participants who completed the study were given a \$25 gift card for their time and transportation.

**Study variables.** The variables used in the study were operationalized by using valid and reliable instruments. In the following section, each measure is explained briefly and the reliability and validity is provided. Full copies of each instrument are included in Appendix A.

The independent variables evaluated for this study are sleep quality, depressive mood, fatigue, and proinflammatory cytokines (IL-6). Dependent variables are pain intensity and quality of life. Table 1 (below) lists study variables. Each instrument is included in Appendix A.

Table 1. Study Variables

Independent Variables				Dependent Variables		Covariates	
Sleep Disturbance	Depressive Mood	Fatigue	Inflammation	Pain (Severity and Interference)	Quality of life outcome	Social Support	Health Behaviors
PSQI Sleep Diary ACTi watch	Depression (CES-D)	Brief Fatigue Inventory	Proinflammatory Cytokines (IL-6)	Brief Pain Inventory	Carol & Ferran -s HrQol	Social Provisions Scale (SPS)	Medications (Analgesics use) Demographics

## Sleep Quality Measures

**Measurement of sleep quality.** For the purposes of this study, subjective and objective measures were used to measure sleep disturbance. Subjective measures included sleep diary, self-report questionnaires, while the objective measure was wrist actigraphy. It is recognized that polysomnography (PSG) is the gold standard to measure sleep quality but is not frequently used in research due to its complexity and expense. Most studies that report sleep quality in CLBP have used self-report questionnaires. However, self-report measures do not always correlate with PSG studies and, as such, have limitations (Silva et al., 2007). Alternative to the

polysomnography studies are newly developed portable devices that can provide less expensive, more accurate objective measures of sleep as compared to self-report scales (van de Water et al., 2011). While some studies have investigated the accuracy of actigraphy to evaluate parameters of sleep compared to PSG in the general population, only one study has studied accuracy of these devices in the CLBP (Van de Water et al., 2011).

**Pittsburgh Sleep Quality Index (PSQI).** The Pittsburgh Sleep Quality Index (PSQI) was used in this study as an index of subjective perception of sleep quality. The PSQI includes 19 questions segregated into seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disorders, use of hypnotics, and daytime dysfunction. Sleep latency were assessed using two questions rated according to time to fall asleep. Sleep duration was be assessed by one question rated 4 on a Likert scale from >7 to <5 hours, and sleep efficiency by hours asleep divided by total of hours in bed. Use of hypnotics and poor daytime functioning are rated by a 4-point Likert scale (not during the past month, less than once per week, once or twice per week, 3 or more times per week). Sleep disorders was assessed with nine questions focused on waking up in the middle of the night or early in the morning, getting up to go to the toilet, difficulty breathing properly, coughing or snoring loudly, being too cold, being too hot, having nightmares, experiencing pain, or other reasons for disturbed sleep. Each question is rated with a 4-point Likert scale (not during the past month, less than once per week, once or twice per week, 3 or more times per week). Subjective sleep was evaluated with one question rated by a 4-point Likert scale from very good to very bad. The seven components were each be scored from 0 (no difficulty) to 3 (severe difficulty), and summed, to give an overall score ranging from 0 to 21. The PSQI has demonstrated good validity and reliability, with

studies reporting a Cronbach alpha of 0.83 for its seven components (Buysse et al., 1989). The validity of PSQI was determined among older adults by examining sleep quality for 78 adults aged 55+ in the community and compared PSQI with actigraphy and concluded that although PSQI can be a valuable tool for adults, it should not be used as substitute for actigraphy.

**Sleep diary.** The sleep diary is a subjective tool that was completed by participants upon waking for seven nights consecutively in addition to the actigraphy and PSQI. Participants were asked to record the time they went to bed, the time it took to fall asleep, time they woke up, amount of time awake after falling asleep, number of awakenings during night, time they woke up and total amount of sleep obtained. Participants were also asked how they would rate their quality of sleep on a scale of 1 to 9 (1=terrible, 9=great). Finally, they were also asked how rested they felt after waking up in the morning on a scale of 0 to 4 (0 – Not at all, 4 – Extremely) Extent of exercise, medications taken, and any illness were also be obtained to identify causes of sleep disturbances.

**Actigraphy.** Alsaadi et al (2014) investigated the criterion validity of Armband and Actiwatch for assessing sleep disturbances in LBP. Fifty LBP patients underwent overnight sleep recordings at the same time and were assessed using both the PSG and Armband. Among the 50 patients, 33 wore an Actiwatch. Criterion validity was calculated using epoch-by-epoch agreement, sensitivity, specificity and prevalence and bias- adjusted kappa (PABAK) for sleep versus wake between each device and PSG. The relationship between PSG and the two devices were assessed using intraclass correlation coefficients (ICC 2, 1). The study participants showed symptoms of sub-threshold insomnia (mean ISI=13.2, 95% CI=6.36) and poor sleep quality (mean PSQI=9.20, 95% CI=4.27). Observed agreement with PSG was 85% and 88% for the

Armband and Actiwatch. Sensitivity was 0.90 for both devices and specificity was 0.54 and 0.67 and PABAK of 0.69 and 0.77 for the Armband and Actiwatch respectively. The ICC (95%CI) was 0.76 (0.61 to 0.86) and 0.80 (0.46 to 0.92) for total sleep time, 0.52 (0.29 to 0.70) and 0.55 (0.14 to 0.77) for sleep efficiency, 0.64 (0.45 to 0.78) and 0.52 (0.23 to 0.73) for wake after sleep onset and 0.13 (0.15 to 0.39) and 0.33 (0.05 to 0.63) for sleep onset latency, for the Armband and Actiwatch, respectively. These results showed that both devices have varied criterion validity across the sleep parameters. Researchers (Lavie et al., 1992, Long et al., 2017, Kravitz et al., 2015 & Connaughton et al., 2014) have also noted excellent validity for measures (by using the Respironics Actigraphy) for total sleep time, good validity for measures of sleep efficiency and wake after onset to poor validity for sleep onset latency.

**Proinflammatory cytokines.** IL-6 is considered a key inflammatory response mediator (Hirano et al., 2005). IL-6 is chosen as representative of an exemplary proinflammatory cytokine, as it is more dependable detected and evaluated than the other classic pro-inflammatory cytokines (TNF alpha and IL-1 beta) (Fernandez-Botran, 2010). These cytokines are multifunctional components of the pro-inflammatory response that are absent under normal circumstances but produced at enhanced levels as a result of environmental and psychosocial stress. All samples were assessed in duplicate. Sensitivity is < 0.7 pg/ml for IL-6 and <3.9 pg/ml for TNF-alpha. Intra assay variability is <7 % for these cytokines. Blood amount of 10 ml were collected by venipuncture and plasma were frozen to -20 degrees Celsius for batch analysis. Plasma cytokines were measured using an enzyme linked immunosorbent assay (ELISA).

**Depressive mood.** Depressive mood was measured by the Center for Epidemiologic Studies Depression Scale (CES-D). This is a 20-item tool used to assess frequency and duration



of depressive symptoms. The CES-D has good construct validity in clinical and community samples, good test-retest reliability and internal consistency alpha of 0.86 (Radloff, 1977). The CES-D asks respondents to rate the frequency with which each symptom or feeling occurred during the previous 7 days. Item content is rated on a 4-point scale ranging from 0 (*rarely or less than one day*) to 3 (*most or all of the time, 5-7 days*), so that total scores range from 0 to 60. Higher scores indicate greater depression. A score  $\geq 16$  indicates risk for depression and a score of greater than 19 is used to assess clinically relevant depressive symptoms.

**Pain.** The Brief Pain Inventory is a self-reporting/interview tool is used patients with pain from chronic diseases or conditions such as cancer, osteoarthritis and low back pain and to assess the severity of pain and the impact of pain on daily functions. It is used to severity of pain, impact of pain on daily function, location of pain, pain medications and amount of pain relief in the past 24 hours or the past week. It takes five minutes to complete the short form, used in this study. It can be used as measures of pain severity and pain interference and Cronbach alpha reliability ranges from 0.77 to 0.91 (Cleeland et al., 1989).

**Quality of life.** The Quality of Life Index (QLI) developed by Ferrans and Powers was used in this study to measure quality of life in terms of satisfaction with life (Ferrans & Powers, 1985). This tool consists of two parts. The first part measures satisfaction in different aspects of life and the second part measures the importance of those same aspects. Scores are based on four categories including health and functioning, psychological/ spiritual, social and economic, and family (Ferrans, 1996; Ferrans & Powers, 1985; Ferrans & Powers, 1992; Ferrans, 1990; Warnecke, Ferrans, Johnson, & et al., 1996).

**Social support.** The Social Provisions Scale (SPS) assesses 6 relational provisions: attachment, social integration, reassurance of worth, reliable alliance, guidance, and nurturance (Cutrona, CE 1984). The degree to which social relationships currently support each provision is rated. Cronbach  $\alpha$  for the SPS is reported to be 0.84, and the reliability is reported to be 0.55 (Russell, D. et al., 1984). Subjective Social Status is defined as a person's sense of place within a hierarchy, which does not always agree with objective status (<http://www.macses.ucsf.edu/research/psychosocial/subjective.php>).

Of note, people who place themselves lower on the social ladder mount larger IL-6 responses to the acute stress challenge, than those who place themselves higher on the ladder. The MacArthur Scale of Subjective Social Status were administered to capture the participant's perception of their place on the social ladder, taking into account standing on multiple aspects of SES and social position. Respondents marked where they would place themselves on a ladder representing where people stand in the USA.

**Health behaviors.** Health behaviors can be altered by pain and, in turn, can influence the inflammatory and behavior responses to pain. Health behaviors were considered as covariates and were include: smoking, alcohol & caffeine intake, physical activity and medication use. (See Appendix for Health Assessment Survey.) Physical activity items were adapted from the Kaiser Physical Activity Survey and address 4 domains of physical activity in women: household and care giving, occupational, sport and exercise, and active living habits {Ainsworth, 2000}. Items to measure food habits were adapted from the Food Habits Questionnaire {Kristal, 1990}. Use of prescription medications and supplements (vitamins, minerals, nutritionals, herbals, soy products, and naturopathic remedies) are also included in the

Health Assessment Survey.

**Analgesic use.** To record the frequency and potency of use of analgesic medications, the participants were requested to log medications taken on a 4-point scale in terms of frequency of use and potency of analgesics. This were scored on a scale of 0 to 4 points (0 indicating no analgesic use, 1 indicating less than daily non-opioid analgesic use, 2 indicating daily non-opioid analgesic use, 3 indicating less than daily opioid use, and 4 indicating daily opioid use) (Esmer et al., 2010). Participants were asked to complete the instruments listed in Appendix A (Table 2).

Table 2. Study Instruments

	Sleep (PSQI)	Depression (CES-D)	Brief Pain Inventory (BPI)	Brief Fatigue Inventory (BFI)
Description	Measures and patterns of sleep	Assesses frequency and duration of depression symptoms	Measures severity of pain and impact on daily functions	Measures fatigue
No of Items	7	20	9	9
Method	Self-admin	Self-admin	Self - admin	Self-admin
Scoring	0-3 scale 3 negative	0-60,16 and above signs of depression	No scoring algorithm. Worst pain can be used to measure pain severity	0 -10 numeric rating scale where 0 is no fatigue or does not interfere and 10 is bad fatigue or completely interferes with activity/ work.
Reliability	High reliability (internal) $\alpha=0.83$ for 7 components	Good test–retest reliability and internal consistency $\alpha=0.86$	Cronbach alpha 0.77 to 0.91	
Validity	High validity in cancer patients	Good construct validity in clinic and commission samples		Excellent correlation with the fatigue component of the Function Assessment of Cancer Therapy ( $r = -0.88$ )

**Discrepancies from the original data collection plan.** A total of 69 participants were enrolled in the study and participated by providing data and blood samples. There were two ways that the sample of participants in the study differed from the planned sample. First, this final sample fell short of the planned sample size ( $N = 98$ ), which was determined based on an a priori power analysis. A sample size of at least 98 participants would have ensured that this study had adequate power to accurately identify any significant effects. With a sample size that does not meet this minimum threshold, in this study there is a chance that with some of the analyses described throughout this section, that a true effect may be missed and instead the null hypothesis may erroneously be accepted (Schoenfeld, 1980).

Second, this sample differed from the planned sample in terms of the age range of participants. The original study plan called for participants between the ages of 35 and 75 years. Several participants' ages fell outside of this range, which allowed us to include more participants to get closer to the planned sample size (though we still fell short, as outlined above). Specifically, four participants were below the planned age of 35 (these participants reported their ages as 22, 24, 30, and 32) and 1 was above the planned maximum age of 75 (this participant reported his/her age as 77). The limitations that result from this study based on these discrepancies between the planned and actual sample size will be discussed further in the Discussion section.

### **Study Limitations**

There are several potential study limitations. First, a cross sectional study design does not permit a determination of causal relationships. However, a cross sectional study can identify associations and guide the development of future hypothesis testing (Cohen et al., 2007). The

second challenge is validity. Internal validity refers to the strength of the inferences from the study. In this study, internal validity might be compromised since there is no control group that is compared with the study participants. External validity is the extent to which the study can be generalized to a universal population across time, place and persons (Carlson & Morrison, 2009). In this study, the sample is small and participants are recruited from a single facility. This will limit the generalizability of the study results. In addition, the proposed study will use convenient sampling, which increases the possibility of selection bias. It is also possible that those individuals with more intense pain or poorer quality of life may choose not to participate, further increasing the chance of selection bias (Heffner, 2011).

A variety of potential confounders need to be considered in investigations of individuals with CLBP. Important factors include: age, gender, race, education, marital status, employment, SES, drug use (prescription, over-the-counter, illicit drug use), smoking, alcohol and caffeine intake, co-morbidities, (prior depression, and psychological disorders), and general health behavior (diet, exercise, BMI).

### **Protection of Human Subjects**

IRB approval was obtained from the Loyola University Health System (LUHS). Extensive efforts were taken to protect data information and personal data of the study participants. Informed consent was being obtained from all study participants prior to study participation by the primary investigator. Study materials were is printed in English and at the fifth grade level of literacy.

According to the Department of Health and Human Services, risk should be justified by anticipatory benefits to research subjects or society as stated in all research ethics codes. Benefits

are the advantages from participating in the study and minimal risk refers to the probability of injury or harm as a result of participating in the study can vary from minimal to significant (2012). In this study, participants encountered minimal risk. This risk was primarily due to physical discomfort related to venipuncture, psychological or emotional distress resulting from sharing their personal information in relation to sleep disturbance, depression and chronic pain. Other potential risks included the loss of time due to travel time and loss of money. Further, some may interpret this as being observed in some manner. The participants were hence compensated for their time and travel expenses to the amount of \$25 after completion of the study. Efforts were being taken to minimize injury caused by venipuncture.

To protect participants against any potential risks, the investigator described in detail the study and the contents of the informed consent to the participants and then obtained consent. Participants were also being explained that they have the right to withdraw from the study at any time and their withdrawal will not affect the care provided to them otherwise.

Although this study might not provide benefits to the participants, it was explained to participants that it was hoped that results from this study will help in identifying how various symptoms can affect chronic low back pain patients and therefore interventions can be looked in to provide better quality of care.

## **Potential Risks**

### **Psychological Risks**

Completing the written instruments concerning psychological health may contribute to an increase in feelings of anxiety or depression. The CES-D was used to screen for depressive symptoms. It is important to emphasize that the CES-D is a screening tool used in population

studies—it is not a diagnostic depression tool. The recommended cutoff score for depression on the CES-D is 27. Each participant's score on the CES-D were evaluated prior to completion of the study appointment. If the participant scored 27 or greater on the CES-D, they were immediately notified of the score and encouraged to contact their primary care or mental health provider. If the participant chooses, the study staff will contact the participant's health care provider or, if they do not have a provider, the subject will be referred to Loyola University Mood Disorder Clinic. Any participant expressing thoughts of harming their self or others will be followed up immediately by accompanying the participant to the Loyola University Emergency Department, or nearest Emergency Department, or calling 911 as appropriate.

### **Blood Collection**

The collection of blood was performed by a registered nurse experienced in venipuncture. Efforts were made to make the participant comfortable during venipuncture and blood collection.

### **Adverse Events**

No adverse events were noted.

### **Confidentiality**

To maintain confidentiality and anonymity of study participants, unique code numbers were used for subject identification and the data files stored at Loyola University Chicago. Paper copies of data (only with unique codes) were stored in compliance with Loyola University Chicago requirements, including but not limited to a locked file cabinet in a locked room specifically designated for data storage for this project. The Master file of participant names and medical record numbers are stored only in a computerized encrypted file stored on a memory drive of a password protected computer that is located in a locked file cabinet within an office

having limited access. Only study personnel, as appropriate, will have access to participant identification (i.e., for purposes of enrollment, follow-up, medical record review).



## CHAPTER FOUR

### RESULTS

#### **Introduction**

Research suggests that chronic lower back pain (CLBP) is the chief complaint of primary care patients and is the number one reason that physicians choose to consult with health care providers. The cost of treating CLBP for the 100 million adult Americans who suffer from this type of pain is \$560 to \$635 million annually (Gaskin & Richards, 2011). Given the high prevalence and societal cost of CLBP, it is important to identify potential psychosocial factors that may contribute to the pain experience. The overall objective of this study was to understand of the extent to which sleep disturbance, depressive mood, and inflammatory processes interact to influence not only the experience of pain but also the quality of life of individuals with CLBP. To accomplish this objective, latent class analysis was used to identify CLPB behavioral symptom clusters and as well to evaluate the interactive relationships among depression, sleep disturbance, and fatigue in these patients. Further, the impact of inflammation on both pain and behavioral symptoms was explored. The following Aims and Hypotheses were addressed:

Aim 1: To identify behavioral symptom clusters in individuals with CLBP.

Hypothesis 1: Behavioral symptom clusters will be identified in individuals with CLBP.

Aim 2: To determine differences in pain experience (pain severity and interference) and quality of life among identified clusters.

Hypothesis 2: Pain experience and quality of life will differ among identified clusters.

Aim 3: Determine differences in inflammatory biomarkers based on symptom clusters and pain experience.

Hypothesis 3: Inflammation will differ with the pain experience, quality of life, and symptom cluster.

Aim 4: Explore regression models to determine predictors of the pain experience and quality of life in individuals with CLBP.

### **Sample Descriptive and Demographic Characteristics**

The sixty-nine participants in this study ranged between ages 22 and 77 years, with a mean age of 55.8 years (standard deviation [SD] = 12.9 years) and a median age of 57.0. Eighteen participants were male (26.1%) and 51 were female (73.9%). Forty participants identified as Caucasian (58.0%), fourteen identified as Hispanic or Latino (20.3%), 11 identified as African American (15.9%), and 4 identified as Asian or Pacific Islander (5.8%). Participants were diagnosed with a range of etiologies for their back pain by their medical provider and confirmed through medical record, including lumbar radiculitis, lumbar stenosis, lumbar facet arthropathy, lumbar disc herniation, and unspecified back pain. Twenty-five participants (38.5%) identified additional pain in the neck or knee area as coexisting medical conditions per medical record. Table 3 summarizes sample demographic characteristics and back pain diagnoses.

Table 3. Demographic Characteristics of the Sample (N=69)

<b>Gender</b>	<b>Frequency %(SD)</b>
Female	51 (73.9)
Male	18 (26.1)
<b>Ethnicity</b>	
Caucasian	40 (58)
Hispanic/Latino	14 (20.3)
African American	11 (15.9)
Asian/ Pacific Islander	4 (5.8)
<b>Diagnosed Conditions</b>	
Lumbar radiculitis/disc herniation	26
Spinal stenosis/Lumbar	7
Lumbar facet arthropathy	17
Sacroiliac joint pain	5
Unspecified back pain	14

*SD = Standard deviation.*

**Statistical analysis.** Descriptive statistics for each of the study variables were computed (see Table 4) and assessed for normality and outliers. All variables were within expected ranges. The skewness and kurtosis values were normally distributed (-3 to 3), indicating no for transformation of these variables. Hence, parametric analyses were used to address study hypotheses. Analgesic use was recoded to a dichotomous variable where non-opioid use was 0 and opioid use is 1.

Table 4. Descriptive Statistics for Study Variables

	Sample Mean (SD) (N=69)	Cluster 1 Mean (SD) (N=34)	Cluster 2 Mean (SD) (N=35)
Average Hours Slept	6.32 (1.61)	5.43 (1.10)	7.70 (1.33)
Sleep Disturbance (PSQI)	9.30 (4.49)	12.44 (2.32)	6.12 (2.79)
Depressive (CESD)	18.29 (12.33)	26.15 (11.56)	11.52 (5.24)
Fatigue (BFI)	5.68 (2.35)	6.76 (1.72)	4.34 (2.41)
Quality of Life	19.21 (0.90)	18.72 (0.73)	19.66 (0.81)
Inflammation (IL-6)	2.78 (1.87)	3.15 (2.17)	2.23 (1.21)
Pain Severity (BPI)	5.90 (1.77)	6.10 (1.92)	5.29 (1.44)
Pain Interference (BPI)	6.30 (2.23)	6.97 (1.87)	5.61 (2.57)
Social Support (SPS)	2.55 (0.48)	2.62 (0.39)	2.43 (0.62)
	Frequency (%)	Frequency (%)	Frequency (%)
Analgesic Use	18 (26)	11 (32)	6 (17)

*Abbreviations: QoL* Quality of life, *CES-D* Center for Epidemiology Studies Depression Scale, *BPI-S* Brief Pain Inventory (Severity), *BPI* Brief Pain Inventory (Interference), *SPS* Social Provisions Scale, *BFI* Brief Fatigue Inventory, *PSQI* The Pittsburgh Sleep Quality Index, *IL-6* Interleukin-6.

**Preliminary results.** Preliminary results revealed that based on established cut off scores, 67% of sample reported  $CESD \geq 16$  (elevated risk for depression) and 85% of the sample reported  $PSQI \geq 5$  (increased sleep disturbance) per Table 5.

Table 5. Bivariate Correlations Between All Study Variables

	QoL	CESD	BPI-S	BPI-I	SPS	BFI	Analgesic	IL6	Hours sleep
CESD	<b>-.54**</b>								
BPI-S	-.11	.19							
BPI-I	<b>-.34*</b>	<b>.41**</b>	<b>.63**</b>						
SPS	.01	.05	.02	.02					
BFI	<b>-.41**</b>	<b>.47**</b>	<b>.47**</b>	<b>.69**</b>	.06				
Analgesic	<b>-.35*</b>	<b>.35**</b>	<b>.40**</b>	<b>.40**</b>	-.21	<b>.37**</b>			
IL6	-.11	.20	<b>.34**</b>	.27	-.05	.20	.1325		
Hours sleep	.20	<b>-.31*</b>	<b>-.29*</b>	-.15	-.10	-.25	.05	-.20	
Sleep Dist.	-.23	<b>.42**</b>	<b>.26*</b>	.17	-.20	<b>.38**</b>	.21	.18	-.24

\*. Correlation is significant at the 0.05 level (2-tailed). \*\*. Correlation is significant at the 0.01 level (2-tailed).  
 Abbreviations: QoL □ Quality of life, CES-D □ Center for Epidemiology Studies Depression Scale, BPI-S □ Brief Pain Inventory (Severity), BPI-I □ Brief Pain Inventory (Interference), SPS □ Social Provisions Scale, BFI □ Brief Fatigue Inventory, PSQI □ The Pittsburgh Sleep Quality Index.

As a part of the preliminary analyses, a correlation analysis was conducted, and Pearson's correlation coefficients were examined between each pair of study variables. As shown in **Table 4**, quality of life was negatively correlated with depressive mood ( $r = -0.54, p = 0.01$ ), pain interference ( $r = -0.34, p = 0.05$ ), fatigue ( $r = -0.41, p = 0.01$ ), and analgesic use ( $r = -0.35, p = 0.05$ ). Depressive mood was significantly positively related to pain interference ( $r = 0.41, p = 0.01$ ), fatigue ( $r = 0.47, p = 0.01$ ), analgesic use ( $r = 0.35, p = 0.01$ ), and sleep disturbance ( $r = 0.42, p = 0.01$ ) and negatively correlated with average amount of sleep per night ( $r = 0.31, p = 0.01$ ). Pain severity was positively related with pain interference ( $r = 0.63, p = 0.01$ ), fatigue ( $r = 0.47, p = 0.01$ ), analgesic use ( $r = 0.40, p = 0.01$ ), inflammation ( $r = 0.34, p = 0.01$ ), and sleep disturbance ( $r = 0.26, p = 0.05$ ), and negatively related with average amount of sleep per night ( $r$

= .29,  $p = 0.05$ ). Pain interference was positively related to fatigue ( $r = .69$ ,  $p = 0.01$ ), and analgesic use ( $r = .40$ ,  $p = 0.01$ ). Fatigue was positively related to sleep disturbances ( $r = .38$ ,  $p = 0.01$ ) and analgesic use ( $r = .37$ ,  $p = 0.01$ ). IL-6 was positively correlated with sleep disturbances ( $r = .33$ ,  $p = 0.01$ ). These preliminary analyses provide support for the hypothesis that these variables are related.

**Differences between clusters.** A series of univariate analyses were conducted to determine whether there were any subgroup differences (age, gender, race/ethnicity, coexisting pain) in any of the main study variables. In this manner, the inclusion of demographic characteristics as covariates for the main study analysis was determined. Given that all study variables were continuous in nature, univariate analyses relied on a technique that tested for any significant mean difference in scores for each measure by subgroup.

To test for gender differences, independent samples t-tests were conducted to determine if there were any significant differences in mean scores for males and females. Independent samples t-tests are appropriate for use when evaluating mean differences in continuous variables between two subgroups. Results indicated that there were no significant difference between male and female participants in quality of life ( $t(59) = 0.77$ ,  $p = .45$ ), depressive mood ( $t(59) = 0.73$ ,  $p = .47$ ), pain severity ( $t(59) = 1.21$ ,  $p = .23$ ), pain interference ( $t(59) = 0.89$ ,  $p = .38$ ), social support ( $t(59) = 0.61$ ,  $p = .55$ ), fatigue ( $t(59) = 1.00$ ,  $p = .32$ ), number of hours of sleep ( $t(59) = 0.79$ ,  $p = .43$ ), sleep disturbance ( $t(59) = 1.35$ ,  $p = .18$ ), analgesic use ( $t(59) = 1.54$ ,  $p = .13$ ), or inflammation ( $t(59) = 0.89$ ,  $p = .38$ ).

To examine whether age was significantly associated with any of these continuous study variables, correlation analyses were conducted and Pearson's correlation coefficients ( $r$ ) were

examined. Correlation analyses are appropriate for use when comparing the association between two continuous variables. In this study, age was a continuous variable and so were each of the study variables. Results of these correlation analyses indicated that age was not significantly associated with any of the study variables ( $r$ 's = -.18 - .14,  $p$ 's > .05).

To test for race/ethnicity differences in the study variables, analyses of variance (ANOVAs) were conducted to determine if there were any significant differences in mean scores based on race/ethnicity. ANOVA is appropriate for use when comparing mean scores between more than two groups – in this case, we compared mean scores between Caucasian, Hispanic/Latino, African American, and Asian/Pacific Islander participants. Results of these ANOVAs indicated that none of the study variables that differed significantly by racial/ethnic group. Other study variables were planned for inclusion as covariates in the main study analysis: social support and use of analgesics. Variables should only be included as covariates if they are found to be significantly associated with the outcomes of interest. In this case, preliminary analyses were conducted to examine whether these covariates were significantly associated with pain severity, pain interference, and quality of life, as these are the dependent variables in this study. Given that all these covariates and dependent variables are continuous in nature, bivariate correlation analyses were conducted, and Pearson's  $r$  values were assessed to determine whether there was a significant association between each covariate-dependent variable pair. **Table 2** earlier in this section provides support for including analgesic use as a covariate in the main study analyses, given that this variable was significantly associated with all of the outcome variables (quality of life, pain severity, and pain interference). In contrast, social support was not

significantly associated with any of the outcome variables, so this variable was not included as a covariate in any of the main analyses.

**Aim 1: To identify behavioral symptom clusters in individuals with CLBP.** To address this first aim and examine whether the first hypothesis – that behavioral symptom clusters would be identifiable in individuals with CLBP – a latent class analysis (LCA) was conducted using the mixture modeling technique within Mplus. First a two-class model was tested using the following variables: average amount of average amount of sleep per night, sleep disturbance, depressive mood, and fatigue. Results from this analysis (shown in Table 6) indicate that this two-class model provided a good fit for the data. Next, a three-class model was tested using the same variables with the same Mplus technique. This model also indicated a good fit for the data.

Table 6. Results of the Two-Class Latent Class Analysis Model

	HBS			LBS		
	Estimate	S.E.	<i>p</i>	Estimate	S.E.	<i>p</i>
Average Nightly Sleep	5.43	0.18	<.001	7.7	0.27	<.001
Sleep Disturbance	12.44	0.40	<.001	6.12	0.56	<.001
Depressive Mood	26.15	1.98	<.001	11.52	1.05	<.001
Fatigue	6.68	0.30	<.001	4.35	0.49	<.001

To identify which of these models provided the better fit (two-class vs. three-class), a Vuong-Lo-Mendell-Rubin (VLMR) likelihood ratio test was conducted with the three-class model. This *post hoc* statistical test compares the model with K classes (in this case, three



classes) with a model with K-1 classes (two classes). A significant VLMR test is an indication that the current model provides a significantly better fit to a set of data than the model testing one less class. The results of this *post hoc* analysis indicated that the three-class model did not provide a significantly better fit over the two-class model ( $p = .41$ ), therefore the two-class model was preferable and was used in all follow-up analyses for this study.

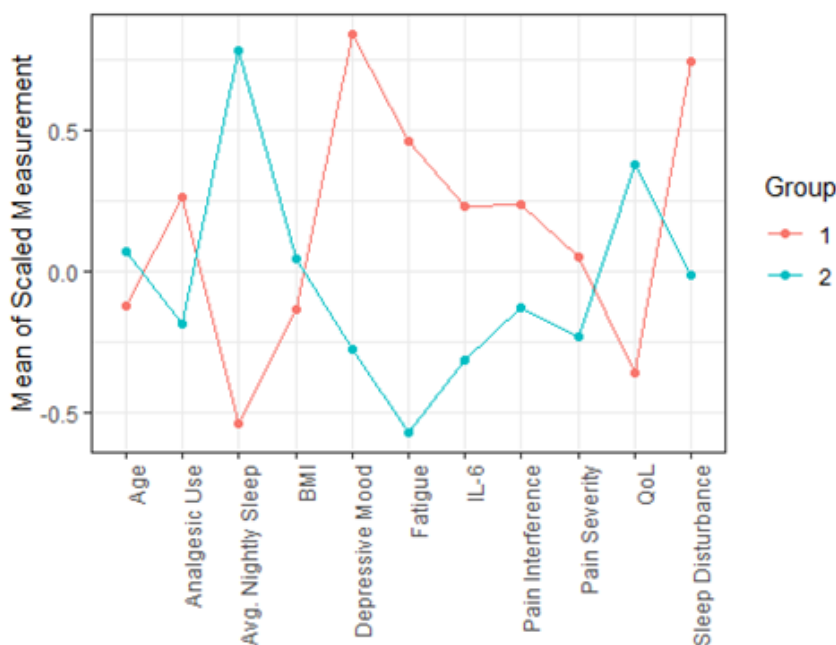
Based on the findings from LCA and *post hoc* VLMR likelihood ratio test, a new cluster variable was created and each participant in the sample was assigned a ‘1’ or ‘2’ to represent which cluster they fell into based on their scores for the measures of average amount of sleep per night, sleep disturbance, depressive mood, and fatigue. Based on LCA two behavioral symptom clusters were identified, Class 1 or "High Behavioral Symptoms" (HBS) characterized by more depressive symptoms, more fatigue, fewer average hours of sleep per night, and more sleep disturbance than participants who were assigned to Class 2, or "Low Behavioral Symptoms" (LBS). Participants who were assigned to HBS or LBS. (Shown in Table 7 and Figure 4).

Table 7. Relative Levels of Behavioral Symptoms

Cluster	Depressive Symptoms	Fatigue	Average Hours Sleep	Sleep Disturbance	IL-6
HBS (n=34)	↑	↑	↓	↑	↑
LBS (n=35)	↓	↓	↑	↓	↓

Average latent class probabilities for most likely class membership by latent class assignment showed strong confidence in class assignment, with a 93.8% match for participants in HBS and a 96.9% match for participants in LBS.

Figure 4. Means of scaled measures (z scores)



The sample was split relatively evenly between these two clusters, with 34 participants in HBS (49.3%) and 35 participants in LBS (50.7%). No participants were excluded from assignment, making this a 100% match. Chi-square analyses were conducted to examine whether the gender or racial/ethnic breakdown of these groups was proportionally different. Participants in HBS were 74% female and 72% of participants in LBS were male; this difference was not significant ( $\chi^2 = 0.73, p = .39$ ). Approximately 58% of each cluster identified as Caucasian, 20% as Hispanic/Latino, 15% as African American, and 5% as Asian/Pacific Islander; which by chi-square test was not significant ( $\chi^2 = 0.25, p = .62$ ). An independent samples t-test was conducted to examine whether the mean age of participants in each cluster was significantly different. The mean age of participants in HBS was 54.12 years and the mean age of those in LBS was 56.76 years. This difference was not statistically significant ( $t = 0.72, p = .47$ ) (Table 8).

Table 8. Demographic Characteristics by Cluster Membership

Cluster	Male	Female	Caucasian	Hispanic	African American	Asian/Pacific Islander	Age
HBS	74%	72%	58%	20%	15%	5%	54.12
LBS	26%	28%					56.76
	$\chi^2 = 0.73, p = .39$		$\chi^2 = 0.25, p = .62$				$t = 0.72,$ $p = .47$

**Aim 2: To determine differences in the pain experience (pain severity and interference) and quality of life among identified clusters.** To address this second aim and examine whether the second hypothesis – that there would be differences in the pain experience and quality of life among identified clusters – a series of univariate general linear models were run (one model for each dependent variable). Cluster was the categorical independent variable, the three continuous dependent variables were quality of life, pain severity, and pain interference.

The first model examined quality of life. Participants in HBS reported lower quality of life scores than participants in LBS (Means = 115.8 vs. 140.9). This difference was significant ( $F(1,57) = 8.38, p < .05, \eta^2 = .16$ ). The second model examined pain severity. Participants in HBS reported higher pain severity than those in LBS (Means = 6.10 vs. 5.29). This difference was not significant ( $F(1,57) = 3.11, p = 0.08, \eta^2 = .06$ ). The third model examined pain interference, and again, participants in HBS reported higher pain interference than those in LBS (means = 6.67 vs. 5.61). This difference was significant ( $F(1,57) = 4.68, p = 0.04, \eta^2 = 0.10$ ). The statistical results of these analyses are presented in Table 9.

Table 9. Analysis Results for HBS and LBS

	Sum of Squares	<i>df</i>	Mean Square	<i>F</i>	<i>p</i>	$\eta^2$
Quality of Life	13.37	1	13.37	22.476	0.00001	0.38
Pain Severity	9.30	1	9.30	3.11	0.08	0.06
Pain Interference	22.75	1	22.75	4.68	0.04	0.10

**Aim 3: Determine differences in inflammatory biomarkers based on symptom clusters and pain experience.** A univariate general model was used to address the third aim and to examine whether the third hypothesis – that there would be differences in inflammatory biomarkers based on symptom cluster– was supported. In this model, inflammation was entered as the continuous dependent variable, cluster was entered as the categorical independent variable, and BMI was entered as continuous covariates. This time, analgesic use was not included as a covariate, as earlier correlation analyses did not identify a significant association between analgesic use and inflammation. Participants in LBS had trend towards significantly lower inflammation levels than participants in HBS when controlling for BMI ( $F(1, 66) = 3.38, p = .07, \eta^2 = .06$ ).

Table 10. Differences in IL-6 Between Clusters

	Sum of Squares	<i>df</i>	Mean Square	<i>F</i>	<i>p</i>	$\eta^2$
Cluster	11.26	1	11.26	3.38	0.07	0.06
BMI	5.80	1	5.80	1.74	0.19	0.03

Exploratory models were evaluated to predict quality of life, pain severity, and pain interference by group; IL-6, and group by IL-6 interaction while controlling for BMI. Findings revealed that LBS has marginally significantly higher quality of life compared to HBS, even controlling for the interaction between IL-6 and Cluster membership. This model also shows that IL-6 is related to QoL when controlling for cluster and that the relationship between IL-6 and QoL differs by cluster. The model predicting pain severity changed substantially with the inclusion of the cluster by IL-6 interaction. Here, the findings showed that LBS had lower pain severity ( $t(49) = -2.61, p = 0.01$ ) and that the relationship between pain severity and IL-6 was significantly higher in LBS compared with HBS ( $t(49) = 2.61, p = 0.01$ ). The results for pain interference were effectively unchanged; pain interference was not significantly related to any of the independent variables ( $p > .011$ ). These results appear in Table 11.

Figure 5. Interaction effects of IL-6 between pain severity, interference, and quality of life among identified clusters

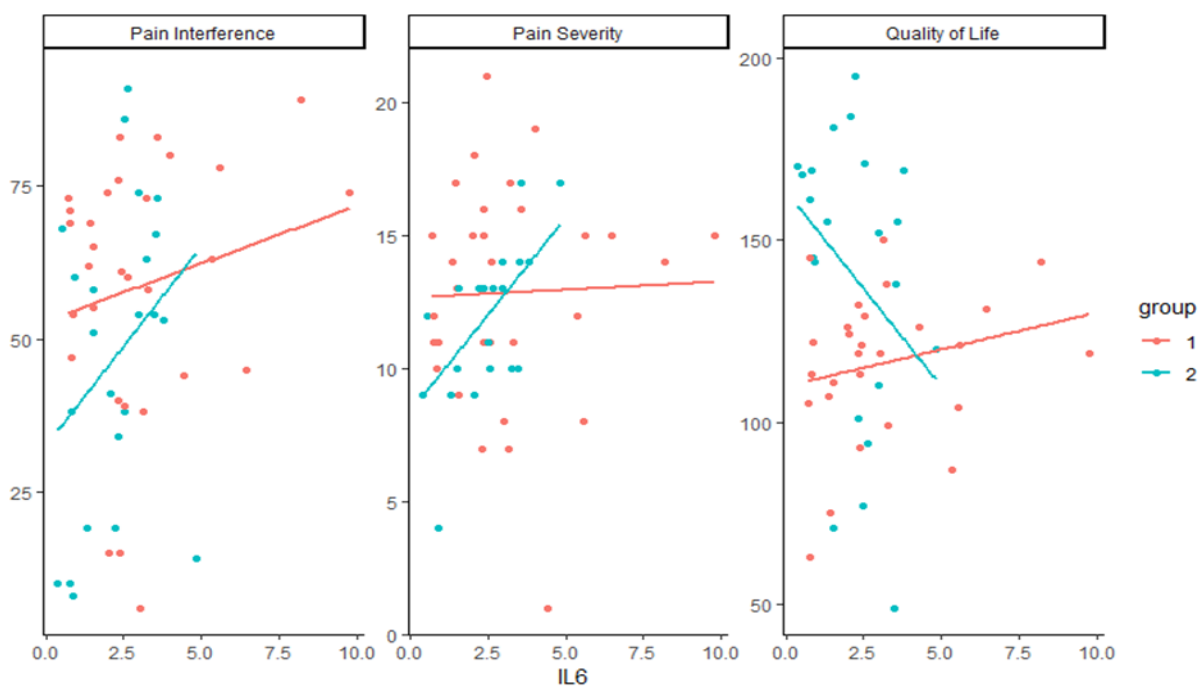


Table 11. Differences in the Pain Sseverity, Interference, and Quality of Life Among Clusters

	<i>B</i>	S.E.	$\beta$	<i>t</i>	<i>p</i>
<b>QoL</b>					
Intercept	55.97	24.10	-	2.01	0.05
Cluster 2	53.75	16.82	0.52	1.80	0.08
IL6	14.99	7.64	0.82	1.96	0.05
BMI	0.003	0.02	0.03	0.13	0.89
Cluster 2:IL6	-12.97	6.23	-0.71	2.083	0.04
<b>Pain Severity</b>					
Intercept	17.29	2.67	-	6.47	0.81
Cluster 2	-4.53	1.89	0.03	-2.40	0.02
IL6	-1.59	0.85	-0.79	-1.87	0.07
BMI	-0.003	0.002	-0.26	-1.66	0.10
Cluster 2:IL6	1.68	0.69	0.84	2.43	0.02
<b>Pain Interference</b>					
Intercept	72.87	17.53	-	4.16	0.00
Cluster 2	-20.06	12.38	-0.33	-1.62	0.11
IL6	-2.48	5.61	-0.19	-0.44	0.66
BMI	0.004	0.01	0.04	0.28	0.78
Cluster 2:IL6	4.33	4.55	0.34	0.95	0.35

**Aim 4: To explore regression models to determine predictors of behavioral clusters and quality of life in individuals with CLBP.** To address Aim 4, which was exploratory in nature and therefore was not paired with a hypothesis, two regression models were conducted, which examined whether specific behavioral factors and inflammation (IL-6 levels) are predictive of the behavioral clusters or quality of life identified by LCA.

In the first model, which was a logistic regression model, analgesic use, BMI, and IL-6 levels were included as the continuous independent variables and the LCA-based behavioral cluster (HBS or LBS) was entered as the categorical dependent variable. The results of this analysis suggested that only IL-6 predicted Cluster membership ( $t(45) = 2.02, p = .04$ ), such that higher IL-6 levels predict a higher probability of belonging to HBS (see results in Table 12).

Table 12. Predictor of Clusters

	<i>B</i>	S.E.	Wald	<i>df</i>	<i>p</i>	Odds Ratio
(Intercept)	1.21	0.73	1.65	1	0.10	3.34
Analgesic	-0.96	0.72	-1.34	1	0.18	0.38
IL6	-0.57	0.28	-2.02	1	0.04	0.57
BMI	0.002	0.001	1.93	1	0.05	1.002

In the second model, which was a linear regression model, analgesic use, BMI, and IL-6 levels were included as the continuous independent variables and quality of life was entered as the continuous dependent variable. This model indicated that analgesic use significantly predicted quality of life, such that great analgesic use was related to lower quality of life. In contrast, neither inflammation (IL-6) nor BMI predicted quality of life.

Table 13. Predictor of Quality of Life

	<i>B</i>	S.E.	$\beta$	<i>t</i>	<i>p</i>
(Intercept)	139.94	8.13	--	17.22	0.00
Analgesic	-21.44	10.10	-.34	-2.12	0.04
IL6	-1.62	2.41	-.04	-0.67	0.51
BMI	0.02	0.02	.14	0.71	0.48

### Summary

This study examined whether sleep disturbance, depressive mood, fatigue, and inflammation interact to impact the experience of pain and quality of life among patients suffering from CLBP. Table 14 shows the study aims and hypotheses and addresses whether support was identified for each hypothesis or whether the null hypothesis was accepted.

Table 14. Summary of Study Findings

	Aim	Hypothesis	Finding
1	To identify behavioral symptom clusters in individuals with CLBP	Behavioral symptom clusters will be identifiable in individuals with CLBP	Fully supported
2	To determine differences in the pain experience (pain severity and interference) and quality of life among identified clusters	There will be differences in the pain experience and quality of life among identified clusters	Partially supported
3	Determine differences in inflammatory biomarkers based on symptom clusters	There will be differences in inflammatory biomarkers based on symptom clusters	Partially supported
4	Explore regression models to determine predictors of behavioral symptom clusters and quality of life in individuals with CLBP	Behavioral and inflammatory predictors will be related to clusters identified and quality of life	Partially supported



Regarding Aim 1, the latent class analysis that was conducted identified two distinct classes of study participants. Participants in HBS reported less sleep on average per night, more sleep disturbance, more depressive moods, and more fatigue compared to participants in LBS. 2. Regarding Aim 2, univariate general linear models found that there was a significant difference in quality of life and pain interference between the two cluster of participants, with those in HBS reported experiencing lower quality of life and pain interference than those in LBS. There was no significant difference, however, in pain severity between the two clusters of participants. Regarding Aim 3, there was no significant difference in inflammatory biomarkers (IL-6) between the two clusters when controlling for BMI. Finally, regarding Aim 4, in which exploratory regression analyses examined whether behavioral factors and inflammatory levels predicted behavioral profile and quality of life, inflammation levels predicted behavioral cluster membership and analgesic use predicted quality of life.

Overall the findings of this study provide important contributions to the understanding of the differential effects that CLBP can have on patient's quality of life and pain experience, based on other factors, including sleep disturbance, depressive mood, fatigue, and inflammation levels. In the next section, these results are summarized and paired with a discussion of the implications associated with the findings from this study. In addition, strengths of this study, limitations to the generalizability of the findings will be discussed, considering the reduced sample size that was utilized based on difficulties with participant recruitment. Finally, the next section will end with a conclusion that suggests future directions for research that may build off this study's findings and will discuss this research team's future work in this area.

## CHAPTER FIVE: DISCUSSION

### SUMMARY OF FINDINGS

#### **Introduction**

The overall purpose of this study was to identify behavioral symptom clusters (i.e., based on measures of sleep disturbance, depressive mood, and fatigue) and to determine the relationship among identified clusters, inflammation (i.e., plasma IL-6), pain and quality of life in patients with CLBP. LCA revealed a two-class model. Participants in Class 1 characterized by High Behavioral Symptoms (HBS) had more depressive mood, fatigue, and sleep disturbance (including less sleep per night) compared to participants in Class 2 characterized by Low behavioral Symptoms (LBS). Univariate general linear models revealed HBS participants reported worse QOL than those in LBS. Pain severity was not significantly different between the classes, but pain interference was significantly different. (though exploratory analysis suggested this may be due to a moderating effect of IL-6 on pain severity). Levels of IL-6 (controlling for BMI) were trending towards significantly greater in HBS participants, compared to LBS, with higher levels of IL-6 correlating with greater pain severity and more sleep disturbance. Further, logistic regression analysis revealed higher levels of IL-6 predicted HBS membership. To the author's knowledge, these findings are the first to evaluate behavioral symptom clusters with respect to inflammation, pain, and quality of life.

These findings suggest that behavioral symptom clusters in those with CLBP contribute

to worse QOL. Moreover, inflammation contributes to the complex relationship between behavioral symptoms and pain severity. Clinical recognition of behavioral symptom clusters can foster more comprehensive pain assessment and tailored interventions for CLBP patients. The following will discuss these findings in comparison to similar studies evaluating depressive mood, sleep disturbance, fatigue and inflammation on the pain experience and QoL of those with CLBP. Clinical implications are identified and future directions for research are derived.

### **CLBP, Depression and Inflammation**

Depression is commonly associated with chronic back pain and can also be a risk factor for both low back pain and sciatica (Parreira P et al., 2018). In our study, depressive mood was measured using the CES-D, a tool designed to screen populations for risk for depression (Radloff, L. S. et al., 1977) and revealed a mean depression scores of 21, with 67% of the sample reporting CES-D scores that were above the cut score (i.e., >16), indicating risk for depression.

Poleshuck et al reported a mean CES-D score of 29.3 for persons with CLBP (Poleshuck et al., 2013). In comparison, our study showed lower mean depression scores (21) but still above the cut-score of 16. Systematic reviews (Howren et al., 2009; Pinheiro et al., 2016) confirm the high prevalence of depressive mood in persons with acute and chronic back pain. For example, among seventeen articles reviewed, eleven reported depressive symptoms at baseline related to worse low back pain outcomes (presence of CLBP, medical care seeking associated with CLBP, and activity-limiting CLBP) in follow-up. All studies regardless of statistical significance showed that there was a positive relationship between depressive symptoms and low back pain (Pinheiro et al., 2015).

Depression can also affect functionality of persons with CLBP. For example, depression

is a significant mediator of the relationship between pain and self-perceived disability in people with CLBP (Marshall et al., 2017), emphasizing the importance of addressing symptoms of depression in those with CLBP. Further, persons with CLBP who had both anxiety and depression had higher pain severity, and higher pain-related disability. Further, the interaction between anxiety and depression predicted changes in pain interference at one-year follow up (Oliviera et al., 2018). The present study found that those reporting greater depressive mood had poorer QOL, greater pain interference with activities, more fatigue, sleep disturbance, fewer hours of sleep per night, and greater analgesic use. Of note, acute back pain may differ from chronic back pain, as a recent study found that depression in persons with acute back pain was not significantly associated with perceived disability (Salt, E et al., 2018). These findings suggest that duration of back pain influences the extent to which depressive symptoms modify pain perception, as well as perception of disability.

Inflammation is a common pathway linking depression and pain. For example, persons with major depression exhibit increased serum and/or plasma concentrations of IL-6 (Alesci et al., 2005; Sluzewska et al., 1995), and this may potentiate pain particularly in pain conditions involving inflammatory processes. In another study, higher IL-6 levels have been associated with both greater pain and greater chronic medical comorbidity in patients with greater depressive symptoms; whereas, IL-6 was unrelated to pain among patients without clinically significant depressive symptoms (Poleshuck et al. 2013). Hence, the authors concluded that depression may increase vulnerability to pain, perhaps through elevated levels of inflammatory markers, such as IL-6. Findings from our study, revealed that IL-6 predicted cluster membership, such that higher IL-6 levels predict a higher probability of belonging to HBS.

Klyne et al., evaluated circulating pro-inflammatory cytokines and C-reactive protein (CRP) to explore the relationship of these inflammatory markers with pain severity and other symptoms in acute low back pain (LBP). That study enrolled ninety-nine individuals who were evaluated within two weeks of onset of acute LBP and compared to fifty-five pain-free controls. Findings revealed that CRP was higher in LBP patients compared to controls and in those with high- than low-pain. In addition, IL-6 was higher in those with high than low-pain ( $p < 0.05$ ), but not compared to controls. The investigators concluded that systemic CRP and IL-6 are important contributors to inflammation in the early post-onset phase of LBP and that various factors such as sleep quality and psychological status can shape these responses (Klyne et al., 2017). Similar to this study, our study participants with HBS were trending towards significantly higher IL-6 levels than participants in the LBS cluster when controlling for BMI. Although participants had chronic but not acute back pain, there is a similarity in the findings with respect to behavioral symptoms and sleep associating with the pro-inflammatory cytokines.

### **CLBP, Fatigue and Inflammation**

Findings from several studies demonstrate that fatigue is prevalent and problematic for individuals with CLBP, and that a complex relationship exists among fatigue, depression, and other symptoms common in those with CLBP (De Rooij et al., 2014; Fishbain et al., 2004; Starkweather 2013; Snekkevik et al., 2014). For instance, De Rooij et al. prospectively evaluated 120 chronic widespread pain patients (CWP), participating in a multidisciplinary rehabilitation treatment. The results revealed that higher levels of pain, interference of pain, depression, and negative emotional cognitions, were associated with a higher level of fatigue; while improvement in depression was related to improvement in fatigue (De Rooij et al., 2014).

The present findings confirm the findings of this group, as persons with an HPS profile reported increased sleep disturbance, increased fatigue, and more pain severity, pain interference, and fatigue scores. Starkweather et al (2013), in a study of individuals with persistent radiculopathy, showed relationships among fatigue, pain, psychosocial factors, and selected biologic markers of immune activation, IL-6 and soluble IL-6 receptor (sIL-6R). Specifically, findings from that study revealed that individuals with moderate to high fatigue levels had greater psychological distress, depressive symptoms, IL-6 and sIL-6R, compared to those with low levels of fatigue.

The present study links fatigue to not only more intense behavioral symptoms, but also higher levels of IL-6. Findings revealed that those with greater fatigue had worse QOL, more depressed mood, more sleep disturbance, increased pain severity and greater pain interference. Additionally, fatigue was also significantly positively associated with sleep disturbances and analgesic use.

Differences in instruments used to measure fatigue across studies, makes it difficult to compare levels of fatigue. In this study, fatigue was measured using the BFI, a tool used to measure fatigue in cancer populations. In another study, Starkweather assessed fatigue in patients with persistent radiculopathy using the Profile of Mood States Fatigue/Inertia (POMS-F/I), a seven-item subscale that contains seven adjectives suggesting weariness, inertia, and low energy level and identified fatigue to be significantly correlated with psychologic distress, depressive symptoms, IL-6, and sIL-6R (Starkweather 2013). However, the level of fatigue was not correlated with pain intensity (Starkweather 2013), which is similar to that of other studies (Snekkevik et al., 2014; Fishbain et al., 2004; Fishbain et al., 2005).

### **CLBP, Sleep and Inflammation**

Individuals suffering from CLBP report increased duration of sleep onset, reduced total sleep time, and lower sleep efficiency (Kelly et al., 2011), consistent with our findings. Using the PSQI we demonstrated that 85% of the sample reported  $PSQI \geq 5$  (over the established cut-score, indicating sleep disturbance), and that greater sleep disturbance was associated with greater pain severity and pain interference, and, not surprisingly, greater daytime fatigue. Also, those individuals who reported more sleep disturbance and also used more analgesics. On the other hand, those who reported more social support had better sleep quality. IL-6 was positively correlated with sleep disturbance. Further, participants with HBS reported less sleep on average per night and more sleep disturbance, compared to those with LBS.

Several studies have evaluated sleep quality and its influence on facilitating and/or exacerbating pain through elevations of pro-inflammatory cytokines, like IL-6. Similar to the present results, reductions in sleep quality and quantity have each been associated with higher daytime circulating levels of IL-6 (Heffner et al., 2012). Recent meta-analysis concluded that sleep deprivation is accompanied by increases in systemic inflammation (Irwin et al, 2015) and systemic inflammation has been found to decrease pain threshold in humans who are sleep deprived (De Godin et al, 2013). In another study, patients with temporomandibular pain disorders (40 females) who were classified as having high disability (Graded Chronic Pain Scale) also had the highest PSQI. Moreover, plasma levels of IL-1 $\beta$ , IL-6, IL-10, and TNF- $\alpha$  were significantly increased in the high-disability group. Further, the plasma cytokine levels were significantly correlated with increased sleepiness (Epworth Sleepiness Scale) and PSQI scores suggestive of sleep disturbance (Park, J. W., & Chung, J. W, 2016). While conclusive data is still

limited for human subjects, the findings of this study are consistent with the above studies in that greater sleep disturbance associated with greater levels of IL-6.

Recent findings suggest the possibility of aberrant glial activation in the establishment and/or maintenance of central sensitization to pain. Nijs et al. reviewed preclinical neurobiochemistry of animals and found high levels of BDNF, IL-1 $\beta$ , TNF- $\alpha$  increase the excitability of the central nervous system neurons. The authors discussed the possibility that glial activity in chronic pain may have been triggered by severe stress exposure, and/or sleeping disturbances, each of which are established initiating factors for chronic pain development (Nijs et al.,2017). Results from this study also indicate the potential for sleep disturbance, as a behavioral factor, to contribute to increased inflammatory cytokine levels. Thus, investigation of the relationship of behavioral symptoms and glial activation is warranted.

### **Symptom Clusters and Chronic Illness**

Findings from this study revealed two distinct behavioral symptom clusters, named HBS and LBS. Participants in HBS reported less sleep on average per night, more sleep disturbance, more depressive mood, and more fatigue compared to participants in LBS. There was a significant difference in pain interference and quality of life between the two participant Classes, with those in LBS experiencing a significantly higher quality of life than those in HBS. Although there was no significant difference, in pain severity there was a trend towards higher levels of circulating IL-6 in HBS compared to LBS, when controlling for BMI. Further, inflammation levels predicted behavioral Class membership. Only a handful of studies have examined symptom clusters in individuals with CLBP. One such study identified three clusters of symptoms in a cohort of patients with chronic low back pain (n=294). These clusters were



derived from multiple psychological questionnaires, with cluster 3 exhibiting the highest scores across cognitive (eg, kinesiophobia, pain catastrophizing, endurance behaviors, low acceptance, low pain self-efficacy) and higher scores in affective factors (e.g., depressed mood, anxiety, stress) and significantly greater lumbar pressure pain sensitivity, more undiagnosed comorbid symptoms, and more widespread pain than other clusters (Rabey et al.,2016). Although the present study only identified two behavioral symptom clusters, it is possible that other cluster phenotypes might be identified when a greater range of symptoms are measured. Nevertheless, the findings from the present study add to the emerging work regarding symptom clusters in CLBP, and whether unique clusters predict worse pain and/or QOL.

There is a more robust literature describing symptom clusters in other patient populations, such as patients with heart failure and cancer. In heart failure patients, two domains of symptom clusters have been identified, clusters of physical symptoms (fatigue, pain, drowsiness, nausea and reduced appetite) and clusters of emotional/cognitive symptoms (anxiety, and depression). Unlike the present study, studies of heart failure patients have not included sleep disturbance in cluster analysis, nor has this area of symptom cluster research included the relationship of clusters to inflammatory cytokines.

Other studies have focused on spinal cord injury (SCI) patients, in an attempt to understand chronic pain and its effect on functional ability and quality of life. A cluster analysis study on SCI patients revealed 3 subgroups: (1) dysfunctional (34.6% of all participants), (2) interpersonally supported (33.0% of participants), and (3) adaptive copers (32.4% of participants), based on pain severity, life interference, affective distress scores, life control, and activities scores (Widerstrom-Noga, Felix, Cruz-Almeida, & Turk, 2007).

The literature evaluating symptom clusters in cancer patients is very robust and quickly translated with impact on patient care. Researchers have even started looking at additional studies to test intervention designed to manage a specific cancer symptom cluster. Such studies have been conducted in cancer patients undergoing chemotherapy, as well as cancer survivors who had completed treatment. Harrington et al (2010) conducted a systematic review of studies (2000-2008) examining late and long-term effects of cancer treatment, and concluded that symptom burden in cancer survivorship was consistent in four cancers (prostate, breast, gynecological and colorectal), with the most common symptoms being depressive symptoms, pain, and fatigue. Dong et al. (2014) identified 33 studies that analyzed symptom clusters in cancer patients that used various statistical methods (principal component analysis, exploratory factor analysis, and hierarchical cluster analysis) to analyze symptom clusters. The four symptom clusters identified were: anxiety-depression, nausea-vomiting, nausea-appetite loss, and fatigue-dyspnea-drowsiness-pain. In another literature synthesis of 21 multinational studies (sample of 4067 cancer patients), revealed that there was a discrete set of symptoms experienced by cancer patients receiving active treatment (Reilly et al., 2013). Ho et al (2015) in a longitudinal study examined the relationships among depression, fatigue and sleep disturbances in premenopausal breast cancer patients compared to postmenopausal women across three-time points. Results revealed that fatigue, depression and sleep disturbances manifest as a symptom cluster. These findings in cancer patients closely mirrors the behavioral symptom clusters identified by the present study evaluating patients with CLBP.

### **Implications for Research, Practice, and Theory**

The findings from the present study identified two clusters of behavioral symptoms in patients with CLBP, with a cluster of high levels of symptoms associating with worse QOL. Moreover, higher IL-6 contributed to the complex relationship between behavioral symptoms and pain severity. Clinical recognition of behavioral symptom clusters can foster more comprehensive pain assessment and tailored interventions for CLBP patients. The implications of this study on furthering nursing research, practice, theory and education are discussed below.

#### **Research**

An important area of research in low back pain is to investigate factors that contribute to the progression of acute pain to chronic pain. It is possible that unique symptom profiles may increase vulnerability for acute pain syndromes to become chronic. In contrast, reducing such symptoms and/or fostering health promoting activities, may counter such pain progression. Health promotion may include environmental and lifestyle (nutrition and physical activity) factors, which may reduce intensity of behavioral symptom and stem the progression of acute to chronic CLBP. Biological mechanisms that might underlie symptom clusters can also help to identify factors for transition of acute to chronic pain. There is a possibility that HBS cluster participants might have increased risk for acute pain persistence that becomes chronic pain. The findings from this study are a first step for examination of inflammatory markers as possible underlying mechanisms for symptom cluster profiles. The extent of other inflammatory processes that underlie the complex relationships among pain, depressive mood, and poor sleep if clarified can build the ability to help manage symptom clusters in CLBP patients. While IL-6 was the only marker tested, further research could analyze other inflammatory markers that may

play a role in CLBP. Another direction of research would be to develop valid instruments to measure symptom clusters. Improved measurement tools can equip nurse scientists to better measure cluster of symptoms in CLBP patients and predict health outcomes.

Behavioral symptom clusters may be reduced by complementary approaches that target unique clusters or symptom phenotypes. Emerging work suggests mindfulness or cognitive behavioral therapy may be beneficial for patients with CLBP. For example, Day et al., conducted a pilot randomized trial to compare the feasibility, tolerability, acceptability, and effects of group-delivered mindfulness meditation (MM), cognitive therapy (CT), and mindfulness-based cognitive therapy (MBCT) for CLBP. For the (Intent- To – Treat) ITT sample, large improvements in post-treatment scores for pain interference, pain intensity, physical function, and depression were found, with no significant between-group differences. Analysis of the follow-up data, however, revealed that MBCT participants improved significantly more than MM participants on pain interference, physical function, and depression (Day et al., 2019). Future studies that test mind-body interventions designed to target symptom clusters might prove to be a more efficient clinical approach that could be used to treat patients in outpatient or community settings.

### **Practice**

Nurses are at the forefront in providing direct patient care. The role of nurses in care of CLBP patients is well documented. In addition to educating patients on prescribed medications, nurses assist patients in referral to non-pharmacological modalities including cognitive behavioral approaches, acupuncture, yoga, meditation, and biofeedback. As noted above, such modalities may reduce emotional and behavioral responses to chronic pain conditions, and

improve quality of life. As a result, it is important to include assessment of a patient's emotions and behavioral symptoms in addition to assessment of pain, and to prescribe complementary approaches to assist the patient in dealing with a chronic pain condition.

Current trends in a comprehensive pain management program include a generic approach to identify risk. Using various symptom cluster profiles in CLBP patients can help nurses identify patients who might benefit more from one type of treatment option versus another. Additionally, the duration of the treatments can also be targeted based on the symptom profile. For example, if a patient reports increased sleep disturbance, and depression and underlying high levels of inflammation, a need for treatment with longer duration to target these symptoms might be beneficial versus a patient with a different profile.

The metaparadigm of nursing focuses on the health, person and environment. Approaching symptoms as clusters brings to practice the essence of nursing where a patient is viewed as a person with coexisting symptoms versus the objective approach of focusing only on pain. The identification of a cluster of behavioral symptoms that associate with poorer quality of life and which interact with inflammation as shown in this study, can serve as a first step to bring symptom cluster awareness to the forefront of clinical management of those with CLBP. In the future, studies can evaluate the clinical impact of interventions that target clusters of symptoms to determine their efficacy and ability to improve quality of life for those with CLBP.

Further, nurses are taking a lead in identifying health promotion activities in various populations. One of the most significant area that nurses can help CLBP patients in practice might be to identify environmental and life style factors that might be contributing to their pain severity and poor quality of life. For instance, offering classes targeting nutrition, exercise and

early counseling to high risk patients might be a good beginning. Measures to assist in health promotion teaching activities can alleviate symptoms and might contribute to reducing opioid overdose and death, thereby increasing life expectancy.

### **Theory**

The philosophical underpinning of existentialism and the theory of TOUS were used to arrive at the conceptual model for the study. The model proposed interactive relationships among depressive mood, sleep quality, and fatigue; which through inflammation impacts the pain experience and quality of life of the person with CLBP which have been tested using regression model. For the future, the model can be further developed for use in the CLBP population after incorporating symptoms and any other variable that might fit in this model. The primary goal of the study was to determine whether symptom clusters are recognizable within the myriad of symptoms that the CLBP participants reported, which was verified and confirmed using LCA. It might be beneficial to create a theoretical model for symptom clusters in CLBP by nurse theorists that can be used to guide future research and education.

### **Study Limitations**

Several study limitations were identified, including limitations related to the design, sample and confounding variables. The following identifies limitations in each of those areas.

**Design.** A cross sectional study design was used in this investigation, and although this design allows more rapid data collection, it has several limitations. One limitation is that the data collected is limited to one point in time, which may not be representative. Cross sectional studies provide only a ‘snapshot’ of the person’s situation, which will be affected by many individual and environmental factors; this may confound outcome measures. Another limitation

is that a cross sectional design does not permit a determination of cause and effect. On the other hand, a cross sectional study can identify associations and generate hypotheses that can be tested in longitudinal studies (Cohen et al., 2007). Random sampling and random assignment, selecting samples from other populations conducted over longer periods of time can decrease the threat due to external validity. There is also the possibility of threat due to statistical regression (Heffner, 2011). This study used several instruments to measure study variables, and may have proved burdensome to some participants. External validity is the extent to which the study can be generalized to a universal population across time, place and persons (Carlson & Morrison, 2009). In this study only one pain clinic was used for recruitment. Study participants were mostly women, above 50 years old and Caucasian; thus, generalizability to a more racially/ethnically and male population is limited.

**Sample.** In this study, the small sample size limits the generalizability and the use of convenience sampling can increase possibility of selection bias. It is also possible that those individuals with more intense pain or poorer quality of life may choose not to participate, further increasing the chance of selection bias (Heffner, 2011). On the other hand, the sample was heterogeneous in terms of type and duration of pain. Etiology of pain ranged from lumbar radiculitis, lumbar stenosis, facet arthropathy to herniated disc. Some participants also had coexisting neck or knee pain. Due to a small sample size, some significant relationships may not have been identified. Out of the 86 participants, six participants withdrew, and eleven participants had missing data, hence restricting the sample size to 69. Lack of time to complete the several questionnaires was one of the reasons given for incomplete data. Participants had to maintain daily sleep diary recordings for a week and complete several questionnaires. Some

participants indicated that the compensation provided for blood draw and the questionnaires was not adequate. Since this study did not have funding support, it limited the compensation offered to participants for their time. Future research can focus on identifying instruments that can measure symptom clusters more efficiently thereby reducing participant burden.

**Covariates.** A variety of potential confounders need to be considered in investigations of individuals with CLBP. Important factors include: age, gender, race, education, marital status, employment, SES, drug use (prescription, over-the-counter, illicit drug use), smoking, alcohol and caffeine intake, co-morbidities, (prior depression, and psychological disorders), and general health behavior (diet, exercise, BMI). For purpose of the study some of these variables were controlled but due to extent of data collected, it was not possible to control for all confounders.

**Measures.** The study used Actigraphy as objective measure for sleep. Data from Actigraphy was collected from only 20 participants in the study due to financial and time constraints, hence data collected were not used in data analysis. Future studies targeting objective measures of sleep can help quantify the hours of sleep even if the sleep quality might be difficult to correlate with any objective measure. The sleep diary and the PSQI were used to measure sleep and only PSQI used to analyze sleep disturbances. The data available from the sleep diary might also be examined for further research on sleep and its implications in CLBP. Future researchers can focus on measuring pain using a more multidimensional measure of the pain experience to better capture the full nature of pain. All data gathered in the study were self-reported except the inflammatory markers. Self-reported data can rarely be verified independently verified and can also carry potential bias. One way to identify congruency of data is the use of objective measures, for instance actigraph and/ or PSG.



### **Strengths of the Study**

The study was designed as a small cross sectional study, which provided results more quickly than a longitudinal design. However, due to design limitations, it requires careful interpretation and confirmation of results in larger longitudinal studies (Hackshaw, A., 2008). Nevertheless, findings from this study can be used as a first step toward understanding how symptom clusters impact quality of life and the pain experience in CLBP. Additionally, the study might be a starting point to understand the role of inflammatory markers from a biological and behavioral perspective of symptoms. Another strength of the study is that it can guide the development and testing of new interventions to improve quality of life and health outcomes based on these results. Lastly, the study findings may enhance interest in the field of psychoneuroimmunology and lead to development and implementation of programs for early interventions with this group of patients. Ultimately the goal is to reduce pain, reduce analgesic use, and decrease behavioral symptoms (i.e., sleep disturbance, depression, and fatigue), all of which will improve QOL.

### **Future Directions**

According to the strategic plan of NINR, the priorities for research in nursing include four areas of scientific focus: symptom science, wellness, self-management and end-of-life care. Promoting innovation and emphasizing innovative strategies for research careers have also been identified as cross-cutting areas to the advancement of nursing science (National Institute of Nursing Research, 2016). Under the profile of symptom science, NINR emphasizes the need to understand symptoms such as pain, fatigue and sleep disturbance. Further, understanding the biological and behavioral aspects of symptoms with the goal of developing and testing new

interventions to improve quality of life and health outcomes have been highlighted (National Institute of Nursing Research, 2016). This purpose and nature of the present study is clearly aligned with the research agenda set by NINR.

Appraisal of CLBP not as a unitary symptom but as a constellation of several interacting symptoms is an important first step toward advancing quality of life in the CLBP population. This study aimed to determine if symptoms in CLBP presented as clusters, which can be a foundational step to assist future researchers to curtail the vicious cycle between various symptoms and pain from a different perspective. When symptoms are examined as clusters there might be a possibility of targeting individuals with unique interventions based on the symptom cluster profile. Overall the findings show that behavioral symptoms cluster in those with CLBP and worsen QOL. Inflammation contributes to the complex relationship between behavioral symptoms and pain severity. Clinical recognition of behavioral symptom clusters can foster more comprehensive pain assessment and tailored interventions for CLBP patients.

APPENDIX A

DATA COLLECTION TOOLS: GENERAL TOOLS

## Demographic Information Form

### Sociodemographic Questionnaire

The MacArthur Network on SES and Health has developed a sociodemographic questionnaire which is currently being used in a number of network sponsored projects. The instrument begins with subjective social status questions developed by the network; (see MacArthur Subjective Social Status Scale in the Psychosocial Notebook). The remaining questions assess educational attainment, occupational status, income and assets. Ideally, all questions would be used; if a subset must be selected, items 1, 2, 3, 4, 6b and 6c, 7 and 9 are recommended.

### Question 1

**Think of this ladder as representing where people stand in their communities.**

People define community in different ways; please define it in whatever way is most meaningful to you. At the **top** of the ladder are the people who have the highest standing in their community. At the **bottom** are the people who have the lowest standing in their community.

**Where would you place yourself on this ladder?**

Please place a large "X" on the rung where you think you stand at this time in your life, relative to other people in your community.



## Question 2

**Think of this ladder as representing where people stand in the United States.**

At the **top** of the ladder are the people who are the best off – those who have the most money, the most education and the most respected jobs. At the **bottom** are the people who are the worst off – who have the least money, least education, and the least respected jobs or no job. The higher up you are on this ladder, the closer you are to the people at the very top; the lower you are, the closer you are to the people at the very bottom.

**Where would you place yourself on this ladder?**

Please place a large "X" on the rung where you think you stand at this time in your life, relative to other people in the United States.



**Question 3. What is the highest grade (or year) of regular school you have complete?  
(Check one.)**

Check box	Elementary		High School		College		Graduate School
	01		09		13		17
	02		10		14		18
	03		11		15		19
	04		12		16		20+
	05						
	06						
	07						
	08						

**Question 4. What is the highest degree you earned?**

Check Box	
	High school diploma or equivalency (GED)
	Associate Degree (Junior College
	Bachelor's Degree
	Master's Degree
	Doctorate
	Professional (MD,JD,DDS,etc)
	Other (please specify)
	None of the above (less than High School)

**Question 5. Which of the following best describes your current main daily activities and/or responsibilities?**

Check Box	
	Working full-time
	Working part-time
	Unemployed or laid off
	Looking for work
	Keeping house or raising children full-time
	Retired

**Question 6. With regard to your current or most recent job activity:****In what kind of business or industry do (did) you work?**

(For example: hospital, newspaper publishing, mail order house, auto engine manufacturing, breakfast cereal manufacturing.)

**What kind of work do (did) you do? (Job Title)**

(For example: registered nurse, personnel manager, supervisor of order department, gasoline engine assembler, grinder operator.)

**How much did you earn, before taxes and other deductions, during the past 12 months?**

Check box	
	Less than \$5,000
	\$5,000 through \$11,999
	\$12,000 through \$15,999
	\$16,000 through \$24,999
	\$25,000 through \$34,999
	\$35,000 through \$49,999
	\$50,000 through \$74,999
	\$75,000 through \$99,999
	\$100,000 and greater
	Don't know
	No response

**Question 7. How many people are currently living household, including yourself?**

	Number of people in household?
	Of these people, how many are children?
	Of these people, how many are adults?
	Of the adults, how many bring income into household?

**Question 8. Is the home where you live:**

Check Box	
	Owned or being bought by you (or someone in the household)?
	Rented for money?
	Occupied without payment of money or rent?
	Other (specify)

[Some might try to get a “market value” estimate of the value of owned homes and an estimate of how much principal was outstanding on the mortgage.]

**Question 9. Which of these categories best describe your total combined income for the past 12 months?**

**This should include income (before taxes) from all sources, wages, rent from properties, social security, disability and or veteran’s benefits, unemployment benefits, workman’s compensation, help from relatives (including child payments and alimony), and so on.**

Check Box	
	Less than \$5,000
	\$5,000 through \$11,999
	\$12,000 through \$15,999
	\$16,000 through \$24,999
	\$25,000 through \$34,999
	\$35,000 through \$49,999
	\$50,000 through \$74,999
	\$75,000 through \$99,999
	\$100,000 or greater
	Don’t know
	No response



**Question 10. If you lost all your current source(s) of household income(your paycheck, public assistance, or other forms of income), how long could you continue to live at your current address and standard of living.**

Check box	
	Less than 1 month
	1 to 2 months
	3 to 6 months
	7 to 12 months
	More than 1 year

**Question 11. Suppose you needed money quickly, and you cashed in all of your (and your spouse's) checking and savings accounts, and any stocks and bonds. If you added up what you would get, about how much would this amount to?**

Check box	
	Less than \$500
	\$500 to \$4,999
	\$5,000 to \$9,999
	\$10,000 to \$19,999
	\$20,000 to \$49,999
	\$50,000 to \$99,000
	\$100,000 to \$199,999
	\$200,000 to \$499,999
	\$500,000 and greater
	Don't know
	No response

**If you now subtracted out any debt that you have (credit card debt, unpaid loans including car loans, home mortgage), about how much would you have left?**

Check box	
	Less than \$500
	\$500 to \$4,999
	\$5,000 to \$9,999
	\$10,000 to \$19,999
	\$20,000 to \$49,999
	\$50,000 to \$99,000
	\$100,000 to \$199,999
	\$200,000 to \$499,999
	\$500,000 and greater
	Don't know
	No response

APPENDIX B

DATA COLLECTION TOOLS: PAIN AND QUALITY OF LIFE TOOL

Ferrans and Powers  
 QUALITY OF LIFE INDEX  
 GENERIC VERSION - III

PART 1. For each of the following, please choose the answer that best describes how satisfied you are with that area of your life. Please mark your answer by circling the number. There are no right or wrong answers. HOW SATISFIED ARE YOU WITH:

---

1. Your health? 1 2 3 4 5 6

---

2. Your health care? 1 2 3 4 5 6

---

3. The amount of pain that you have? 1 2 3 4 5 6

---

4. The amount of energy you have for everyday activities? 1 2 3 4 5 6

---

5. Your ability to take care of yourself without help? 1 2 3 4 5 6

---

6. The amount of control you have over your life? 1 2 3 4 5 6

---

7. Your chances of living as long as you would like? 1 2 3 4 5 6

---

8. Your family's health? 1 2 3 4 5 6

---

9. Your children? 1 2 3 4 5 6

---

10. Your family's happiness? 1 2 3 4 5 6

---

11. Your sex life? 1 2 3 4 5 6

---

12. Your spouse, lover, or partner? 1 2 3 4 5 6

---

13. Your friends? 1 2 3 4 5 6

---

14. The emotional support you get from your family? 1 2 3 4 5 6

---

15. The emotional support you get from people other than your family? 1 2 3 4 5 6

---

Page 2 HOW SATISFIED ARE YOU WITH: Very Dissatisfied Moderately Dissatisfied Slightly Dissatisfied  
 Slightly Satisfied Moderately Satisfied Very Satisfied

---

16. Your ability to take care of family responsibilities? 1 2 3 4 5 6

---

17. How useful you are to others? 1 2 3 4 5 6

---

18. The amount of worries in your life? 1 2 3 4 5 6

---

19. Your neighborhood? 1 2 3 4 5 6

---

20. Your home, apartment, or place where you live? 1 2 3 4 5 6

---

21. Your job (if employed)? 1 2 3 4 5 6

---

22. Not having a job (if unemployed, retired, or disabled)? 1 2 3 4 5 6

---

23. Your education? 1 2 3 4 5 6

---

24. How well you can take care of your financial needs? 1 2 3 4 5 6

---

25. The things you do for fun? 1 2 3 4 5 6

---

26. Your chances for a happy future? 1 2 3 4 5 6

---

27. Your peace of mind? 1 2 3 4 5 6

---

28. Your faith in God? 1 2 3 4 5 6

---

29. Your achievement of personal goals? 1 2 3 4 5 6

---

30. Your happiness in general? 1 2 3 4 5 6

---

31. Your life in general? 1 2 3 4 5 6

---

32. Your personal appearance? 1 2 3 4 5 6

---

33. Yourself in general? 1 2 3 4 5 6

---

PART 2. For each of the following, please choose the answer that best describes how important that area of your life is to you. Please mark your answer by circling the number. There are no right or wrong answers. HOW IMPORTANT TO YOU IS:

1. Your health? 1 2 3 4 5 6

---

2. Your health care? 1 2 3 4 5 6

---

\_ 3. Having no pain? 1 2 3 4 5 6

---

\_ 4. Having enough energy for everyday activities? 1 2 3 4 5 6

---

\_ 5. Taking care of yourself without help? 1 2 3 4 5 6

---

\_ 6. Having control over your life? 1 2 3 4 5 6

---

---

\_ 7. Living as long as you would like? 1 2 3 4 5 6

---

\_ 8. Your family's health? 1 2 3 4 5 6

---

\_ 9. Your children? 1 2 3 4 5 6

---

\_ 10. Your family's happiness? 1 2 3 4 5 6

---

\_ 11. Your sex life? 1 2 3 4 5 6

---

\_ 12. Your spouse, lover, or partner? 1 2 3 4 5 6

---

\_ 13. Your friends? 1 2 3 4 5 6

---

\_ 14. The emotional support you get from your family? 1 2 3 4 5 6

---

\_ 15. The emotional support you get from people other than your family? 1 2 3 4 5 6

---

Page 4 HOW IMPORTANT TO YOU IS: Very Unimportant Moderately Unimportant Slightly Unimportant Slightly Important Moderately Important Very Important

---

\_\_ 16. Taking care of family responsibilities? 1 2 3 4 5 6

---

\_\_ 17. Being useful to others? 1 2 3 4 5 6

---

\_\_ 18. Having no worries? 1 2 3 4 5 6

---

\_\_ 19. Your neighborhood? 1 2 3 4 5 6

---

\_\_ 20. Your home, apartment, or place where you live? 1 2 3 4 5 6

---

\_\_ 21. Your job (if employed)? 1 2 3 4 5 6

---

\_\_ 22. Having a job (if unemployed, retired, or disabled)? 1 2 3 4 5 6

---

\_\_ 23. Your education? 1 2 3 4 5 6

---

\_\_ 24. Being able to take care of your financial needs? 1 2 3 4 5 6

---

\_\_ 25. Doing things for fun? 1 2 3 4 5 6

---

\_\_ 26. Having a happy future? 1 2 3 4 5 6

---

\_\_ 27. Peace of mind? 1 2 3 4 5 6

---

\_\_ 28. Your faith in God? 1 2 3 4 5 6

---

\_\_ 29. Achieving your personal goals? 1 2 3 4 5 6

---

\_\_ 30. Your happiness in general? 1 2 3 4 5 6

---

\_\_ 31. Being satisfied with life? 1 2 3 4 5 6

---

\_\_ 32. Your personal appearance? 1 2 3 4 5 6

---

\_\_ 33. Are you to yourself? 1 2 3 4 5 6

---

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APPENDIX C

DATA COLLECTION TOOLS: MODERATING VARIABLE TOOLS

### Social Provisions Scale

Instructions: Using the scale below, please circle the number after each statement that indicates how much each statement describes your situation. If you feel a statement is VERY TRUE, you would circle STRONGLY AGREE. If you feel a statement CLEARLY does not describe your relationships, you would answer STRONGLY DISAGREE.

1=STRONGLY DISAGREE

2= DISAGREE

3= AGREE

4=STRONGLY DISAGREE

1	There are people I know who will help me if I really need it	1	2	3	4
2	I do not have close relationships with others	1	2	3	4
3	There is no one I can turn to in times of stress	1	2	3	4
4	There are people who call on me to help them	1	2	3	4
5	There are people who like the same social activities I do	1	2	3	4
6	Other people do not think I am good at what I do	1	2	3	4
7	I feel responsible for taking care of someone else	1	2	3	4
8	I am with a group of people who think the same way I do about things	1	2	3	4
9	I do not think that other people respect what I do	1	2	3	4
10	If something went wrong, no one would help me	1	2	3	4
11	I have close relationships that make me feel good	1	2	3	4
12	I have someone to talk to about decisions in my life	1	2	3	4
13	There are people who value my skills and abilities	1	2	3	4
14	There is no one who have the same interested and concerns as me	1	2	3	4
15	There is no one who needs me to take care of them	1	2	3	4
16	I have a trustworthy person to turn to if I have problems	1	2	3	4
17	I feel a strong emotional tie with at least one other person	1	2	3	4
18	There is no one I can count on for help if I really need it	1	2	3	4
19	There is no one I feel comfortable talking about problems with	1	2	3	4
20	There are people who admire my talents and abilities	1	2	3	4
21	I do not have a feeling of closeness with anyone	1	2	3	4
22	There is no one who likes to do the things I do	1	2	3	4
23	There are people I can count on in an emergency	1	2	3	4
24	No one needs me to take care of them	1	2	3	4

### **Analgesics Use**

Dear Participant,

Please circle the number that indicates use of analgesics in the past week.

- 0 - No analgesic use
- 1 - Less than daily non-opioid analgesic use
- 2- Daily non-opioid analgesic use
- 3- Less than daily opioid use
- 4- Daily opioid use

APPENDIX D

DATA COLLECTION TOOLS: PSYCHOLOGICAL TOOLS

### PITTSBURGH SLEEP QUALITY INDEX (PSQI)

1. During the past month, when have you usually gone to bed at night?
2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?
3. During the past month, when have you usually gotten up in the morning?
4. During the past month, how many hours of actual sleep did you get at night? (This maybe different than the number of hours you spend in bed.)
5. During the past month, how often have you had trouble sleeping because you...
 

(a) Cannot get to sleep within 30 minutes.	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(b) Wake up in the middle of the night or early morning.	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(c) Have to get up to use the bathroom.	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(d) Cannot breathe comfortably.	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(e) Cough or snore loudly.	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(f) Feel too cold.	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(g) Feel too hot.	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(h) Had bad dreams.	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(i) Have pain.	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
6. During the past month, how would you rate your sleep quality overall?
 

	Very good	Fairly good	Fairly bad	Very bad
--	-----------	-------------	------------	----------
7. During the past month, how often have you taken medicine (prescribed or “over the counter”) to help you sleep?
 

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
--	---------------------------	-----------------------	----------------------	----------------------------
8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?
 

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
--	---------------------------	-----------------------	----------------------	----------------------------
9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?
 




	No problem at all	Only a very slight problem	Somewhat of a problem	A very big problem
--	-------------------	----------------------------	-----------------------	--------------------

**ID:** \_\_\_\_\_ **Start Date:** \_\_\_\_/\_\_\_\_/\_\_\_\_

## Sleep Diary

Please keep this booklet by your bed, and fill it out last thing at night and first thing in the morning everyday of this study protocol. Please fill out the sheet marked BEDTIME just before you go to sleep at night. Fill out the sheet marked WAKETIME the first thing the following morning. We realize that estimates of time to falling asleep and time awake during the night are not going to be exact, just do the best you can.

When filling out the Bedtime Diary, we would like to know about the exercise you did closest to your bedtime. The table below contains examples of different exercise levels.

<b>Level of Exercise</b>	
Light (walk)	 <p>Walking, shopping, light work at home, carrying light items.</p>
Medium (jog)	 <p>Jogging, heavy work at home, moderate exercise</p>
Heavy (run)	 <p>Running, tennis, stair climbing, strenuous exercise.</p>

# BEDTIME



**Keep by Your Bedside—Please fill this out LAST thing at night**

Today is: Sun M T W Th F Sat Today's date is: \_\_\_\_\_

Today, I napped for a total of..... \_\_\_\_\_ minutes

Today, I was ill (e.g., cold, fever, nausea)..... 1 = Yes 2 = No

Today I exercised for a total of..... \_\_\_\_\_minutes

Today, the level of my exercise was ..... 0 = none 1 = light 2 = medium 3 = heavy

If you exercised, check the time you exercised?  
 \_\_\_\_\_morning\_\_\_\_\_afternoon\_\_\_\_\_evening

**You have told us what medications you take regularly.** Did you take **any other** medications today?

If so, what were those medications?

---



---



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Today, I took off my ActiWatch. 1 = Yes 2 = No

# WAKETIME



## Keep by Your Bedside—Please fill this out FIRST thing in the morning

Today is: Sun M T W Th F Sat

Today's date is: \_\_\_\_\_

Last night I got into bed at... \_\_\_\_:\_\_\_\_ AM PM

I actually tried to go to sleep at... \_\_\_\_:\_\_\_\_ AM PM

I think it took me about... \_\_\_\_\_minutes to fall asleep

This morning I finally woke at... \_\_\_\_:\_\_\_\_ AM PM

I actually got out of bed to start my day at... \_\_\_\_:\_\_\_\_ AM PM

Last night after I finally fell asleep, I remember waking up this many times during the night

(Circle one): 0 1 2 3 4 5 or more

Altogether, these awakenings lasted about \_\_\_\_\_ minutes.

The overall quality of your night's sleep: (Circle one; 1=terrible, 9=great)

1 2 3 4 5 6 7 8 9

Please circle the appropriate number to indicate how you feel **this morning**, after waking up.

This morning I feel:	not at all	a little	moderately	quite a bit	extremely
Rested	0	1	2	3	4



## Center for Epidemiologic Studies Depression Scale (CES-D), NIMH

Below is a list of the ways you might have felt or behaved. Please tell me how often you have felt this way during the **past week**. Circle **one** number on each line.

	<b>During the Past Week</b>			
	Rarely or none of the time (less than 1 day)	Some or a little of the time (1–2 days)	Occasionally or a moderate amount of time (3–4 days)	All of the time (5–7 days)
1. I was bothered by things that usually don't bother me	0	1	2	3
2. I did not feel like eating; my appetite was poor	0	1	2	3
3. I felt that I could not shake off the blues even with help from my family or friends	0	1	2	3
4. I felt I was just as good as other people	0	1	2	3
5. I had trouble keeping my mind on what I was doing	0	1	2	3
6. I felt depressed	0	1	2	3
7. I felt that everything I did was an effort	0	1	2	3
8. I felt hopeful about the future	0	1	2	3
9. I thought my life had been a failure	0	1	2	3
10. I felt fearful	0	1	2	3
11. My sleep was restless	0	1	2	3
12. I was happy	0	1	2	3
13. I talked less than usual	0	1	2	3
14. I felt lonely	0	1	2	3
15. People were unfriendly	0	1	2	3
16. I enjoyed life	0	1	2	3
17. I had crying spells	0	1	2	3
18. I felt sad	0	1	2	3
19. I felt that people dislike me	0	1	2	3
20. I could not get "going"	0	1	2	3

**PROMIS Item Bank v1.0-Emotional Distress-Anxiety □ Short Form 4a****Emotional Distress-Anxiety – Short Form 4a**

Please respond to each question or statement by marking one box per row.

In the past 7 days... Never Rarely Sometimes Often Always

I felt fearful..... ◆ 1 ◆ 2 ◆ 3 ◆ 4 ◆ 5

I found it hard to focus on anything other than my anxiety..... ◆ 1 ◆ 2 ◆ 3 ◆ 4 ◆ 5

My worries overwhelmed me..... ◆ 1 ◆ 2 ◆ 3 ◆ 4 ◆ 5

I felt uneasy ..... ◆ 1 ◆ 2 ◆ 3 ◆ 4 ◆ 5

## Brief Fatigue Inventory

Date: \_\_\_\_\_

Time: \_\_\_\_\_

Name: \_\_\_\_\_  
Last First Middle initial

Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the past week? Yes \_\_\_\_\_ No \_\_\_\_\_

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right now.

0 1 2 3 4 5 6 7 8 9 10  
No fatigue As bad as you can imagine

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your usual level of fatigue during the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10  
No fatigue As bad as you can imagine

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your worst level of fatigue during the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10  
No fatigue As bad as you can imagine

4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:

A. General activity

0 1 2 3 4 5 6 7 8 9 10  
Does not interfere Completely interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10  
Does not interfere Completely interferes

C. Walking ability

0 1 2 3 4 5 6 7 8 9 10  
Does not interfere Completely interferes

D. Normal work (includes work outside the home and daily chores at home)

0 1 2 3 4 5 6 7 8 9 10  
Does not interfere Completely interferes

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10  
Does not interfere Completely interferes

F. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10  
Does not interfere Completely interferes

APPENDIX E  
PERMISSION LETTERS FOR INSTRUMENTS

### SYMPTOM ASSESSMENT TOOL LICENSE AGREEMENT

This Symptom Assessment Tool License Agreement (the "Agreement," including both Part I License Information and Part II Terms & Conditions) is entered into as of the Effective Date by and between The Board of Regents ("Board") of The University of Texas System ("System"), an agency of the State of Texas, whose address is 201 West 7<sup>th</sup> Street, Austin, Texas 78701, on behalf of The University of Texas M. D. Anderson Cancer Center ("MD Anderson"), a member institution of System and the Licensee (identified below). Board and Licensee may each hereinafter be individually referred to as a "Party" and collectively as the "Parties."

Board owns the Symptom Assessment Tool. Licensee desires to obtain the right to use, reproduce, and/or distribute copies of, the Symptom Assessment Tool for the Permitted Use described herein.

NOW, THEREFORE, in consideration of the promises, conditions, covenants and warranties herein contained, the Parties agree as follows:

#### PART I LICENSE INFORMATION

1.	<b>Effective Date</b>	Dec 10 , 2017
2.	<b>The Symptom Assessment Tool licensed hereunder are any and all tools listed below and/or set forth under Exhibit A to this Agreement:</b>  <b>BFI- English</b>  <b>*All Symptom Assessment Tools are provided in English unless specified otherwise above.</b>	
3.	<b>Form of reproduction (place "x" in boxes that apply):</b> <input type="checkbox"/> Electronic <input checked="" type="checkbox"/> Print (paper)	
4.	<b>Form of distribution (place "x" in boxes that apply):</b> <input type="checkbox"/> Electronic <input checked="" type="checkbox"/> Print (paper)	
5.	<b>Permitted Use (description of study): Student research (thesis, dissertation)</b> <b>Within any clinics or hospitals participating in the study described</b>	
6.	<b>Licensed Territory (place "x" in all boxes that apply):</b> <input type="checkbox"/> Within worldwide facilities of Licensee <input checked="" type="checkbox"/> Within any clinics or hospitals participating in the study described in the Permitted Use <input type="checkbox"/> Other (Specify here): _____	



**NON-COMMERCIAL LICENSE AGREEMENT  
Office of Grants and Scholarly Research (OGSR)**

**License Number:** QM040817

**Licensee Name:** Anitha Saravanan c/o Loyola University Chicago

**Licensee Address:** Marcella Niehoff School of Nursing, 2160 South First Avenue, Maywood, IL 60153 US

**Approved Purpose:** Symptom Clusters and underlying inflammation in Chronic Low Back Pain

**Study Type:** Non-commercial academic research and/or thesis – Unfunded Student

**Data Collection Method:** Paper

**Therapeutic Area:** Bones, Joints and Muscles

**Indication:** Health & Wellness

**Royalty Fee:** None, because this License is granted in support of the non-commercial Approved Purpose

**A. Effective Date:** This Non-Commercial License Agreement (the "Agreement") from the Office of Grants and Scholarly Research (OGSR) is made by and between OptumInsight Life Sciences, Inc. (f/k/a QualityMetric Incorporated) ("Optum"), 1301 Atwood Ave, Suite 311N, Johnston, RI 02919 and Licensee. This Agreement is entered into as of the date of last signature below and is effective for the Study Term set forth on Appendix B.

**B. Appendices:** Capitalized terms used in this Agreement shall have the meanings assigned to them in Appendix A and Appendix B. The appendices attached hereto are incorporated into and made a part of this Agreement for all purposes.

**C. Grant of License:** Subject to the terms of this Agreement, Optum grants to Licensee a non-exclusive, non-transferable, non-sublicensable worldwide license to use, solely for the Approved Purpose and during the Study Term, the Licensed Surveys, Software, SMS Scoring Solution, and all intellectual property rights related thereto ("Survey Materials"), in the authorized Data Collection Method, Modes of Administration, and Approved Languages indicated on Appendix B; and to administer the Licensed Surveys only up to the total number of Administrations (and to make up to such number of exact reproductions of the Licensed Surveys necessary to support such Administrations) in any combination of the specific Licensed Surveys and Approved Languages, Data Collection Method, and Modes of Administration.

EXECUTED by the duly authorized representatives as set forth below.

**OptumInsight Life Sciences, Inc.**

**Anitha Saravanan c/o Loyola University Chicago**

Signature: \_\_\_\_\_

Signature: 

Name: \_\_\_\_\_

Name: Anitha Saravanan

Title: \_\_\_\_\_

Title: RN, M&N, ANP-BC, PCCN

Date: \_\_\_\_\_

Date: 06/12/2017

5/29/2017 PSQI Request Saravanan,  
Anitha

<https://outlook.luc.edu/owa/#viewmodel=ReadMessageItem&ItemID=AAMkADMyNDk3ZDhjLTNhYzUtNDhiMC05NmFkLWZjMzk5ZGQ1NzY0MABGAAAA...> 1/2

## PSQI Request

Sent on behalf of Dr. Buysse

Dear Anitha,

You have my permission to use the PSQI for your research study. You can find the instrument, scoring instructions, the original article, links to available translations, and other useful information at [www.sleep.pitt.edu](http://www.sleep.pitt.edu) under the Research/Instruments tab. Please ensure that the PSQI is accurately reproduced in any on-line version (including copyright information). We request that you do cite the 1989 paper in any publications that result. Note that Question 10 is not used in scoring the PSQI. This question is for informational purposes only, and may be omitted during data collection per requirements of the particular study. This copyright in this form is owned by the University of Pittsburgh and may be reprinted without charge only for non-commercial research and educational purposes. You may not make changes or modifications of this form without prior written permission from the University of Pittsburgh. If you would like to use this instrument for commercial purposes or for commercially sponsored research, please contact the Office of Technology Management at the University of Pittsburgh at 412-648-2206 for licensing information.

Good luck with your research.

Sincerely,

Daniel J. Buysse, M.D.

Professor of Psychiatry and Clinical and Translational Science

University of Pittsburgh School of Medicine

E-1123 WPIC

3811 O'Hara St.

Pittsburgh, PA 15213

T: (412) 246-6413

F: (412) 246-5300

[buyssej@upmc.edu](mailto:buyssej@upmc.edu)

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Gasiorowski, Mary <[GasiorowskiMJ@upmc.edu](mailto:GasiorowskiMJ@upmc.edu)>

Fri 5/26/2017 11:24 AM

To: Saravanan, Anitha <[asaravanan@luc.edu](mailto:asaravanan@luc.edu)>;

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- HealthMeasures: a resource encompassing four measurement systems: PROMIS®, NIH Toolbox®, Neuro-QoL, and ASCQ-MESM
- Measurement System: a collection of health measurement instruments under one brand, such as PROMIS or NIH Toolbox
- Provider: the Department of Medical Social Sciences at Northwestern University Feinberg School of Medicine
- User: anyone who employs a HealthMeasures Measurement System or Instrument in a research, clinical, educational, or other setting
- Publicly Available: HealthMeasures Instruments which are available for download at healthmeasures.net

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Provider recognizes the importance of continued scientific development of the NIH Toolbox measures to meet the needs of researchers, but emphasizes the importance of maintaining rigorous measurement standards. Therefore, User may make modifications to NIH Toolbox Cognition, Motor, Emotion and Sensation tests and test items if, and only if, the following conditions are met:

1. Specific modification plans must be enumerated and submitted *in writing* to Provider for approval. This request must include the specific changes to be made and the rationale for the changes. This written request must be signed by the lead researcher.
2. User may not make modifications to any component of NIH Toolbox without written consent of Provider.
3. All modifications should be fully validated against the existing NIH Toolbox measure(s) on which they were based. Plans for a concurrent validation study should be included in the written request for modifications. If no validation study is planned, this must be noted in the written request, along with an explanation.
4. User must send validation study results to Provider for review prior to publication citing any results of said study or any results citing use of NIH Toolbox.
5. Provider will review validation study data and will inform User if modification to NIH Toolbox measure(s) constitute an “Approved Adaptation” or a “Non-Validated Adaptation” of NIH Toolbox. Provider will update HealthMeasures.net accordingly to inform other users and prospective users of these modifications, along with contact information for the lead researcher.
6. User must cite NIH Toolbox in any and all presentations, publications, or other third-party sharing of research data, indicating whether any measures used constitute Approved Adaptations or Non-Validated Adaptations.
7. **Provider maintains all rights to Approved Adaptations as well as Non-Validated Adaptations of NIH Toolbox tests and test items made by User. User may under no circumstances license,**

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## **MAINTENANCE OF NIH TOOLBOX TEST SECURITY AND TEST USE**

- Each person or institution using the NIH Toolbox Measures must agree to comply with these basic principles of test security.
- Test takers must not receive test answers before beginning the test. Test questions are not to be reproduced or paraphrased in any way.
- Access to test materials must be limited to qualified persons with a responsible, professional interest who agree to safeguard their use.
- Test materials and scores may be released only to persons qualified to interpret and use them properly.

- If a test taker or the parent of a child who has taken a test wishes to examine test responses or results, the parent or test taker may be permitted to review the test and the test answers in the presence of a representative of the school, college, or institution that administered the test. Such review should not be permitted in those jurisdictions where applicable laws require the institution to provide a photocopy of the test subsequent to review. If User is not certain of the effect of the laws in User's jurisdiction, the User should contact their jurisdiction's professional organization.

### **USER QUALIFICATIONS**

Test users must have the appropriate knowledge, skills, training and experience to responsibly use NIH Toolbox measures. "Test users" are those persons responsible for the selection, administration, scoring and interpretation of tests and the communication of results. Provider reserves the right to ask individuals requesting access to NIH Toolbox Cognition measures to provide documentation that they have the experience and training necessary to use those measures, or are working under the supervision of someone qualified to use those measures. NIH Toolbox Cognition measures are classified as "C-Level." C-Level tests require a high degree of expertise in test interpretation, and thus can only be requested by a User with state licensure or certification to practice in a field related to the request, or a doctorate degree in psychology, education, or a closely related field, with formal training in the ethical administration, scoring, and interpretation of clinical assessments related to the intended use of the assessment. Any users of C-Level assessments must be supervised by one or more users with C-Level qualifications, which must have been provided in advance to Provider per this process.

### **RULES GOVERNING USE OF THE NIH TOOLBOX BY VARIOUS CATEGORIES OF USERS**

Universities, schools, organizations, businesses, clinics, and hospitals are subject to the guidelines set forth above and must have appropriately qualified individuals on staff in order to use the NIH Toolbox tests.

**PROTECTIVE ORDERS.** User agrees to seek a protective order safeguarding the confidentiality of

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test materials classified by Provider as "C-level" assessments if User is required to produce such materials in court or administrative proceedings.

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Thomas M. Achenbach, PhD

Child Behavior Checklist for Youth

Torbjörn Åkerstedt Karolinska Sleep Diary

Stanley E. Althof

Center for Marital and Sexual Health Sexual Functioning Questionnaire

Julie Barroso, PhD

HIV-Related Fatigue Scale

Dorcas Beaton

Disabilities of the Arm, Shoulder and Hand (DASH)

Basia Belza

Multidimensional Assessment of Fatigue

Smita Bhatia

Minneapolis-Manchester Quality of Life Instrument – Adolescent Version

Jill Binkley, PT

Lower Extremity Functional Scale

Thomas Borkovec

Penn State Worry Questionnaire

Ron Borland

Perceived dependence items from International Tobacco Control Policy Evaluation Study (ITC)

Lynn Breau

Non-communicating Children's Pain Checklist

Bengt Brorsson

Swedish Health Related Quality of Life Survey

Richard Brown, PhD Parkinson Fatigue Scale

Elly Budiman-Mak, MD Foot Function Scale

Arnold Buss

Buss-Durkee Hostility Inventory

Daniel J. Buysse

Pittsburgh Sleep Quality Index

Andrei Calin, MD

Bath Ankylosing Spondylitis Function Index (BASFI)

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Approved Version 1.12-2017

David Cella, PhD

Functional Assessment of Chronic Illness Therapy (FACIT) Center on Outcomes, Research, and Education Item Banks

Larry Chambers, PhD

McMaster Health Index Questionnaire

Trudie Chadler  
14-Item fatigue scale  
Amy Copeland  
Smoking Consequences Questionnaire  
Ann Coscarelli  
Cancer Rehabilitation Evaluation System (CARES)  
Kimberly A. Cote  
Brock Sleep and Insomnia Questionnaire  
Laura Creti  
Sexual History Form  
Peter Dent, MD  
Juvenile Arthritis Self-Report Index (JASI)  
Ed Diener  
Satisfaction with Life Scale  
Joe DiFranza  
Autonomy over smoking scale  
Dr. Colleen Dilorio Epilepsy Self-Efficacy Scale  
George Domino Assessment of Sleep Sleep Questionnaire  
Maxime Dougados, MD Dougados Functional Index (DFI)  
Alan B. Douglass  
Sleep Disorders Questionnaire  
David Drobos  
Questionnaire of Smoking Urges - Long Form  
M Tuncay Duruoaz, MD Duruoaz Hand Index  
Jack D. Edinger, Professional Resource Exchange Edinger's Sleep History Questionnaire  
Colin A. Espie  
Beliefs and Attitudes about Sleep Scale  
Dysfunctional Beliefs and Attitudes about Sleep Scale - 10 Glasgow Content of Thoughts Inventory  
Insomnia Impact Scale  
Sleep Disturbance Questionnaire  
JF Etter  
The Cigarette Dependence Scale, English-language version  
Sydney Ey  
Youth Life Orientation Test  
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Jeremy Fairbank, MD  
Oswestry Low Back Pain Disability Questionnaire (OLBPDQ)  
Catherine S. Fichten Sleep Diary  
Sleep Questionnaire  
Robert Ficke  
Performance Outcomes Measures Project  
J.D. Fisk  
Fatigue Impact Scale  
Ross Flett Affectometer-2  
James F Fries, MD  
Health Assessment Questionnaire (HAQ)

Marie Gage  
 Self-Efficacy Gauge (SEG)  
 Richard Gracely  
 Descriptor Differential Scale of Pain Affect (DDS - Pain Affect item)  
 Johanna CJM de Haes, PhD Rotterdam Symptom Checklist  
 Stephen Haley, PhD  
 Late Life Function and Disability Instrument: Function Component  
 Danete Hann, PhD and Paul Jacobsen, PhD Fatigue Symptom Inventory  
 Todd Heatherton  
 Fagerstrom Test for Nicotine Dependence  
 Vicki Helgeson Benefit Finding Scale  
 Philip S Helliwell, MD, PhD  
 Revised Leeds Disability Questionnaire  
 Sarah Hewlett MD  
 Rheumatoid Arthritis Self-Efficacy Scale (RASE)  
 Ian Hindmarch  
 Quality of Life of Insomniacs  
 Leeds Sleep Evaluation Questionnaire (LESQ)  
 Mark Hlatky, MD  
 Duke Activity Status Index (DASI)  
 Timothy J. Hoelscher Insomnia Impact Scale  
 William L. Holzemer PPBL  
 E. Scott Huebner, PhD  
 Multidimensional Students' Life Satisfaction Scale (MSLSS) Student's Life Satisfaction Scale  
 Paul Jacobsen  
 Fatigue Symptom Inventory  
 Alan Jette AMPAC  
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 Jeffrey G. Johnson, PhD  
 Patient Health Questionnaire for Adolescents (PHQ-A)  
 Robert Kerns WHYMOI  
 Dinesh Khanna  
 UCLA Scleroderma Clinical Trials Consortium Gastrointestinal Tract (SCTC GIT) 2.0  
 Dr Sunil Kripalani  
 Self-efficacy for Appropriate Medication Adherence Scale (SEAMS)  
 Lauren Krupp  
 Fatigue Severity Scale  
 Sleep Symptom Questionnaire  
 Jin-Shei Lai, PhD  
 Pediatric Fatigue Item Bank  
 Kathryn A. Lee  
 Numerical Rating Scale for Fatigue  
 Stephen J. Lepore Social Constraint Scale  
 Debra Lerner, PhD  
 Work Limitations Questionnaire  
 Kenneth Lichstein Sleep Questionnaire



Mark S. Litwin  
 UCLA Prostate Cancer Index  
 Daniel Lovell, MD  
 Juvenile Arthritis Functional Assessment Scale  
 Juvenile Arthritis Functional Assessment Report for Children (JAFAR-C)  
 Anne Lynch-Jordan (S. Kashikar-Zuck, & K. Goldschneider) Adolescent Pain Behavior Questionnaire  
 Ayala Malach-Pines Burnout Measure  
 Ralph Marino, MD  
 Capabilities of Upper Extremity (CUE)  
 Sherry McKee  
 The 39-Item Perceived Risk and Benefits Questionnaire  
 John Mayer  
 Brief Mood Introspection Scale  
 Robert Meenan, MD  
 Arthritis Impact Measurement Scales 2 (AIMS2)  
 Tito Mendoza, Charles Cleeland MD Anderson Symptom Inventory  
 Charles M. Morin  
 Insomnia Interview Schedule Sleep Diary  
 Douglas E. Moul  
 Pittsburgh Insomnia Rating Scale  
 Nikolaus Netzer Berlin Questionnaire  
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 Olugbenga Ogedegbe  
 Medication Adherence Self-Efficacy Scale  
 Geraldine Padilla  
 Quality of Life Scale – Cancer  
 Tonya M. Palermo, PhD  
 Child Activity Limitations Interview (CALI)  
 George Parkerson, MD Duke Health Profile  
 Donald Patrick, PhD WHOQOL-100 US Version  
 Pfizer, Inc.  
 International Index of Erectile Function, Erection Harness Scale  
 Megan Piper  
 Wisconsin Inventory of Smoking Dependence Motives  
 Ovide Pomerleau  
 Michigan Nicotine Reinforcement Questionnaire  
 Arnold L. Potosky  
 Prostate Cancer Outcomes Study  
 Quentin R. Regestein Hyperarousal Scale  
 Graham J. Reid (C. Gilbert, & P. McGrath) Pain Coping Questionnaire  
 Gary T. Reker  
 Life Attitude Profile-Revised (LAP-R)  
 Dennis Revicki  
 PROMIS Adult Pain Behavior Bank  
 Robin Richards, MD  
 American Shoulder and Elbow Surgeons Shoulder Form (ASES)

J. Scott Richards  
 UAB Pain Behavior Scale  
 Tracey Riseborough  
 Hospital Anxiety and Depression Scale (HADS)  
 Kathryn Roach, PhD  
 Shoulder Pain and Disability Index  
 Damaris J. Rohsenow  
 Smoking Effects Questionnaire  
 Martin Roland, MA, MRCP  
 Roland-Morris Low Back Pain and Disability Questionnaire  
 Raymond Rosen and Jules Mitchell  
 Brief Index of Sexual Functioning for Women Female Sexual Function Index  
 Thomas Roth  
 Global Sleep Assessment Questionnaire  
 Daniel W. Russell UCLA Loneliness Scale  
 Michael F. Scheier Life Engagement Test  
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 Approved Version 1.12-2017  
 Raf Schwarzer  
 General Self-Efficacy Scale  
 Debra Sciabarrasi Barthel Index  
 William G. Shadel, PhD  
 Smoker Self-concept and Abstainer Self-concept scales  
 Cathy Sherbourne, Robert Brook, Brent Bradley Rand-36 Index of Vitality  
 Saul Shiffman  
 Nicotine Dependence Syndrome Scale  
 Judith Siegel, PhD Multidimensional Anger Inventory  
 Ann Skinner  
 Sickness Impact Profile (SIP)  
 C. R. Snyder (by B. Hoza) Children's Hope Scale  
 John Spertus, MD, MPH Seattle Angina Questionnaire  
 Charles D. Spielberger, PhD  
 State-Trait Anger Expression Inventory (STAXI)  
 Barbara Starfield, MD, MPH  
 Child Health and Illness Profile – Adolescent Edition (CHIP-AE)  
 Michael Steger  
 Meaning in Life Questionnaire – Expanded Version (MLQ-X)  
 Kevin Stein  
 Multidimensional Fatigue Symptom Inventory  
 Mark Sullivan MD  
 Cardiac Self-Efficacy Scale  
 K.L. Syrjala  
 Sexual Function Questionnaire  
 Peter Tugwell, MD McMaster Toronto Arthritis  
 David Tulsky, PhD SCI-QOL  
 TBI-QOL  
 James W. Varni, PhD

PedsQL™ Arthritis Module Version 3.0 Child Report (ages 8-12) PedsQL™ Asthma Module Version 3.0  
 Child Report (ages 8-12) PedsQL™ Cerebral Palsy Module Version 3.0 Child Report (ages 8-12)  
 PedsQL™ Multidimensional Fatigue Scale Standard Version Child Report (ages 8-12) PedsQL™ Pediatric  
 Quality of Life Inventory Version 4.0 Child Report (ages 8-12)

Wayne Velicer and James Prochaska

The Self-Efficacy/Temptations Scale-Long Form Smoking: Decisional Balance Scale Transtheoretical  
 Model Assessment

Johan W. S. Vlaeyen

Checklist for Interpersonal Pain Behavior

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Lynn S. Walker

Pain Response Inventory for Children

John Ware, PhD PIQ-6

SF-36 v2

Medical Outcomes Study Sexual Functioning Scale

David Watson

Positive and Negative Affect Scale-Expanded form (PANAS-X)

Terri E. Weaver

Functional Outcomes of Sleep Questionnaire

Wilse B. Webb

Post-Sleep Inventory

Nadine Weisscher

AMC Linear Disability Score (ALDS)

Nick Wetton

Crown-Crisp Experiential Index

Hornng-Shiuann Wu, PhD

Cancer-Related Fatigue Instrument

## REFERENCES

- Aaronson LS, Teel CS, Cassmeyer V, Neuberger GB, Pallikkathayil L, Pierce J, Press AN, Williams PD, Wingate A. Defining and measuring fatigue. *Image: Journal of Nursing Scholarship*.
- Adam K, Oswald I. Protein synthesis, bodily renewal and the sleep-wake cycle. *Clin Sci (Lond)*. 1983;65:561–567.
- Adam K, Oswald I. Sleep is for tissue restoration. *J R Coll Physicians Lond*. 1977;11:376–388.
- Adler, N. E., and J. Stewart 2007, posting date. The MacArthur scale of subjective social status.
- Adler, N. E., and J. Stewart 2007, posting date. The MacArthur scale of subjective social status. Retrieved [date] at <https://macses.ucsf.edu/research/psychosocial/subjective.php>
- Ainsworth BE<sup>1</sup>, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR Jr, Schmitz KH, Emplaincourt PO, Jacobs DR Jr, Leon AS. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc*. 2000 Sep;32(9 Suppl):S498-504.
- Alsaadi SM, McAuley JH, Hush JM, Bartlett DJ, McKeough ZM, et al. (2014) Assessing Sleep Disturbance in Low Back Pain: The Validity of Portable Instruments. *PLoS ONE* 9(4): e95824. doi:10.1371/journal.pone.0095824
- American Academy of Pain Management. (2010). Retrieved April 15, 2014, from [Painmed.org: http://www.painmed.org/Workarea/DownloadAsset.aspx?id=3372](http://www.painmed.org/Workarea/DownloadAsset.aspx?id=3372).
- American Nurses Association. *Code of Ethics for Nurses With Interpretive Statements*. Washington, DC: Author; 2001.
- American Nurses Association. *Nursing: Scope and Standards of Practice*. 2nd ed. Washington, DC: Author; 2004.
- American Nurses Association. *Nursing's Social Policy Statement*. 2nd ed. Washington, DC: Author; 2010.
- Ancoli-Israel S. The impact and prevalence of chronic insomnia and other sleep disturbances associated with chronic illness. *Am J Manag Care* 2006;12:S221-9.

- Andersson GB. Epidemiological features of chronic low-back pain. *Lancet*.1999;354(9178):581–585.
- Anseau M, Dierick M, Buntinkx F, Cnockaert P, De SJ, Van Den HM, et al. High prevalence of mental disorders in primary care. *J Affect Disord* 2004;78:49–55.
- Argoff C. Mechanisms of pain transmission and pharmacologic management. *Curr Med Res Opin* 2011;27:2019e31.
- Arima T, Svensson P, Rasmussen C, Nielsen KD, Drewes AM, Arendt-Nielsen L. The relationship between selective sleep deprivation, nocturnal jaw-muscle activity and pain in healthy men. *J Oral Rehabil* 2001; 28: 140—148.
- Armstrong TS. Symptoms experience: a concept analysis. *Oncol Nurs Forum* 2003;30:601-606.
- Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315-24.
- Aronowitz, R. A. (2001). When do symptoms become a disease?. *Annals of internal medicine*, 134, 803-808.
- Atkinson, J. H., Ancoli-Israel, S., Slater, M. A., Garfin, S. R., & Gillin, C. (1988). Subjective sleep disturbance in chronic back pain. *The Clinical journal of pain*, 4(4), 225-232.
- Axén, I. (2015). Pain-related Sleep Disturbance—A Prospective Study with Repeated Measures. *Clin J Pain*.
- Baer MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. *Arch Intern Med*. 2003;163:2433–45.
- Banks, Sara M., and Robert D. Kerns. "Explaining high rates of depression in chronic pain: A diathesis-stress framework." *Psychological bulletin* 119.1 (1996): 95.
- Banth, S., & Ardebil, M. D. (2015). Effectiveness of mindfulness meditation on pain and quality of life of patients with chronic low back pain. *International journal of yoga*, 8(2), 128.
- Barrett, H., McClelland, J. M., Rutkowski, S. B., & Siddall, P. J. (2003). Pain characteristics in patients admitted to hospital with complications after spinal cord injury. *Archives of physical medicine and rehabilitation*, 84(6), 789-795.
- Barsevick, A. M. (2007, September). The elusive concept of the symptom cluster. In *Oncology nursing forum* (Vol. 34, No. 5).
- Basbaum AI, Fields HL. Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. *Annu Rev Neurosci* 1984;7: 309–38.

- Bentsen SB, Hanestad BR, Rustøen T, Wahl AK. Quality of life in chronic low back pain patients treated with instrumented fusion. *J Clin Nurs*. 2008;17(15):2061–2069.
- Blackburn-Munro, G., & Blackburn-Munro, R. E. (2001). Chronic pain, chronic stress and depression: coincidence or consequence?. *Journal of neuroendocrinology*, 13(12), 1009-1023.
- Borbely AA, Tobler I. Endogenous sleep-promoting substances and sleep regulation. *Physiol Rev* 1989;69:605–70.
- Börsbo, B., Gerdle, B., & Peolsson, M. (2010). Impact of the interaction between self-efficacy, symptoms and catastrophising on disability, quality of life and health in with chronic pain patients. *Disability and rehabilitation*, 32(17), 1387-1396.
- Bouhuys AL, Flentge F, Oldehinkel AJ, van den Berg MD (2004): Potential psychosocial mechanisms linking depression to immune function in elderly subjects. *Psychiatry Res* 127:237–245.
- Bower, J. E., & Irwin, M. R. (2016). Mind–body therapies and control of inflammatory biology: a descriptive review. *Brain, behavior, and immunity*, 51, 1-11.
- Boyle, J., Eriksson, M. E., Gribble, L., Gouni, R., Johnsen, S., Coppini, D. V., & Kerr, D. (2012). Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain impact on pain, polysomnographic sleep, daytime functioning, and quality of life. *Diabetes care*, 35(12), 2451-2458.
- Brown RE, Basheer R, McKenna JT, Strecker RE, McCarley RW. Control
- Buchbinder, R., Blyth, F. M., March, L. M., Brooks, P., Hoyt, A. D., & Hoy, D. G. (2013). Placing the global burden of low back pain in context. *Best Practice & Research Clinical Rheumatology*, 27(5), 575-589.
- Bulthuis Y, Vollenbrock-Hutten M, Hermens H, et al. Psychological distress, disturbed sleep and physical activity during the night in chronic low-back pain patients. *J Back*
- Buyse D. J., Reynolds C. F., III., Monk T. H., Berman S. R., Kupfer D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 28, 193–213.
- Campbell G, Bruno R, Darke S , et al. Prevalence and correlates of suicidal thoughts and suicide attempts in people prescribed pharmaceutical opioids for chronic pain. *Clin J Pain* 2015.
- Capuron, L., Ravaut, A., Miller, A. H., & Dantzer, R. (2004). Baseline mood and psychosocial characteristics of patients developing depressive symptoms during interleukin-2 and/or interferon-alpha cancer therapy. *Brain, behavior, and immunity*, 18(3), 205-213.

- Carley, J. A., Karp, J. F., Gentili, A., Marcum, Z. A., Reid, M. C., Rodriguez, E., ... & Weiner, D. K. (2015). Deconstructing chronic low back pain in the older adult: step by step evidence and expert-based recommendations for evaluation and treatment: part IV: depression. *Pain Medicine*, *16*(11), 2098-2108.
- Carlson, M. D., & Morrison, R. S. (2009). Study design, precision, and validity in observational studies. *Journal of palliative medicine*, *12*(1), 77-82.
- Carroll J, Cassidy D, Pierre Côté, Depression as a risk factor for onset of an episode of troublesome neck and low back pain, *Pain*, Volume 107, Issues 1–2, January 2004, Pages 134-139.
- Carver CS, Johnson SL, Joormann J. Serotonergic function, two-mode models of self-regulation, and vulnerability to depression: what depression has in common with impulsive aggression. *Psychol Bull* 2008;134:912e43.
- Center for Substance Abuse Treatment. Managing Chronic Pain in Adults With or in Recovery From Substance Use Disorders. Rockville (MD): Substance Abuse and Mental Health Services Administration (US); 2012. (Treatment Improvement Protocol (TIP) Series, No. 54.) 3, Chronic Pain Management. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK92054/668-676>.
- Centers for Disease Control and Prevention. Grand rounds: prescription drug overdoses—a U.S. epidemic. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6101a3.htm>. Accessed May 19, 2012.
- Centers for Disease Control and Prevention. Web-based Injury Statistics Query and Reporting System (WISQARS) [online]. (2014) Available from URL: <http://www.cdc.gov/injury/wisqars/fatal.html>.
- Centers for Disease Control and Prevention. Web-based Injury Statistics Query and Reporting System (WISQARS) [online]. (2014) Available from URL: <http://www.cdc.gov/injury/wisqars/fatal.html>.
- Chase T, Murphy DL. Serotonin and central nervous system function. *Annu Rev Pharmacol* 1973; 13:181–97.
- Chen, M., & Tseng, H. (2005). Identification and Verification of Symptom Clusters in Cancer Patients. *Journal of Supportive Oncology*, *6* (Suppl 4), 28-9.
- Chiu YH, Silman AJ, Macfarlane GJ, et al. Poor sleep and depression are independently associated with a reduced pain threshold. Results of a population based study. *Pain* 2005;115(3):316–21.

- Cleeland CS. Measurement of pain by subjective report. In: Chapman CR, Loeser JD, eds. *Issues in Pain Measurement*. New York: Raven Press; pp. 391-403, 1989 *Advances in Pain Research and Therapy*; Vol. 12.
- Cohen, L., Manion, L., & Morrison, K. (2007). *Research methods in education*. London: Routledge.
- Connaughton, J., Patman, S., & Pardoe, C. (2014). Are there associations among physical activity, fatigue, sleep quality and pain in people with mental illness? A pilot study. *Journal of psychiatric and mental health nursing*, 21(8), 738-745.
- Costanzo ES, Lutgendorf SK, Sood AK, Anderson B, Sorosky J, Lubaroff DM. 2005. Psychosocial factors and interleukin-6 among women with advanced ovarian cancer. *Cancer* 104:305-313.
- Crow, W. T., & Willis, D. R. (2009). Estimating cost of care for patients with acute low back pain: a retrospective review of patient records. *The Journal of the American Osteopathic Association*, 109(4), 229-233.
- Currie, S.R. and Wang, J. (2004) Chronic back pain and major depression in the general Canadian population. *Pain*, 107, 54-60
- Cutrona CE. 1984. Social support and stress in the transition to parenthood. *J. Abnorm. Psychol.* 93:378-390.
- Cutrona CE. 1984. Social support and stress in the transition to parenthood. *J. Abnorm. Psychol.* 93:378-390.
- Dagenais, S., Caro, J., & Haldeman, S. (2008). A systematic review of low back pain cost of illness studies in the United States and internationally. *The spine journal*, 8(1), 8-20.
- Danner M, Kasl SV, Abramson JL, Vaccarion V. Association between depression and elevated C-reactive protein. *Psychosom. Med.* 2003;65:347-356
- Davies, S. (2016). Evolving Pain Services: Preclinic Groups Speed Assessment and Lower Costs. *Pain Medicine*, 17(2), 211-211.
- Day, M. A., Ward, L. C., Ehde, D. M., Thorn, B. E., Burns, J., Barnier, A., ... & Jensen, M. P. (2019). A Pilot Randomized Controlled Trial Comparing Mindfulness Meditation, Cognitive Therapy, and Mindfulness-Based Cognitive Therapy for Chronic Low Back Pain. *Pain Medicine*.
- Daya VG, Bentley AJ. Perception of experimental pain is reduced after provoked waking from rapid eye movement sleep. *J Sleep Res* 2010;19:317-22.



- De Rooij, A., van der Leeden, M., de Boer, M. R., Steultjens, M. P., Dekker, J., & Roorda, L. D. (2015). Fatigue in patients with chronic widespread pain participating in multidisciplinary rehabilitation treatment: a prospective cohort study. *Disability and rehabilitation*, 37(6), 490-498.
- Dennis C. Turk, Akiko Okifuji, Lisa Scharff, Chronic pain and depression: role of perceived impact and perceived control in different age cohorts, *Pain*, Volume 61, Issue 1, April 1995, Pages 93-101.
- Deyo, R. A., Dworkin, S. F., Amtmann, D., Andersson, G., Borenstein, D., Carragee, E., ... & Goertz, C. (2015). Report of the NIH Task Force on research standards for chronic low back pain. *Physical therapy*, 95(2), e1-e18.
- Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: A practical guide for clinicians and researchers. *Journal of Psychosomatic Research*. 2004;56:157–170.
- Dodd M, Janson S, Facione N, et al. Advancing the science of symptom management. *J Adv Nurs* 2001;33:
- Dodd MJ, Miaskowski C, Lee KA. Occurrence of symptom clusters. *J Natl Cancer Inst Monogr* 2004;32:76-78.
- Dong, S. T., Butow, P. N., Costa, D. S., Lovell, M. R., & Agar, M. (2014). Symptom clusters in patients with advanced cancer: a systematic review of observational studies. *Journal of pain and symptom management*, 48(3), 411-450.
- Dworkin RH & Gitlin MJ. Clinical aspects of depression in chronic pain patients. *Clin J Pain* 1991; 7: 79–94.
- Dziak, J. J., Lanza, S. T., & Tan, X. (2014). Effect Size, Statistical Power and Sample Size Requirements for the Bootstrap Likelihood Ratio Test in Latent Class Analysis. *Structural equation modeling : a multidisciplinary journal*, 21(4), 534-552.
- Edwards, R. R., Almeida, D. M., Klick, B., Haythornthwaite, J. A., & Smith, M. T. (2008). Duration of sleep contributes to next-day pain report in the general population. *PAIN®*, 137(1), 202-207.
- Effect of short sleep duration on daily activities--United States, 2005-
- Elliott, T. E., Renier, C. M., & Palcher, J. A. (2003). Chronic pain, depression, and quality of life: correlations and predictive value of the SF-36. *Pain medicine*, 4(4), 331-339.
- Erickson, J. M., MacPherson, C. F., Ameringer, S., Baggott, C., Linder, L., & Stegenga, K. (2013). Symptoms and symptom clusters in adolescents receiving cancer treatment: a review of the literature. *International journal of nursing studies*, 50(6), 847-869.

- Eriksen J, Sjogren P, Bruera E, Ekholm O, Rasmussen NK. Critical issues on opioids in chronic non-cancer pain: an epidemiological study. *Pain*. 2006 Nov;125(1–2):172–179. [PubMed]
- Fan, G., Filipczak, L., & Chow, E. (2007). Symptom clusters in cancer patients: a review of the literature. *Curr Oncol*, 14(5), 173-179.
- Fasick, V., Spengler, R. N., Samankan, S., Nader, N. D., & Ignatowski, T. A. (2015). The hippocampus and TNF: Common links between chronic pain and depression. *Neuroscience & Biobehavioral Reviews*, 53, 139-159.
- Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G\*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*, 39(2), 175-191.
- Fernandez, M., Colodro-Conde, L., Hartvigsen, J., Ferreira, M. L., Refshauge, K. M., Pinheiro, M. B., ... & Ferreira, P. H. (2017). Chronic low back pain and the risk of depression or anxiety symptoms: insights from a longitudinal twin study. *The Spine Journal*.
- Ferrans, C. E., & Powers, M. J. (1985). Quality of life index: development and psychometric properties. *Advances in nursing science*, 8(1), 15-24.
- Ferrans, C. E., Cohen, F. L. & Smith, K. M. The quality of life of persons with narcolepsy. *Loss Grief Care*, 1992, 5: 23–32.
- Ferrans, C. E.: 1990, 'Quality of life: conceptual issues', *Seminars in Oncology Nursing* 6, pp. 248–254.
- Ferrans, C. E.: 1996, 'Development of a conceptual model of quality of life', *Scholarly Inquiry for Nursing Practice: An International Journal* 10, pp. 293–304.
- Finan, P. H., Goodin, B. R., & Smith, M. T. (2013). The association of sleep and pain: an update and a path forward. *The Journal of Pain*, 14(12), 1539-1552.
- Fishbain, D. A., Cutler, R. B., Cole, B., Lewis, J., Smets, E., Rosomoff, H. L., & Rosomoff, R. S. (2004). Are patients with chronic low back pain or chronic neck pain fatigued?. *Pain Medicine*, 5(2), 187-195.
- Fishbain, D. A., Hall, J. A., Risser, R. C., & Gonzales, J. S. (2009). Does pain cause the perception of fatigue in patients with chronic pain? Findings from studies for management of diabetic peripheral neuropathic pain with duloxetine. *Pain Practice*, 9(5), 354-362.
- Floam S, Simpson N, Nemeth E, et al. Sleep characteristics as predictor variables of stress systems.

Foo, H., & Mason, P. (2003). Brain stem modulation of pain during sleep and waking. *Sleep Med Rev*;7:145–54.

Ford, D. E., & Kamerow, D. B. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? *JAMA* 1989; 262: 1479—1484.

Fox, S., & Lyon, D. (2007). Symptom Clusters and Quality of Life in Survivors of Ovarian Cancer. *Cancer Nursing* , 30 (5), 354-361.

Freburger JK, Holmes GM, Agans RP, Jackman AM, Darter JD, Wallace AS, Castel LD, Kalsbeek WD, Carey TS: The rising prevalence of chronic low back pain. *Arch Intern Med.* 2009, 169: 251-258. Gallegos, A. M., Lytle, M. C., Moynihan, J. A., & Talbot, N. L. (2015). Mindfulness-based stress reduction to enhance psychological functioning and improve inflammatory biomarkers in trauma-exposed women: A pilot study.

Garland, S. N., Johnson, J. A., Savard, J., Gehrman, P., Perlis, M., Carlson, L., & Campbell, T. (2014). Sleeping well with cancer: a systematic review of cognitive behavioral therapy for insomnia in cancer patients. *Neuropsychiatric Disease & Treatment*, 10.

Gaskin, D. J., & Richard, P. (2011). The economic costs of pain in the United States.

Gatchel RJ. A biopsychosocial overview of pretreatment screening of patients with pain. *Clin J Pain* 2001; 17: 192—199.

Gislason T, Almqvist M. Somatic diseases and sleep complaints. An epidemiological study of 3,201 Swedish men. *Acta Med Scand* 1987;221:475– 81.

Goode, A., Cook, C., Brown, C., Isaacs, R., Roman, M., & Richardson, W. (2011). Differences in comorbidities on low back pain and low back related leg pain. *Pain Practice*, 11(1), 42-47.

Gore, M., Sadosky, A., Stacey, B. R., Tai, K. S., & Leslie, D. (2012). The burden of chronic low back pain: clinical comorbidities, treatment patterns, and health care costs in usual care settings. *Spine*, 37(11), E668-E677.

Gormsen, L., Rosenberg, R., Bach, F. W., & Jensen, T. S. (2010). Depression, anxiety, health-related quality of life and pain in patients with chronic fibromyalgia and neuropathic pain. *European Journal of Pain*, 14(2), 127-e1.

Gorth, D. J., Shapiro, I. M., & Risbud, M. V. (2015). Discovery of the Drivers of Inflammation Induced Chronic Low Back Pain: From Bacteria to Diabetes. *Discovery medicine*, 20(110), 177-184.

Green LA, Fryer GE Jr, Yawn BP, Lanier D, Dovey SM. The ecology of medical care revisited. *N Engl J Med.* 2001;344:2021-5.

- Greenberg PE, Kessler RC, Birnbaum HG, Leong SA, Lowe SW, Berglund PA, Corey Lisle PK. The economic burden of depression in the United States: how did it change between 1990 and 2000? *J Clin Psychiatry*. 2003;64:1465–75.
- Gupta, A., Silman, A. J., Ray, D., Morriss, R., Dickens, C., MacFarlane, G. J., ... & McBeth, J. (2006). The role of psychosocial factors in predicting the onset of chronic widespread pain: results from a prospective population-based study. *Rheumatology*, 46(4), 666-671.
- Gureje O, Kola L, Ademola A, Olley BO. Profile, comorbidity and impact of insomnia in the Ibadan study of ageing. *Int J Geriatr Psychiatry* 2009;24:686-93.
- Haack, M., & Mullington, J. M. (2005). Sustained sleep restriction reduces emotional and physical well-being. *Pain*, 119(1), 56-64.
- Hagen EM, Svensen E, Eriksen HR, et al. Comorbid subjective health complaints in low back pain. *Spine*. 2006;31:1491–1495.
- Hahn SR. Physical symptoms and physician-experienced difficulty in the physician-patient relationship. *Ann Intern Med*. 2001;134:897-904.
- Hakki Onen S, Alloui A, Jourdan D, Eschaliere A, Dubray C. Effects of rapid eye movement (REM) sleep deprivation on pain sensitivity in the rat. *Brain Res* 2001;900:261-7.
- Hanlon EC, Van Cauter E. Quantification of sleep behavior and of its impact on the cross-talk between the brain and peripheral metabolism. *Proc Natl Acad Sci U S A* 2011;108 Suppl 3:15609-16.
- Harman K, Pivik RT, D'Eon JL, et al. Sleep in depressed and nondepressed participants with chronic low back pain: electroencephalographic and behaviour findings. *Sleep*. 2002; 25:775–783.
- Harrington, C. B., Hansen, J. A., Moskowitz, M., Todd, B. L., & Feuerstein, M. (2010). It's not over when it's over: long-term symptoms in cancer survivors—a systematic review. *The International Journal of Psychiatry in Medicine*, 40(2), 163-181.
- Haworth, S.K. and Dluhy, N.M. (2001) Holistic symptom management: modelling the interaction phase. *Journal of Advanced Nursing*, 36 (2), pp. 302-310.
- Heffner, K. L., France, C. R., Trost, Z., Ng, H. M., & Pigeon, W. R. (2011). Chronic low back pain, sleep disturbance, and interleukin-6. *The Clinical journal of pain*, 27(1), 35.
- Henschke, N., Ostelo, R. W., van Tulder, M. W., Vlaeyen, J. W., Morley, S., Assendelft, W. J., & Main, C. J. (2010). Behavioural treatment for chronic low-back pain. *The Cochrane Library*.

- Henwood, P., & Ellis, J. A. (2004). Chronic neuropathic pain in spinal cord injury: the patient's perspective. *Pain research and Management*, 9(1), 39-45.
- Herr, J. K., Salyer, J., Flattery, M., Goodloe, L., Lyon, D. E., Kabban, C. S., & Clement, D. G. (2015). Heart failure symptom clusters and functional status—a cross-sectional study. *Journal of advanced nursing*, 71(6), 1274-1287.
- Herr, J. K., Salyer, J., Lyon, D. E., Goodloe, L., Schubert, C., & Clement, D. G. (2014). Heart failure symptom relationships: a systematic review. *Journal of Cardiovascular Nursing*, 29(5), 416-422.
- Hicks RA, Moore JD, Findley P, Hirshfield C, Humphrey V. REM sleep deprivation and pain thresholds in rats. *Percept Mot Skills* 1978;47:848-50.
- Hitzig, S. L., Tonack, M., Campbell, K. A., McGillivray, C. F., Boschen, K. A., Richards, K., & Craven, B. C. (2008). Secondary health complications in an aging Canadian spinal cord injury sample. *American Journal of Physical Medicine & Rehabilitation*, 87(7), 545-555.
- Ho, S. Y., Rohan, K. J., Parent, J., Tager, F. A., & McKinley, P. S. (2015). A longitudinal study of depression, fatigue, and sleep disturbances as a symptom cluster in women with breast cancer. *Journal of pain and symptom management*, 49(4), 707-715.
- Holliday S, Hayes C, Dunlop A. Opioid use in chronic non-cancer pain—part 1: Known knowns and known unknowns. *Aust Fam Physician* 2013;42(3):98–102.
- Hornig, Y. S., Hwang, Y. H., Wu, H. C., Liang, H. W., Mhe, Y. J., Twu, F. C., & Wang, J. D. (2005). Predicting health-related quality of life in patients with low back pain. *Spine*, 30(5), 551-555.
- Howren, M. B., Lamkin, D. M., & Suls, J. (2009). Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosomatic medicine*, 71(2), 171-186.
- Hoy, D., Bain, C., Williams, G., March, L., Brooks, P., Blyth, F., ... & Buchbinder, R. (2012). A systematic review of the global prevalence of low back pain. *Arthritis & Rheumatism*, 64(6), 2028-2037.
- Huanan, I. P., Verbunt, J. A., Peters, M. L., Delespaul, P., Kindermans, H. P., Roelofs, J., ... & Seelen, H. A. (2010). Do depression and pain intensity interfere with physical activity in daily life in patients with Chronic Low Back Pain?. *Pain*, 150(1), 161-166.
- Humphreys, J.; Lee, K. A.; Carrieri-Colman, V.; Puntillo, K.; Faucett, J.; Janson, S.; Aouizerat, B.; Donesky-Cuenca, D. and UCSF School of Nursing Symptom Management Faculty Group (2008) Theory of Symptom Management. In: Smith, M. J. and Liehr, P. R., eds. *Middle Range Theory for Nursing*, 2nd edn. New York, Springer Publishing Company, pp. 145-158.

- Hutchinson S. & Wilson H. (1998) The theory of unpleasant symptoms and Alzheimer's disease. *Scholarly Inquiry for Nursing Practice* 12, 143–158.
- Huth, M. M., & Broome, M. E. (2007). A snapshot of children's postoperative tonsillectomy outcomes at home. *Journal for Specialists in Pediatric Nursing*, 12(3), 186-195.
- Imeri L, Opp MR. How (and why) the immune system makes us sleep. *Nat Rev Neurosci* 2009;10:199-210.
- Irwin, M. R., Olmstead, R., & Carroll, J. E. (2016). Sleep disturbance, sleep duration, and inflammation: a systematic review and meta-analysis of cohort studies and experimental sleep deprivation. *Biological psychiatry*, 80(1), 40-52.
- Ivan P.J. Huanan, Jeanine A. Verbunt, Madelon L. Peters, Philippe Delespaul, Hanne P.J. Kindermans, Jeffrey Roelofs, Marielle Goossens, Henk A.M. Seelen, Do depression and pain intensity interfere with physical activity in daily life in patients with Chronic Low Back Pain?, *PAIN*, Volume 150, Issue 1, July 2010, Pages 161-166.
- Jackson, J. L., & Kroenke, K. (2001). The effect of unmet expectations among adults presenting with physical symptoms. *Annals of Internal Medicine*, 134(9\_Part\_2), 889-897.
- Janusek, L. W., Albuquerque, K. V., & Mathews, H. L. (2006). Psycho-immune response of women with breast cancer to mindfulness based stress reduction. *Brain, Behavior, and Immunity*, 20(3), 1-2.
- Janusek, L.W., Albuquerque, K., Chroniak, K.R., Chroniak, C., and Mathews, H.L. Effect of mindfulness based stress reduction on immune function, quality of life and coping in women newly diagnosed with early stage breast cancer. *Brain, Behavior and Immunity*, 22(6):969-81, 2008.
- Jaremka, L. M., Andridge, R. R., Fagundes, C. P., Alfano, C. M., Pivoski, S. P., Lipari, A. M., ... & Carson III, W. E. (2014). Pain, depression, and fatigue: loneliness as a longitudinal risk factor. *Health Psychology*, 33(9), 948.
- Jausset, I., Morin, C. M., Ivers, H., & Dauvilliers, Y. (2017). Incidence, worsening and risk factors of daytime sleepiness in a population-based 5-year longitudinal study. *Scientific Reports*, 7.
- Jennifer A. Haythornthwaite, William J. Sieber, Robert D. Kerns, Depression and the chronic pain experience, *Pain*, Volume 46, Issue 2, 1991, Pages 177-184.
- Jensen TS, Karppinen J, Sorensen JS, et al. Vertebral endplate signal changes (Modic change): a systematic literature review of prevalence and association with non-specific low back pain. *Eur Spine J*. 2008;17:1407–1422.

- Johnson, R. L., Gerhart, K. A., McCray, J., Menconi, J. C., & Whiteneck, G. G. (1998). Secondary conditions following spinal cord injury in a population-based sample. *Spinal cord*, 36(1).
- Jurgens, C. Y., Moser, D. K., Armola, R., Carlson, B., Sethares, K., & Riegel, B. (2009). Symptom Clusters of Heart Failure. *Research in Nursing & Health*, 32(5), 551–560.
- Kaila-Kangas, L., Haukka, E., Miranda, H., Kivekäs, T., Ahola, K., Luukkonen, R., ... & Leino-Arjas, P. (2014). Common mental and musculoskeletal disorders as predictors of disability retirement among Finns. *Journal of affective disorders*, 165, 38-44.
- Kamper, S. J., Apeldoorn, A. T., Chiarotto, A., Smeets, R. J., Ostelo, R. W. J. G., Guzman, J., & Van Tulder, M. W. (2014). Multidisciplinary biopsychosocial rehabilitation for chronic low back pain (Review).
- Karmann AJ, Kundermann B, Lautenbacher S. [Sleep deprivation and pain: a review of the newest literature]. *Schmerz* 2014;28:141–6.
- Keeley, P., Creed, F., Tomenson, B., Todd, C., Borglin, G., & Dickens, C. (2008). Psychosocial predictors of health-related quality of life and health service utilisation in people with chronic low back pain. *PAIN®*, 135(1), 142-150.
- Khalid I, Roehrs TA, Hudgel DW, et al. Continuous positive airway pressure in severe obstructive sleep apnea reduces pain sensitivity. *Sleep* 2011;34:1687–91.
- Kiecolt-Glaser JK, Dura JR, Speicher CE, Trask OJ, Glaser R. 1991. Spousal caregivers of dementia victims: longitudinal changes in immunity and health. *Psychosom. Med.* 53:345-362.
- Kim, H. J., McGuire, D. B., Tulman, L., & Barsevick, A. M. (2005). Symptom clusters: concept analysis and clinical implications for cancer nursing. *Cancer nursing*, 28(4), 270-282.
- Klyne, D. M., Barbe, M. F., & Hodges, P. W. (2017). Systemic inflammatory profiles and their relationships with demographic, behavioural and clinical features in acute low back pain. *Brain, behavior, and immunity*, 60, 84-92.
- Koffel, E., Kroenke, K., Bair, M. J., Leverty, D., Polusny, M. A., & Krebs, E. E. (2015). The bidirectional relationship between sleep complaints and pain: Analysis of data from a randomized trial.
- Koleck, M., Mazaux, J. M., Rasclé, N., & Bruchon-Schweitzer, M. (2006). Psycho-social factors and coping strategies as predictors of chronic evolution and quality of life in patients with low back pain: A prospective study. *European Journal of Pain*, 10(1), 1-1.

- Komaroff AL. Symptoms: in the Head or in the Brain?. *Ann Intern Med.* 2001;134:783-785. doi: 10.7326/0003-4819-134-9\_Part\_1-200105010-00016
- Kravitz, H. M., Zheng, H., Bromberger, J. T., Buysse, D. J., Owens, J., & Hall, M. H. (2015). An Actigraphy Study of Sleep and Pain in Midlife Women—The SWAN Sleep Study. *Menopause (New York, NY)*, 22(7), 710.
- Krishnan KR, France RD, Pelton S, McCann UD, Davidson J, Urban BJ. Chronic pain and depression. II. Symptoms of anxiety in chronic low back pain patients and their relationship to subtypes of depression. *Pain.* 1985;22:289–94.
- Kristal A.R., Shattuck A.L., Henry H.J., (1990). Patterns of dietary behavior associated with selecting diets low in fat: reliability and validity of a behavioral approach to dietary assessment, *Journal of the American Dietetic Association*, 90(2), 214-20.
- Kroenke K, Spitzer RL, Williams JB, Linzer M, Hahn SR, deGruy FV 3rd, et al. Physical symptoms in primary care. Predictors of psychiatric disorders and functional impairment. *Arch Fam Med.* 1994;3:774-9. [PMID: 7987511]
- Kroenke K. A Practical and Evidence-Based Approach to Common Symptoms: A Narrative Review. *Ann Intern Med.* 2014;161:579-586. doi: 10.7326/M14-0461s
- Kroenke K. Patients presenting with somatic complaints: epidemiology, psychiatric comorbidity and management. *Int J Methods Psychiatr Res.* 2003;12:34- 43. [PMID: 12830308]
- Kroenke K. Studying symptoms: sampling and measurement issues. *Ann Intern Med.* 2001;134:844-53. [PMID: 11346320]
- Kroenke, K., Arrington, M. E., & Mangelsdorff, A. D. (1990). The prevalence of symptoms in medical outpatients and the adequacy of therapy. *Archives of internal medicine*, 150(8), 1685.
- Kroenke, K., Outcalt, S., Krebs, E., Bair, M. J., Wu, J., Chumbler, N., & Yu, Z. (2013). Association between anxiety, health-related quality of life and functional impairment in primary care patients with chronic pain. *General hospital psychiatry*, 35(4), 359-365.
- Kroenke, K., Outcalt, S., Krebs, E., Bair, M. J., Wu, J., Chumbler, N., & Yu, Z. (2013). Association between anxiety, health-related quality of life and functional impairment in primary care patients with chronic pain. *General hospital psychiatry*, 35(4), 359-365.
- Kundermann B, Sernal J, Huber MT, Krieg JC, Lautenbacher S. Sleep deprivation affects thermal pain thresholds but not somatosensory thresholds in healthy volunteers. *Psychosom Med* 2004;66:932-7.



- Kwekkeboom, K. L., Cherwin, C. H., Lee, J. W., & Wanta, B. (2010). Mind-body treatments for the pain-fatigue-sleep disturbance symptom cluster in persons with cancer. *Journal of pain and symptom management*, 39(1), 126-138.
- Landis CA, Lentz MJ, Rothermel J, et al. Decreased sleep spindles and spindle activity in midlife women with fibromyalgia and pain. *Sleep*. 2004;27:741–750.
- Lanquillon, S., Krieg, J. C., Bening-Abu-Shach, U., & Vedder, H. (2000). Cytokine production and treatment response in major depressive disorder. *Neuropsychopharmacology*, 22(4), 370.
- Latham J, Davis BD. The socioeconomic impact of chronic pain. *Disabil Rehabil* 1994; 16: 39—44.
- Lautenbacher, S., Kundermann, B., & Krieg, J. C. (2006). Sleep deprivation and pain perception. *Sleep medicine reviews*, 10(5), 357-369.
- Lavie P, Epstein R, Tzischinsky O, et al. Actigraphic measurements of sleep in rheumatoid arthritis: comparison of patients with low back pain and healthy controls. *J Rheumatol*.1992;19:362–365.
- Lawrence, R. C., Felson, D. T., Helmick, C. G., Arnold, L. M., Choi, H., Deyo, R. A., ... & Jordan, J. M. (2008). Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part II. *Arthritis & Rheumatology*, 58(1), 26-35.
- Lee, H., Hübscher, M., Moseley, G. L., Kamper, S. J., Traeger, A. C., Mansell, G., & McAuley, J. H. (2015). How does pain lead to disability? A systematic review and meta-analysis of mediation studies in people with back and neck pain. *Pain*, 156(6), 988-997.
- Lengacher, C. A., Reich, R. R., Post-White, J., Moscoso, M., Shelton, M. M., Barta, ... M., & Budhrani, P. (2012). Mindfulness based stress reduction in post-treatment breast cancer patients: an examination of symptoms and symptom clusters. *Journal of behavioral medicine*, 35(1), 86-94.
- Lentz MJ, Landis CA, Rothermel J, Shaver JL. Effects of selective slow wave sleep disruption on musculoskeletal pain and fatigue in middle aged women. *J Rheumatol* 1999;26:1586-92.
- Lenz, E., Pugh, L., Milligan, R., Gift, A., & Suppe, F. (1997). The Middle-Range Theory of Unpleasant Symptoms: An Update. *Advances in Nursing Science* (19), 14-27.
- Lenz, E., Suppe, F., Gift, A., Pugh, L., & Milligan, R. (1995). Collaborative development of middle-range nursing theories: Toward a theory of unpleasant symptoms. *Advances in Nursing Science*, 17(3), 1-13.

- Liu, L., Fiorentino, L., Natarajan, L., Parker, B. A., Mills, P. J., Sadler, G. R., ... & Ancoli-Israel, S. (2009). Pre-treatment symptom cluster in breast cancer patients is associated with worse sleep, fatigue and depression during chemotherapy. *Psycho-Oncology*, 18(2), 187-194.
- Long, X., Fonseca, P., Haakma, R., & Aarts, R. M. (2017, May). Actigraphy-based sleep/wake detection for insomniacs. In *Wearable and Implantable Body Sensor Networks (BSN), 2017 IEEE 14th International Conference on*(pp. 1-4). IEEE.
- Luo X , Pietrobon R , Sun SX , et al. Estimates and patterns of direct health care expenditures among individuals with back pain in the United States . *Spine (Phila Pa 1976)* 2004 ; 29 : 79 – 86
- Magni G., Caldieron C., Rigatti-Luchini S., Merskey H. Chronic musculoskeletal pain and depressive symptoms in the general population. An analysis of the 1st National Health and Nutrition Examination Survey data. *Pain*. 1990;43(3):299–307.
- Manchikanti, L., Pampati, V., Damron, K., Beyer, C., & Barnhill, R. (2002). Evaluation of psychological status in chronic low back pain: comparison with general population. *Pain Physician*, 5(2), 149-155.
- Manchikanti, L., Singh, V., Datta, S., Cohen, S. P., & Hirsch, J. A. (2009). Comprehensive review of epidemiology, scope, and impact of spinal pain. *Pain physician*, 12(4), E35-70.
- Marchand, F., Perretti, M., & McMahon, S. B. (2005). Role of the immune system in chronic pain. *Nature reviews. Neuroscience*, 6(7), 521.
- Marin R, Cyhan T, Miklos W: Sleep disturbance in patients with chronic low back pain. *Am J Phys Med Rehabil* 2006;85:430–435.
- Marina B. Pinheiro, Manuela L. Ferreira, Kathryn Refshauge, Christopher G. Maher, Juan R. Ordoñana, Tude B. Andrade, Alexandros Tsathas, Paulo H. Ferreira, Symptoms of depression as a prognostic factor for low back pain: a systematic review, *The Spine Journal*, Volume 16, Issue 1, 1 January 2016, Pages 105-116
- Marshall, P. W., Schabrun, S., & Knox, M. F. (2017). Physical activity and the mediating effect of fear, depression, anxiety, and catastrophizing on pain related disability in people with chronic low back pain. *PloS one*, 12(7), e0180788.
- Marty, M., Rozenberg, S., Duplan, B., Thomas, P., Duquesnoy, B., Allaert, F., & Section Rachis de la Société Française de Rhumatologie. (2008). Quality of sleep in patients with chronic low back pain: a case-control study. *European Spine Journal*, 17(6), 839-844.
- McClement, S.E.; Woodgate, R.L. and Degner, L. (1997) Symptom distress in adult patients with cancer. *Cancer Nursing*, 20 (4), pp. 236-243.

- McCracken, L. M., Gross, R. T., Sorg, P. J., & Edmands, T. A. (1993). Prediction of pain in patients with chronic low back pain: effects of inaccurate prediction and pain-related anxiety. *Behaviour research and therapy*, 31(7), 647-652.
- McDaniel, R. and Rhodes, V.A. (1995) Symptom experience. *Seminars in Oncology Nursing*, 11 (4), pp. 232-234.
- Miaskowski C, Dodd M, Lee K. Symptom clusters: the new frontier in symptom management research. *J Natl Cancer Inst Monogr* 2004;32:17-21.
- Miller, L. R., & Cano, A. (2009). Comorbid chronic pain and depression: who is at risk?. *The Journal of Pain*, 10(6), 619-627.
- Moix J, Kovacs FM, Martin A, et al. Catastrophizing, state anxiety, anger, and depressive symptoms do not correlate with disability when variations of trait anxiety are taken into account. a study of chronic low back pain patients treated in Spanish pain units. *Pain Med* 2011;12:1008-17
- Moldofsky H, Scarisbrick P. Induction of neurasthenic musculoskeletal pain syndrome by selective sleep stage deprivation. *Psychosom Med* 1976;38:35-44.
- Moldofsky HM, Scarisbrick PB, England RB, Smythe HM. Musculoskeletal symptoms and nonrem sleep disturbance in patients with "fibrositis syndrome" and healthy subjects. *Psychosom Med* 1975;37:341-51.
- Mork PJ, Nilsen TI. Sleep problems and risk of fibromyalgia: Longitudinal data from the Norwegian HUNT-study. *Arthritis Rheum.* 2011;64:281-4.
- Mork PJ, Nilsen TI. Sleep problems and risk of fibromyalgia: Longitudinal data from the Norwegian HUNT-study. *Arthritis Rheum.* 2011;64:281-4.
- Morley S, Eccleston C, Williams A. Systematic review and meta-analysis of randomized controlled trials of cognitive behavior therapy and behavior therapy for chronic pain in adults, excluding headache. *Pain.* 1999 Mar;80((1-2)):1-13.
- Morone G, Paolucci T, Alcuri MR, Vulpiani MC, Matano A, Bureca I. Quality of life improved by multidisciplinary back school program in patients with chronic non-specific low back pain: a single blind randomized controlled trial. *EurJ Phys Rehabil Med* 2011;47:533-41.
- Moser, D. K., Lee, K. S., Wu, J. R., Mudd-Martin, G., Jaarsma, T., Huang, T. Y., ... & Riegel, B. (2014). Identification of symptom clusters among patients with heart failure: an international observational study. *International journal of nursing studies*, 51(10), 1366-1372.

- Mota DCF, Pimenta CAM. Self-report instruments for fatigue assessment: A systematic review. *Research and Theory for Nursing Practice: An International Journal*. 2006;20:49–76
- Motl, R., & McAuley, E. (2009). Symptom Cluster as a Predictor of Physical Activity in Multiple Sclerosis: Preliminary Evidence. *Journal of Pain and Symptom Management*, 38 (2), 270-280. *Musculoskeletal Rehabil.* 2004; 17:69–76.
- Murray, C. J., Abraham, J., Ali, M. K., Alvarado, M., Atkinson, C., Baddour, L. M., ... & Bolliger, I. (2013). The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. *Jama*, 310(6), 591-606.
- Musselman, D.L., Miller, A.H., Porter, M.R., Manatunga, A., Gao, F., Penna, S., Pearce, B.D., Landry, J., Glover, S., McDaniel, J.S., Nemerov, C.B., 2001. Higher than normal plasma interleukin-6 concentrations in cancer patients with depression: preliminary findings. *Am. J. Psychiatry*. 158, 1252–1257
- Muthén, L. K., & Muthén, B. O. (2012). Mplus. *The comprehensive modelling program for applied researchers: User's guide*, 5.
- Myers, J. (2009). A comparison of the theory of unpleasant symptoms and the conceptual model of chemotherapy-related changes in cognitive function. *Oncology Nursing Forum*, 36(1), E1-10.
- Nascimento DC, Andersen ML, Hipolide DC, Nobrega JN, Tufik S. Pain hypersensitivity induced by paradoxical sleep deprivation is not due to altered binding to brain mu-opioid receptors. *Behav Brain Res* 2007;178:216-20.
- National Institute of Nursing Research. Bringing science to life: NINR strategic plan [cited 2017 June 6]. Available from: URL: [https://www.ninr.nih.gov/sites/www.ninr.nih.gov/files/NINR\\_StratPlan2016\\_reduced.pdf](https://www.ninr.nih.gov/sites/www.ninr.nih.gov/files/NINR_StratPlan2016_reduced.pdf)
- National Sleep Foundation. 2000 Sleep in America poll: summary of findings. National Sleep Foundation, ed. Washington, DC, 2000.
- Naughton, F., Ashworth, P., & Skevington, S. M. (2007). Does sleep quality predict pain-related disability in chronic pain patients? The mediating roles of depression and pain severity. *Pain*, 127(3), 243-252.
- Newcomer KL, Shelerud RA, Vickers Douglas KS, et al. Anxiety levels, fear-avoidance beliefs, and disability levels at baseline and at 1 year among subjects with acute and chronic low back pain. *PM R* 2010;2:514–20
- Nightingale, F. (1859/1946). *Notes on nursing*. Philadelphia, PA: Edward Stern & Co.

- Nijs, J., Loggia, M. L., Polli, A., Moens, M., Huysmans, E., Goudman, L., ... & Clauw, D. (2017). Sleep disturbances and severe stress as glial activators: key targets for treating central sensitization in chronic pain patients?. *Expert opinion on therapeutic targets*, 21(8), 817-826.
- Noble M, Tregear SJ, Treadwell JR. Schoelles: long-term opioid therapy for chronic noncancer pain: a systematic review and meta-analysis of efficacy and safety. *J Pain Symptom Manage*.2008;35(2):214–228.
- Noonan, V. K., Kopec, J. A., Zhang, H., & Dvorak, M. F. (2008). Impact of associated conditions resulting from spinal cord injury on health status and quality of life in people with traumatic central cord syndrome. *Archives of physical medicine and rehabilitation*, 89(6), 1074-1082.
- O'brien, E. M., Waxenberg, L. B., Atchison, J. W., Gremillion, H. A., Staud, R. M., McCrae, C. S., & Robinson, M. E. (2011). Intraindividual variability in daily sleep and pain ratings among chronic pain patients: bidirectional association and the role of negative mood. *The Clinical journal of pain*, 27(5), 425-433.
- O'Donoghue, G. M., Fox, N., Heneghan, C., & Hurley, D. A. (2009). Objective and subjective assessment of sleep in chronic low back pain patients compared with healthy age and gender matched controls: a pilot study. *BMC musculoskeletal disorders*, 10(1), 1.
- of sleep and wakefulness. *Physiol Rev* 2012;92:1087-187.
- Ohayon MM. Relationship between chronic painful physical condition and insomnia. *J Psychiatr Res* 2005;39:151–9.
- Older SA, Battafarano DF, Danning CL, Ward JA, Grady EP, Derman S, Russell IJ. The effects of delta wave sleep interruption on pain thresholds and fibromyalgia-like symptoms in healthy subjects; correlations with insulin-like growth factor I. *J Rheumatol* 1998; 25: 1180—1186.
- Oliveira, D. S., Vélia Ferreira Mendonça, L., Sofia Monteiro Sampaio, R., de Castro-Lopes, M. P. D., & Ribeiro de Azevedo, L. F. (2018). The Impact of Anxiety and Depression on the Outcomes of Chronic Low Back Pain Multidisciplinary Pain Management—A Multicenter Prospective Cohort Study in Pain Clinics with One-Year Follow-up. *Pain Medicine*.
- Onen, S. H., Alloui, A., Gross, A., Eschallier, A., & Dubray, C. (2001). The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subjects. *Journal of sleep research*, 10(1), 35-42.
- Osborn, M., & Smith, J. A. (2015). The personal experience of chronic benign lower back pain: An interpretative phenomenological analysis. *British Journal of Pain*, 9(1), 65-83.

Oxford English Dictionary, 2nd ed New York, Oxford Univ Pr:1992.

Park, J. W., & Chung, J. W. (2016). Inflammatory Cytokines and Sleep Disturbance in Patients with Temporomandibular Disorders. *Journal of Oral & Facial Pain & Headache*, 30(1).

Parker, K.P.; Kimble, L.P.; Dunbar, S.P. and Clark, P.C. (2005) Symptom interactions as mechanisms underlying symptom pairs and clusters. *Journal of Nursing Scholarship*, 37 pp. 209-215.

Parreira, P., Maher, C., Steffens, D., Hancock, M., & Ferreira, M. (2018). Risk factors for low back pain and sciatica: an umbrella review. *The Spine Journal*..

Patricia M. Averill, Diane M. Novy, David V. Nelson, Leigh A. Berry, Correlates of depression in chronic pain patients: a comprehensive examination, *Pain*, Volume 65, Issue 1, April 1996, Pages 93-100.

Paulozzi LJ. Prescription drug overdoses: a review. *Journal of Safety Research*, 2012; <http://dx.doi.org/10.1016/j.jsr.2012.08.009>.

Pedersen, L. M., Schistad, E., Jacobsen, L. M., Røe, C., & Gjerstad, J. (2015). Serum levels of the pro-inflammatory interleukins 6 (IL-6) and-8 (IL-8) in patients with lumbar radicular pain due to disc herniation: a 12-month prospective study. *Brain, behavior, and immunity*, 46, 132-136.

Pegram, S. E., Lumley, M. A., Jasinski, M. J., & Burns, J. W. (2017). Psychological trauma exposure and pain-related outcomes among people with chronic low back pain: Moderated mediation by thought suppression and social constraints. *Annals of Behavioral Medicine*, 51(2), 316-320.

Pilowsky, Crettenden, Townley. Sleep disturbance in pain clinic patients. *Pain* 1985;23:27–33.

Pinheiro, M. B., Ferreira, M. L., Refshauge, K., Colodro-Conde, L., González-Javier, F., Hopper, J. L., ... & Ferreira, P. H. (2016). Symptoms of Depression and Risk of Low Back Pain: A Prospective Co-twin Study. *The Clinical journal of pain*.

Piper BF. Fatigue: Current bases for practice. In: Funk SG, Tornquist EM, Chapagne MT, Copp LA, Wiese R, editors. *Key aspects of comfort*. New York: Springer; 1989. pp. e187–e198

Polatin PB, Kinney RK, Gatchel RJ, Lillo E, Mayer TG. Psychiatric illness and chronic back pain. The mind and the spine—which goes first? *Spine* 1993; 18: 66–71.

Polatin, P. B., Kennedy, R. K., Gatchel, R. J., Lillo, E., & Mayer, T. G. (1993). Psychiatric illness and chronic low-back pain: The mind and the spine—which goes first?. *Spine*, 18(1), 66-71.

- Poleshuck, E. L., Talbot, N. L., Moynihan, J. A., Chapman, B. P., & Heffner, K. L. (2013). Depressive symptoms, pain, chronic medical morbidity, and interleukin-6 among primary care patients. *Pain Medicine, 14*(5), 686-691.
- Portenoy RK, Farrar JT, Backonja MM, et al. Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. *Clin J Pain. 2007 May;23*(4):287–299.
- Pugh, L. C., & Milligan, R. A. (1993). A framework for the study of childbearing fatigue. *Advances in Nursing Science, 15*, 60-70.
- Rabey, M., Smith, A., Beales, D., Slater, H., & O'Sullivan, P. (2017). Differing psychologically-derived clusters in people with chronic low back pain are associated with different multidimensional profiles. *Musculoskeletal Science & Practice, 28*, e10.
- Radloff, L. S. (1977). The CES-D scale: a self-report depression scale for research in the general population. *Applied psychological measurement, 1*(3), 385-401.
- Ravenscroft, A. J. (2000). Chronic pain after spinal cord injury: a survey of practice in spinal injury units in the USA. *Spinal Cord, 38*(11), 658.
- Reeve B, Hays RD, Bjorner JB, Cook KF, Crane PK, Teresi JA, et al. Psychometric evaluation and calibration of health-related quality of life item banks: plans for the Patient-Reported Outcomes Measurement Information System (PROMIS). *Med Care 2007; 45*:S22–31
- Reich, R. R., Lengacher, C. A., Klein, T. W., Newton, C., Shivers, S., Ramesar, S., ... & Johnson-Mallard, V. (2017). A Randomized Controlled Trial of the Effects of Mindfulness-Based Stress Reduction (MBSR [BC]) on Levels of Inflammatory Biomarkers Among Recovering Breast Cancer Survivors. *Biological Research For Nursing, 1099800417707268*.
- ReillyeF, C. M., Bruner, D. W., Mitchell, S. A., Minasian, L. M., Basch, E., Dueck, A. C., ... & Reeve, B. B. (2013). A literature synthesis of symptom prevalence and severity in persons receiving active cancer treatment. *Supportive Care in Cancer, 21*(6), 1525-1550.
- Reinoso-Barbero FM, Andres IP. Effects of opioid microinjections in the nucleus of the solitary tract on the sleep-wakefulness cycle states in cats. *Anesthesiology 1995;82*:144–52.
- Reme SE, Tangen T, Moe T, et al. Prevalence of psychiatric disorders in sick listed chronic low back pain patients. *Eur J Pain 2011;15*:1075–80
- Rhodes, V.A. and Watson, P.M. (1987) Symptom distress: The concept past and present. *Seminars in Oncology Nursing, 3* pp. 242-247.
- Rintala, D. H., Loubser, P. G., Castro, J., Hart, K. A., & Fuhrer, M. J. (1998). Chronic pain in a community-based sample of men with spinal cord injury: prevalence, severity, and

- relationship with impairment, disability, handicap, and subjective well-being. *Archives of physical medicine and rehabilitation*, 79(6), 604-614.
- Risbud, M. V., & Shapiro, I. M. (2014). Role of cytokines in intervertebral disc degeneration: pain and disc content. *Nature Reviews Rheumatology*, 10(1), 44-56.
- Roehrs T, Hyde M, Blaisdell B, et al. Sleep loss and REM sleep loss are hyperalgesic. *Sleep* 2006;29:145–51.
- Rosenkranz, M. A., Davidson, R. J., MacCoon, D. G., Sheridan, J. F., Kalin, N. H., & Lutz, A. (2013). A comparison of mindfulness-based stress reduction and an active control in modulation of neurogenic inflammation. *Brain, behavior, and immunity*, 27, 174-184.
- Roth T, Price JM, Amato DA, et al. The effect of eszopiclone in patients with insomnia and coexisting rheumatoid arthritis: a pilot study. *Prim Care Companion J Clin Psychiatry* 2009;11:292–301.
- Rubin DI. Epidemiology and Risk Factors for Spine Pain. *Neurol Clin.* 2007; May;25(2):353-71.
- Russell D, Cutrona CE, Rose J, Yurko K. 1984. Social and emotional loneliness: an examination of Weiss's typology of loneliness. *J. Pers. Soc. Psychol.* 46:1313-1321.
- Russell D, Cutrona CE, Rose J, Yurko K. 1984. Social and emotional loneliness: an examination of Weiss's typology of loneliness. *J. Pers. Soc. Psychol.* 46:1313-1321.
- Rutledge DN, Mouttapa M, Wood PB. Symptom clusters in fibromyalgia: Potential utility in patient assessment and treatment evaluation. *Nursing Research* 2009; 58: 359-367.
- Sabatowski, R., Gálvez, R., Cherry, D. A., Jacquot, F., Vincent, E., Maisonobe, P., ... & 1008-045 Study Group. (2004). Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial. *Pain*, 109(1), 26-35.
- Sahin, N., Karahan, A. Y., Devrimsel, G., & Gezer, I. A. (2017). Comparison among pain, depression, and quality of life in cases with failed back surgery syndrome and non-specific chronic back pain. *Journal of Physical Therapy Science*, 29(5), 891-895.
- Sallanon M, Janin M, Buda C, Jouvet M. Serotonergic mechanisms and sleep rebound. *Brain Res* 1983;268:95–104.
- Salt, E., Wiggins, A. T., Hooker, Q., Crofford, L., Rayens, M. K., & Segerstrom, S. (2018). The effects of pain severity, pain catastrophizing, depression, and exercise on perceived disability in acute low back pain patients. *Research and theory for nursing practice*, 32(4), 436-448.



- Schoenfeld, D. (1980). Statistical considerations for pilot studies. *International Journal of Radiation Oncology, Biology, Physics*, 6(3), 371-374.
- Schrimpf, M., Liegl, G., Boeckle, M., Leitner, A., Geisler, P., & Pieh, C. (2015). The effect of sleep deprivation on pain perception in healthy subjects: a meta-analysis. *Sleep medicine*, 16(11), 1313-1320.
- Sharpe, M., & Carson, A. (2001). "Unexplained" somatic symptoms, functional syndromes, and somatization: do we need a paradigm shift?. *Annals of internal medicine*, 134(9\_Part\_2), 926-930.
- Shawn R Currie, JianLi Wang, Chronic back pain and major depression in the general Canadian population, *Pain*, Volume 107, Issues 1–2, January 2004, Pages 54-60.
- Silva GE, Goodwin JL, Sherrill DL, Arnold JL, Bootzin RR, et al. (2007) Relationship between reported and measured sleep times: the sleep heart health study (SHHS). *J Clin Sleep Med* 3: 622–630.
- Sivertsen B, Krokstad S, Overland S, Mykletun A. The epidemiology of insomnia: associations with physical and mental health. The HUNT-2 study. *J Psychosom Res* 2009;67:109-16.
- Sivertsen B, Krokstad S, Overland S, Mykletun A. The epidemiology of insomnia: associations with physical and mental health. The HUNT-2 study. *J Psychosom Res* 2009;67:109-16.
- Sivertsen B, Krokstad S, Overland S, Mykletun A. The epidemiology of insomnia: associations with physical and mental health. The HUNT-2 study. *J Psychosom Res* 2009;67:109-16.
- Sivertsen B, Lallukka T, Petrie KJ, et al. Sleep and pain sensitivity in adults. *Pain* 2015;156(8):1433–9.
- Skevington, S. M., & Wright, A. (2001). Changes in the quality of life of patients receiving antidepressant medication in primary care: validation of the WHOQOL-100. *The British Journal of Psychiatry*, 178(3), 261-267.
- Smith MT, Edwards RR, McCann UD, Haythornthwaite JA. The effects of sleep deprivation on pain inhibition and spontaneous pain in women. *Sleep* 2007;30:494-505.
- Smith MT, Perlis ML, Smith MS, et al. Sleep quality and presleep arousal in chronic pain. *J Behav Med* 2000;23:1–13.
- Smith N, Jordan M, White R, Bowman J, Hayes C. Assessment of adults experiencing chronic non-cancer pain: A randomized trial of group versus individual format at an Australian tertiary pain service. *Pain Med* 2015.
- Snekkevik, H., Eriksen, H. R., Tangen, T., Chalder, T., & Reme, S. E. (2014). Fatigue and Depression in Sick-Listed Chronic Low Back Pain Patients. *Pain Medicine*, 15(7), 1163-1170.

- Starkweather, A. (2013). Psychologic and biologic factors associated with fatigue in patients with persistent radiculopathy. *Pain Management Nursing, 14*(1), 41-49.
- Stein MB, Roy-Byrne PP, Craske MG, Bystritsky A, Sullivan G, Pyne JM, et al. Functional impact and health utility of anxiety disorders in primary care outpatients. *Med Care 2005;43:1164–70*
- Stiasny-Kolster K, Pfau DB, Oertel WH, et al. Hyperalgesia and functional sensory loss in restless legs syndrome. *Pain 2013;154:1457–63.*
- Stoller M. Economic effects of insomnia. *Clin Ther 1994; 16: 873—897.*
- Sutton BC, Opp MR. Musculoskeletal sensitization and sleep: chronic muscle pain fragments sleep of mice without altering its duration. *Sleep 2014;37:505-13.*
- Tang, N. K., Wright, K. J., & Salkovskis, P. M. (2007). Prevalence and correlates of clinical insomnia co-occurring with chronic back pain. *Journal of sleep research, 16*(1), 85-95.
- Taylor, D. J., Mallory, L. J., Lichstein, K. L., Durrence, H. H., Riedel, B. W., & Bush, A. J. (2007). Comorbidity of chronic insomnia with medical problems. *Sleep, 30*(2), 213-218.
- Teel,C.S.; Meek,P.; McManamara,A.M. and Watson,L. (1997) Perspectives unifying symptom interpretation. *Image-Journal of Nursing Scholarship, 29* (2), pp. 175-181.
- Trost, Z., Sturgeon, J., Guck, A., Ziadni, M., Nowlin, L., Goodin, B., & Scott, W. (2019). Examining Injustice Appraisals in a Racially Diverse Sample of Individuals With Chronic Low Back Pain. *The Journal of Pain, 20*(1), 83-96.
- Ulrich JA, Liebenberg EC, Thuillier DU, et al. ISSLS prize winner: repeated disc injury causes persistent inflammation. *Spine. 2007;32:2812–2819*
- Underwood, M., & Sandhu, H. (2015). Sleep in patients with dystonia: A systematic review on the state of research and perspectives. *Sleep Medicine Reviews, 30*(1), e13.
- United States Bone and Joint Initiative: The Burden of Musculoskeletal Diseases in the United States (BMUS), Fourth Edition, forthcoming. Rosemont, IL. Available at <http://www.boneandjointburden.org>. Accessed on (Feb 26, 2019).
- Ursin R. Serotonin and sleep. *Sleep Med Rev 2002;6:55e69.* 16. Bannon MJ, Roth RH. Pharmacology of mesocortical dopamine neurons. *Pharm Rev 1983;35:68.*
- Van de Water ATM, Holmes A, Hurley DA (2011) Objective measurements of sleep for non-laboratory settings as alternatives to polysomnography—a systematic review. *J Sleep Res 20: 183–200.*

- Veehof, M. M., Oskam, M. J., Schreurs, K. M., & Bohlmeijer, E. T. (2011). Acceptance-based interventions for the treatment of chronic pain: a systematic review and meta-analysis. *PAIN®*, *152*(3), 533-542.
- Volkow ND, Wang GJ, Telang F, et al. Sleep deprivation decreases binding of [11C]raclopride to dopamine D2/D3 receptors in the human brain. *J Neurosci* 2008;28:8454–61.
- Von Korff, M., Crane, P., Lane, M., Miglioretti, D. L., Simon, G., Saunders, K., ... & Kessler, R. (2005). Chronic spinal pain and physical–mental comorbidity in the United States: results from the national comorbidity survey replication. *Pain*, *113*(3), 331-339.
- Walker, A. K., Kavelaars, A., Heijnen, C. J., & Dantzer, R. (2014). Neuroinflammation and comorbidity of pain and depression. *Pharmacological reviews*, *66*(1), 80-101.
- Walsh JK, Muehlbach MJ, Lauter SA,etal. Effects of triazolam on sleep, day time sleepiness, and morning stiffness in patients with rheumatoid arthritis. *J Rheumatol* 1996;245–52.
- Warnecke, R. B., Ferrans, C. E., Johnson, T. P., Chapa-Resendez, G., O'Rourke, D. P., Chavez, N., ... & Lad, T. (1996). Measuring quality of life in culturally diverse populations. *Journal of the National Cancer Institute. Monographs*, (20), 29-38.
- Waterschoot FP, Dijkstra PU, Hollak N, de Vries HJ, Geertzen JH, Reneman MF, Dose or content? Effectiveness of pain rehabilitation programs for patients with 74 chronic low back pain: a systematic review. *PAIN* 75 2014;155:179–89.
- Watson, D., & Pennebaker, J. W. (1989). Health complaints, stress, and distress: exploring the central role of negative affectivity. *Psychological review*, *96*(2), 234.
- Weber, K. T., Satoh, S., Alipui, D. O., Virojanapa, J., Levine, M., Sison, C., ... & Chahine, N. O. (2015). Exploratory study for identifying systemic biomarkers that correlate with pain response in patients with intervertebral disc disorders. *Immunologic research*, *63*(1-3), 170-180.
- Widerstrom-Noga E., Cruz-Almeida Y., Krassioukov A. (2004). Is there a relationship between chronic pain and autonomic dysreflexia in persons with cervical spinal cord injury. *J. Neurotrauma*21, 195–204
- Williams, R., & Murray, A. (2015). Prevalence of depression after spinal cord injury: a meta-analysis. *Archives of physical medicine and rehabilitation*, *96*(1), 133-140.
- Wilson KG, Mikail SF, D'Eon JL, Minns JE. Alternative diagnostic criteria for major depressive disorder in patients with chronic pain. *Pain* 2001; 91: 227—234.
- Wittig RM, Zorick FJ, Blumer D, Heilbronn M, Roth T. Disturbed sleep in patients complaining of chronic pain. *J Nerv Mental Dis* 1982;170:429-31.

- Wu, H. S., & Harden, J. K. (2015). Symptom burden and quality of life in survivorship: a review of the literature. *Cancer nursing*, 38(1), E29-E54.
- Yu D. S., Chan, H. Y., Leung, D. Y., Hui, E., & Sit, J. W. (2016). Symptom clusters and quality of life among patients with advanced heart failure. *Journal of geriatric cardiology: JGC*, 13(5), 408.
- Zammit, G. K., Weiner, J., Damato, N., Sillup, G. P., & McMillan, C. A. (1999). Quality of life in people with insomnia. *Sleep: Journal of Sleep Research & Sleep Medicine*.

## VITA

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