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Table of Contents

Title page	i
Acknowledgements	ii
Table of Contents	iii
List of Tables	iv
List of Figures	v
Abstract	vi
Chapter One: Introduction	1
Chapter Two: Literature Review	5
Chapter Three: Institutional Review Board Summary Plan	25
Chapter Four: Study Results	52
References	75
Vita	82

FIBROMYALGIA

List of Tables

1. Studies Reviewed	12
2. Study Measures	58
3. Demographic Data	63
4. Sleep by Group	64
5. Arousals by Group	65
6. HRV by Group	66
7. FMS Group Correlations	66
8. Non-FMS Group Correlations	67
9. Significant Correlations by Group	68
10. ASP Correlations by Group	69

List of Figures

1. Literature Search Methods	11
2. PNI-based Biobehavioral Model of Symptoms in FMS	54

Abstract

BIOBEHAVIORAL CORRELATES IN FIBROMYALGIA

By Ann Trivigno McNallen, CNM, MSN

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

Virginia Commonwealth University, 2012

Major Director: Nancy L. McCain, DSN, RN, Professor, VCU School of Nursing

Introduction: Fibromyalgia (FMS) is a chronic pain syndrome characterized by non-restorative sleep, and fatigue. Over 75% of individuals with FMS complain of poor sleep quality and fatigue. These have been ranked by patients with FMS as having great impact on quality of life. A literature review suggested that poor sleep quality may be a predictor of increased stress and FMS symptom onset in those affected. However, no experimental studies have demonstrated a causal relationship between poor sleep and stress in people with FMS.

Methods: Using a single stage cross-sectional design, the primary study aim was to compare 25 women with FMS and 25 women without FMS, on the following variables: autonomic nervous system activity; perceived stress; sleep quality; immune function (cytokines); and fatigue. The secondary aim was to explore the relationships among the above variables within each group. A third aim was to assess the validity of the Autonomic Symptoms Profile by comparing it to measures of heart rate variability and selected sleep indices.

Significant Results: The FMS group had worse sleep quality, more autonomic symptoms, and greater fatigue than the non-FMS group; they also had higher TNF- α levels. The non-FMS group was more likely to have OSA. Non-FMS participants who had OSA also had higher IL-1 β values than the FMS group. Study variables that correlated with each other in the FMS group

differed from those seen in the non-FMS group, with the exception of the positive correlation of total arousals with AHI in both groups. In the FMS group, fatigue was positively correlated with perceived stress, autonomic symptoms, and TNF- α ; stress was positively correlated with autonomic symptoms; and AHI was negatively correlated with IL-1 β levels as well as the above noted correlation with total arousals. In the non-FMS group, sleep quality was positively correlated with fatigue, and sleep quality and fatigue were positively correlated with IL-1 β . IL-1 β also positively correlated with TNF- α . Total arousals were negatively correlated with mean RR interval. SDNN was correlated with RR interval and negatively correlated with AHI. The hypothesis tests related to construct validity of the ASP indicated no significant supportive correlations.

Keywords: fibromyalgia, stress, sleep quality, ANS dysfunction, fatigue, cytokines

FIBROMYALGIA

Chapter One

FIBROMYALGIA

Sleep quality is highly problematic for most people with fibromyalgia (FMS). It appears to be related to autonomic nervous system (ANS) symptoms of dysfunction, such as intestinal irritability, syncope, and excessive sensitivity to external stimuli, as well as perceived stress, in people with FMS. Yet, no experimental studies thus far have demonstrated a causal relationship between poor sleep and stress in people with FMS. The biological mechanisms underlying such a relationship have not been fully articulated either, although a genetic predisposition to ANS dysfunction has been posited. The interplay of such a genetic predisposition, coupled with an adverse life event is viewed by some investigators as a likely scenario for the new onset of chronic widespread pain (CWP). Enhanced understanding of the biobehavioral mechanisms that result in FMS is a priority research focus.

The two studies that comprise this dissertation seek to explore this area of interest. In Chapter Two, an integrative literature review suggests that poor sleep quality may precede the onset of CWP, which is the hallmark of FMS diagnosis. The 12 studies included in the review agree that poor sleep quality is associated with greater perceived stress and more pain in those with FMS, but because of their correlational designs a causal link between poor sleep, stress, and pain cannot be posited. The directional nature of these reported associations remains highly controversial. Chapter Three is the Institutional Review Board application for permission to conduct an observational study, which includes the study design in detail.

Chapter Four reports the results of that observational study; it compared two groups of women presenting to the VCU Center for Sleep Medicine for evaluation of poor sleep quality; one group with FMS, and one without such a diagnosis. These

FIBROMYALGIA

women were compared on measures of perceived stress, perceived sleep quality, fatigue, and presence of ANS symptoms. They were assessed via polysomnography for objective measures of sleep, and heart rate variability. Cytokine levels were also obtained and compared.

Within the conceptual model of psychoneuroimmunology, this study initially posited that biological and behavioral cofactors interact with the ANS in women with FMS to produce dysfunctional changes in the ANS response to perceived stress, which in turn might alter sleep quality and cytokine expression. Poor sleep quality also leads to cytokine changes; both perceived stress and poor sleep quality interact with the ANS in a circular fashion, which could result in generalized pain and fatigue.

The study findings revealed that the FMS group had significantly worse sleep quality, more autonomic symptoms, and greater fatigue than the non-FMS group; they also had higher tumor necrosis factor-alpha (TNF- α) cytokine levels. The non-FMS group was significantly more likely to have obstructive sleep apnea (OSA). Non-FMS participants who had OSA also had significantly higher Interleukin-1 beta (IL-1 β) cytokine values than those in the FMS group.

In the FMS group, fatigue was positively correlated with perceived stress, autonomic symptoms, and TNF- α ; stress was positively correlated with autonomic symptoms; and apnea-hypopnea index (a measure of OSA presence and severity) was negatively correlated with IL-1 β levels.

In the non-FMS group, sleep quality was positively correlated with fatigue, and sleep quality and fatigue were positively correlated with IL-1 β . IL-1 β also positively

FIBROMYALGIA

correlated with TNF- α . Study variables that significantly correlated with each other in the FMS group differed completely from those seen in the non-FMS group.

These findings suggested a need to refine the postulated biobehavioral model of FMS as a response to a dysfunction of the ANS. Specifically, it may be that genetic predisposition, psychosocial experience, and behavioral cofactors interact in women with FMS to produce ANS changes that alter response to perceived stress and increase sympathetic nervous system (SNS) predominance during sleep. The SNS is viewed as persistently hyperactive, yet paradoxically hypoactive to stressors such as nighttime arousals, which may affect cytokine expression. Autonomic symptoms, including poor sleep quality, and perceived stress may lead to additional cytokine changes, all of which interact with the ANS in a circular fashion, resulting in generalized fatigue. This study may shed light on the complex relationships of sleep quality, stress, and autonomic symptoms in FMS in anticipation of formulating targeted interventions for sleep symptom management.

Chapter Two

FIBROMYALGIA

Fibromyalgia (FMS) is a chronic widespread pain syndrome characterized by diffuse musculoskeletal pain, non-restorative sleep, fatigue, and psychological distress (Schaefer, 2003). It affects approximately 5 million Americans (Lawrence et al., 2008), 90% of whom are women (Bennett, Jones, Turk, Russell, & Matallana, 2007). The economic impact of this condition is substantial as individuals with FMS often have trouble maintaining long-term employment due to increasing disability (Birtane, Uzunca, Tastekin, & Tuna, 2007). Those who complain of significant fatigue are six times more likely to report being disabled (Nicassio, Moxham, Schuman, & Gevirtz, 2002). Mean annual healthcare expenditures per FMS patient were reported to be more than \$10,000 in a 2008 study (Silverman et al., 2009). Over 75% of FMS patients internationally complain of poor sleep quality and fatigue (Belt, Kronholm, & Kauppi, 2009; Landis et al., 2003). These have been deemed critical in the management of FMS (Nicassio et al., 2002; Ericsson & Mannerkorpi, 2007; Moldofsky, 2008). Current views of FMS suggest it may be a neuroimmuno-endocrine inflammatory disorder exacerbated by stress (Perrot, Dickenson, & Bennett, 2008).

Although FMS is considered a stress disorder, and highly implicated in poor sleep quality, associations among stress and sleep quality in people with FMS have not been studied extensively. The aim of this paper is to review the findings of studies about these particular relationships. This integrative review seeks to answer the following question: what does current research suggest about the relationships among stress, sleep and FMS symptomatology?

Background

Considered a state of threatened homeostasis (Martinez-Lavin, 2007), stress alters various neuroimmuno-endocrine mechanisms (Kang, 2003). The stress response system, comprised mainly of the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA)

FIBROMYALGIA

axis, operates dynamically to maintain homeostasis. The ANS is the interface between one's perceptions and physiology that triggers a person's responses to a particular situation. Potential ANS responses to stress include elevated blood pressure, heart, and respiratory rates, pupil dilation, vasoconstriction, and shunting of circulation from the intestines to the skeletal muscles.

Perceived stress is defined as a person's cognitive appraisal of insufficient coping resources (Lazarus & Folkman, 1984), and is thought to increase sympathetic nervous system (SNS) activity (Martinez-Lavin, 2007). Studies of individuals with FMS have detected stress intolerance (Sephton et al., 2007) and increased basal SNS tone (Lush et al., 2009). FMS patients' reports that their pain is intensified by stress have been corroborated by researchers (Bradley, 2008). In a cross-sectional survey of 201 individuals, level of perceived stress was found to account for the greatest amount of variance associated with FMS symptoms (Murray, Murray, & Daniels, 2007).

The degree to which pain is experienced as a stressor may be exacerbated in people with FMS as compared to other people with chronic pain. Zautra et al.(2005) found that people with FMS displayed heightened stress responses as compared to people with osteoarthritis (OA) who reported similar pain levels. They found that stress-related increases in pain were more exacerbated by negative mood in individuals with FMS patients than in people with OA (Zautra et al., 2005). Additionally, general coping styles of people with FMS may differ from those of healthy controls (Ablin, Cohen, Neumann, Kaplan, & Buskila, 2008); this alteration in coping ability has been thought to leave those with FMS more vulnerable to stress than individuals with similar chronic pain conditions (Davis, Zautra, & Reich, 2001; Weissbecker, Floyd, Dedert, Salmon, & Sephton, 2006).

FIBROMYALGIA

Nearly 100% of people with FMS have reported poor sleep quality (Rizzi et al., 2004). Individuals with FMS scored significantly worse than healthy controls on instruments measuring sleep quality in two studies; they reported sleeping an average of only four to six hours per night (Osorio, Gallinaro, Lorenzi-Filho, & Lage, 2006; Bigatti, Hernandez, Cronan, & Rand, 2008). Osorio et al. (2006) found that Pittsburgh Sleep Quality Index (PSQI) scores were three times higher in participants with FMS than healthy controls on all questionnaire components except use of sleep medications. Sleep problems most commonly reported by those with FMS include difficulty falling asleep, nighttime arousals and fatigue on arising (Shah, Feinberg, & Krishnan, 2006; Bigatti et al., 2008; Osorio et al., 2006).

This self-report data has been supported by studies that explored sleep quality in FMS using polysomnography (PSG) (Shah et al., 2006) and actigraphy (Landis et al., 2003). Those with FMS have been found to be more easily aroused from sleep (Shah et al., 2006; Rizzi et al., 2004) and have higher levels of physical activity at night than control participants (Shah et al., 2006; Korszun et al., 2002; Landis et al., 2003). PSG has indicated that people with FMS have interrupted deep sleep, i.e. repeated arousals due to insertion of rapid-eye-movement (REM) sleep, also known as alpha wave intrusions or alpha-delta sleep (Peterson, 2007; Shah et al., 2006). Abad et al.(2008) found that individuals with FMS had significantly shorter stage 2 sleep durations than healthy controls and that shorter overall sleep duration was predictive of increased pain in those with FMS. Landis et al. (2004) reported that stage 1 non-rapid-eye-movement (NREM) sleep was significantly increased and sleep spindle activity in stage 2 sleep was significantly decreased in participants with FMS as compared to healthy controls. These findings positively correlated with pain levels in those with FMS. Rizzi et al.(2004) found that study participants with FMS had a 29% increase in the rate of cyclic alternating patterns

FIBROMYALGIA

compared to healthy controls and noted that this disturbance in sleep microstructure dynamics highly correlated with reports of poor sleep quality in those with FMS. Other PSG findings that have been reported in FMS include decreased total sleep time, decreased delta sleep, and decreased REM sleep percentages (Harding & Hawkins, 2005).

Poor sleep has been associated with greater pain (Bigatti et al., 2008; Agargun et al., 1999) and fatigue (Landis et al., 2003; Hamilton et al., 2008) in those with FMS. In a longitudinal study of 492 people with FMS, sleep disturbance was found to have a predictive relationship to pain (Bigatti et al., 2008). Conversely, improving sleep quality has been reported to decrease levels of pain and fatigue in people with FMS and has been viewed as a barometer for clinical symptom management (Perrot et al., 2008; Peterson, 2007). Women with FMS have been reported to have 19 to 25% rates of sleep apnea/hypopnea (Shaver, 2008). In comparison, the rate of sleep apnea hypopnea syndrome has been reported to be 2% in women less than age 65 in one cohort study of state employees (Young, Peppard, & Gottlieb, 2002). Yet identification and treatment of comorbid sleep disorders in people with FMS, such as obstructive sleep apnea, has not consistently led to improvement in FMS symptoms (Dadabhoy, Crofford, Spaeth, Russell, & Clauw, 2008).

Methods

A literature search was conducted in summer 2009 and updated April 2011 for the years ranging from 1990 to 2011. Databases searched included: the Cochrane Library; Medline; Web of Science; ISI Web of Knowledge; PsychInfo; and CINAHL. Search terms used were: stress; perceived stress; psychological stress; psychological distress; sleep; sleep quality; insomnia; and fibromyalgia. Positive and negative affect were included terms if they were related in the study to stress or distress. Criteria for inclusion were that the citations be quantitative research studies

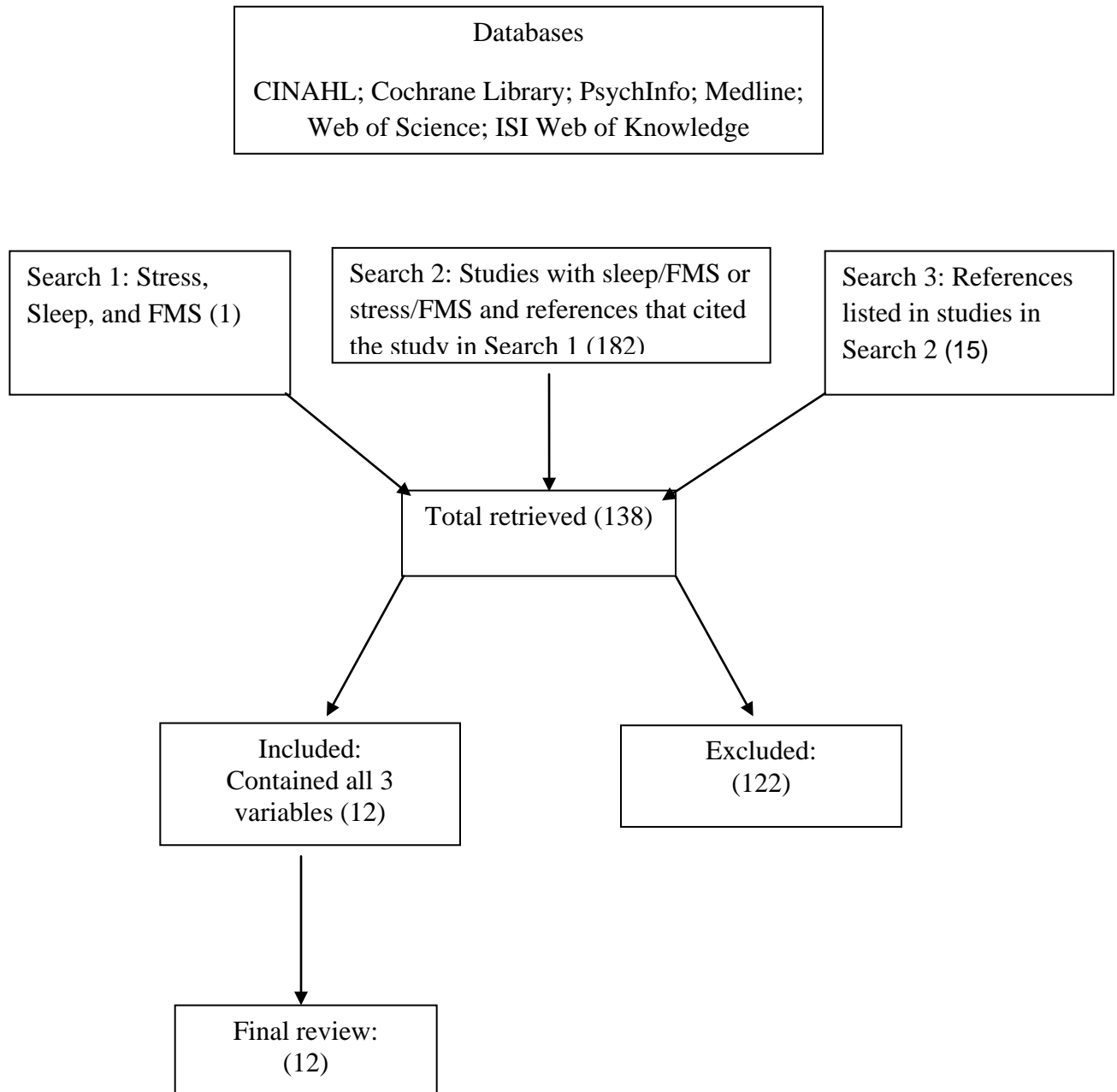
FIBROMYALGIA

that examined stress and sleep quality in study participants with FMS. One citation was found that included three variables (stress, sleep quality, and FMS). As a result of this small return, citations were then examined that included at least two of these factors. Also perused were studies that cited the first retrieved article and included either stress and FMS or sleep and FMS. Their listed references were also searched for any studies that might meet inclusion criteria. A total of 142 citations were retrieved; 57 were excluded because they contained only two of the three variables of interest; 23 were excluded as medication studies, 2 were excluded as not available in English, 42 were excluded because they did not contain any of the variables of interest, and 3 were excluded as survey articles. Finally, 12 studies were found that contained all three variables (stress, sleep quality, and FMS). This search strategy is depicted in Figure 1.

FIBROMYALGIA

Figure 1

Literature Search Methods



FIBROMYALGIA

Table 1

Studies Reviewed

Study	Purpose	Design	Sample
Uveges et al. (1990)	Compare psychological profiles of people with FMS and RA, based on pain, health status, stress, and sleep quality.	Cross-sectional	N=47
Shaver et al. (1997)	Compare sleep quality, psychological distress, PSG data and stress arousal in women with and without FMS.	Retrospective cohort	N=22
Landis et al. (2004)	Compare pain, depression, psychological distress, mood, sleep, and immune biomarkers in women with and without FMS.	Prospective cohort	N=70
Hamilton Catley & Karlson (2007)	Assess the role of sleep duration and quality in stress responses of women with FMS.	Prospective	N=49
Gupta et al. (2007)	Can new onset CWP be predicted by psychological distress, health seeking behavior, poor sleep, or traumatic events?	Prospective cohort	N=3185
McBeth et al. (2007)	Do HPA stress response abnormalities moderate between HPA function and new onset of CWP?	Prospective cohort	N=241
TheadomCromptley & Humphrey (2007)	Explore the effect of sleep and coping on health-related QoL* in people with FMS.	Cross-sectional	N=101
Hamilton et al. (2008)	Assess the role of sleep in affect, stress reactivity, and recovery from stress in people with FMS.	Prospective	N=89
Theadom & Cromptley (2008)	Compare sleep-related dysfunctional beliefs, stress and sleep quality of people with FMS with controls.	Prospective cohort	N=166
Davies et al. (2008)	Does good quality sleep predict resolution of CWP?	Prospective cohort	N=679
White, Faull & Jones (2009)	Explore stress and sleep quality in a phone survey sample of people with FMS 10 years after a rehab intervention and compare results with earlier intake data.	Prospective cohort	N=29
Riva et al. (2010)	Examine free salivary cortisol levels and sleep quality in people with FMS as compared to controls.	Cross-sectional	N=58

*CWP= chronic widespread pain

*QoL= quality of life

Results

These 12 studies point to a circular relationship between sleep quality and stress in individuals with FMS. They all agree that poor sleep quality is associated with greater perceived stress and more pain in those with FMS, but because of their correlational designs a causal link between the two was not posited. The direction of this relationship remains in question. Does greater stress predict poor sleep quality or vice versa? Is the relationship bidirectional? Might it differ from person to person, or even within a person at different times? The following studies shed some light over time on this issue, but it is far from resolved.

PSG Changes

Landis et al. (2004) compared pain, psychological factors, subjective and objective sleep quality, lymphocyte phenotypes and activation markers, and natural killer cell activity in women with and without FMS. Psychological factors studied included depression, psychological distress, mood state, anxiety, post-traumatic stress syndrome (PTSD), bipolar disorder, and alcohol or drug abuse. Pain was assessed by tender point and pressure pain threshold elicitation. Sleep was evaluated by PSG and participant reports. Participants with FMS reported more depression, more psychological distress, less vigor, lower pain threshold, and rated sleep quality worse than the control group. PSG data demonstrated that only the group difference in NREM stage 2 sleep was statistically significant, however. The authors noted that the participants with FMS reported poor sleep quality out of proportion to the modest differences seen on PSG as compared to controls.

Shaver et al. (1997) compared sleep quality, psychological distress, PSG data, and physiological stress in women with and without FMS. Physiological stress was determined by heart rate, muscle tension, temperature, and skin conductance. Urinary catecholamines and

FIBROMYALGIA

cortisol were assayed. Participants with FMS reported significantly worse sleep than the controls and also scored significantly higher on anxiety, somatization, and obsessive-compulsive subscales. PSG data indicated that participants with FMS had significantly more stage 1 sleep, more sleep stage changes, and more sleep fragmentation than controls, but only during the first half of the night. No significant differences in PSG data were seen between the two groups for the entire night. Physiological stress did not differ significantly between the two groups.

Riva et al. (2010) assessed pain, perceived stress, salivary cortisol levels, heart rate variability, and PSG measures of sleep quality in women with and without FMS. They reported that women with FMS had lower cortisol levels than controls, as well as less total sleep time, and poorer sleep efficiency. No correlation was found between PSG data and cortisol levels in either group.

Sleep and CWP

Davies et al. (2008) explored the hypotheses that good sleep quality would predict the resolution of symptoms of chronic widespread pain (CWP) within 15 months, and that these relationships would be independent of any confounding psychological factors. CWP was defined based on the American College of Rheumatology (ACR) criteria for FMS_[VSM1] (Wolfe et al., 2010). A follow-up questionnaire 15 months later assessed pain status. Of the four components of sleep quality, (sleep onset; sleep maintenance; early wakening; restorative sleep) after controlling for psychosocial factors, only restorative sleep was associated with CWP resolution. The authors concluded that restorative sleep was independently associated with the resolution of CWP in their study respondents.

FIBROMYALGIA

Sleep, Stress, and CWP

Hamilton et al. (2008) hypothesized that sleep disturbance is a predictor of daily affect, reaction to stressors, and recovery from stress in women with FMS. They used participants' recordings of their positive and negative affective states, the occurrence of positive and negative events, and their sleep quality. Duration and quality of sleep predicted the type of affective state and ease of cognitive functioning in their participants. Poor sleep quality seemed to inhibit the restoration of a participant's positive affect following a day with a high number of negative events, whereas type of daily events and affect did not predict future sleep quality. They concluded that sleep duration and quality seem to play central roles in daily functioning for people with FMS, predicting subsequent daily mood, ease of cognitive functioning, and degree of pain. They speculated that sleep disturbance may lie upstream of central processing anomalies that have been theorized to drive the onset of FMS.

Hamilton, Catley and Karlson (2007) then examined sleep duration and quality as a correlate of stress reactivity and pain in people with either rheumatoid arthritis (RA) or FMS. They hypothesized that quality and duration of sleep would moderate affective responses to stress and pain. They found that participants with FMS reported more pain and worse sleep quality than the participants with RA, yet sleep duration and averaged positive and negative affect did not differ between the groups. They concluded that sleep disturbance appeared to interfere with participants' adjustments to stress and pain, whereas good quality restorative sleep moderated response to stress and pain. The researchers noted that pain seemed to be the most important determinant of subjective sleep quality, yet sleep deprivation also alters a person's pain threshold. They were unable to determine whether improved sleep quality is a mechanism for, or a marker of, improvement.

FIBROMYALGIA

Gupta et al. (2007) explored the relative contributions of psychological distress, health-seeking behavior, sleep problems, and traumatic life events to the development of new onset of CWP. CWP was defined using the ACR criteria for FMS. Three factors independently contributed to the odds of participants' experiencing new onset CWP, in a dose-response fashion: illness behavior, somatic symptoms, and sleep disturbance. Reports of multiple physical symptoms, help-seeking for health problems, sleep disturbance, and the occurrence of an adverse life event increased the likelihood of a participant having new onset CWP in the next 15 months 20-fold. The presence of at least one of the above factors predicted 93% of new cases of CWP. Their conclusion was that sleep disturbance and adverse life events often preceded the onset of CWP within 15 months.

Stress, Sleep, and CWP

Uveges et al. (1990) compared participants with FMS and RA on measures of psychological distress, pain, health status, stress, sleep disturbance and coping. The FMS group reported significantly more psychological distress, more pain, more life stress, more sleep disturbance, and more impaired health status than the RA group. The groups did not differ in their use of coping strategies. The FMS group did not have more physical disability than the RA group. Participants with FMS reported more psychological distress and a greater occurrence of sleep disturbance than participants with RA with comparable pain levels. The researchers concluded that the high levels of life stress reported by people with FMS may have affected their overall psychological responses.

Theadom, Cropley, and Humphrey (2007) explored the effect of sleep and coping on health-related QoL in people with FMS using mailed questionnaires. They examined sleep quality, coping, positive and negative affect, physical functioning, social functioning, pain,

FIBROMYALGIA

fatigue, emotional wellbeing, and general health. Poor sleep was reported by 99% of the participants. The occurrence of negative affect reported by participants was significantly correlated with their reports of poor sleep quality and lower use of coping strategies. No association was detected between sleep quality and particular coping strategies.

Theadom and Cropley (2008) then sought to compare sleep-related dysfunctional beliefs, stress levels and sleep quality of participants with and without FMS. They used questionnaires of dysfunctional beliefs and attitudes about sleep, perceived stress, fatigue, pain, and sleep quality. They found that, compared to controls, participants with FMS reported significantly higher levels of perceived stress, dysfunctional beliefs about sleep, pain, fatigue, and poorer sleep quality. The dysfunctional beliefs and attitudes about sleep of the participants with FMS were significantly associated with their pain, fatigue, and poorer sleep quality. More perceived stress was associated with higher levels of fatigue, pain, more sleep disturbance, and greater daytime dysfunction in the participants with FMS. The most common sleep disturbances reported were increased sleep latency insomnia and sleep maintenance insomnia.

McBeth et al. (2007) hypothesized that HPA-axis stress response abnormalities would moderate the effect of HPA functions and new onset of CWP, independently of psychosocial factors. Participants without CWP but at risk of developing it, based on their psychosocial profile, had their HPA axis function assessed and were followed over 15 months. CWP was defined using the ACR criteria for FMS. Psychosocial factors studied included psychological distress; health anxiety; illness behavior; depression; anxiety; and sleep disturbance. HPA axis function was determined by serum cortisol levels in response to a pain threshold examination and a low-dose dexamethasone suppression test, as well as salivary cortisol levels obtained in the morning and evening to assess diurnal HPA axis function. At follow-up, new-onset CWP was

FIBROMYALGIA

identified by the same criteria. Any occurrence of stressful life events was elicited. 11.6% of the participants developed CWP. High levels of cortisol post-dexamethasone, low morning salivary cortisol, and high evening salivary cortisol were all significantly associated with CWP onset.

One or more of these three factors identified 93% of the new onset CWP cases; their effects were independent of each other, but additive as predictors of CWP. Higher levels of sleep disturbance, having experienced two or more high-stress events, and higher illness behavior were associated with some, but not a significantly increased, risk of CWP. They concluded that HPA axis dysfunction predicted an increased risk of the new onset of CWP.

White et al. (2009) conducted a telephone survey of 29 respondents with FMS who had participated in an intensive rehabilitation program 10 years earlier, and compared their reports from the initial interviews to the present ones. They found that in the intervening years stress levels had declined but that sleep quality had not changed. Yet, they also found that lower reported stress levels did covary with improved sleep quality.

Discussion

Uveges et al. (1990), Landis et al. (2004), White et al. (2009), and Shaver et al. (1997) all confirmed the association between stress and sleep quality in women with FMS but made no directional claims. Hamilton and Catley (2007) reported that sleep disruption interferes with a positive adjustment to stress, whereas restorative sleep moderates the response to stress in people with FMS. In a follow-up study they concluded that poor sleep quality prevented the restoration of positive affect following a day with a high number of negative events, whereas daily events and affect did not predict future sleep quality (Hamilton et al., 2008). They opted for poor sleep quality being a predictor of increased stress in FMS patients. Theadom and Cropley (2008) and Theadom, Cropley and Humphrey (2007) confirmed the association between stress and poor

FIBROMYALGIA

sleep quality; they noted that both factors contributed to predictions of pain and fatigue. Davies et al. (2008) reported that restorative sleep was associated with resolution of symptoms of CWP, but found no relationship between psychological distress and sleep quality. Gupta et al. (2007) reported that both sleep and stress are implicated in the onset of new CWP. McBeth et al. (2007) also found that recent stressful life experiences predicted new CWP onset.

The evidence thus far suggests that poor sleep quality may be a predictor of increased stress and FMS symptom onset in those affected. However, no experimental studies have demonstrated a causal relationship between poor sleep and stress in people with FMS. One reason for this uncertainty is that the biological mechanisms underlying such a relationship have not been fully articulated, although a genetic predisposition to ANS dysfunction has been posited by investigators. The interplay of such a genetic predisposition, coupled with an adverse life event seems a likely scenario for the new onset of CWP. Enhanced understanding of the core biological mechanisms that result in FMS is a priority research focus. The search for useful biomarkers of both stress level and sleep quality in people with FMS is a fertile area for basic research endeavors as well. Of these 12 studies, the authors of seven indicated that further research into the nature of sleep quality and interventions designed to improve it are needed for the development of FMS symptom management approaches. Further investigation into the role of sleep quality in relation to the predisposition to, or treatment of FMS is warranted as well.

FIBROMYALGIA

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Chapter Three

VCU RESEARCH PLAN TEMPLATE

Use of this template is required to provide your VCU Research Plan to the IRB. Your responses should be written in terms for the non-scientist to understand. If a detailed research protocol (e.g., sponsor’s protocol) exists, you may reference that protocol. **NOTE: If that protocol does not address all of the issues outlined in each Section Heading, you must address the remaining issues in this Plan. It is NOT acceptable to reference a research funding proposal.**

ALL Sections of the Human Subjects Instructions must be completed with the exception of the Section entitled “Special Consent Provisions.” Complete that Section if applicable. When other Sections are not applicable, list the Section Heading and indicate “N/A.”

NOTE: The Research Plan is required with ALL submissions and MUST follow the template, and include version number or date, and page numbers.

DO NOT DELETE SECTION HEADINGS OR THE INSTRUCTIONS.

I. TITLE

A BIOBEHAVORAL MODEL OF FIBROMYALGIA

II. STAFFING

A. In the table below (add additional rows as needed), indicate: (1) key project personnel including the principal investigator and individuals from other institutions, (2) their qualifications, and (3) a brief description of their responsibilities.

NAME OF INDIVIDUAL	QUALIFICATIONS	RESPONSIBILITIES
Nancy L. McCain	RN, DSN, FAAN	Principal investigator (PI).
Ann T. McNallen	RN, CNM, MSN, PhD Candidate	Student investigator will serve as the primary contact for the study and be responsible for all data collection.

B. Describe the process that you will use to ensure that all persons assisting with the research are adequately informed about the protocol and their research-related duties and functions.

The PI will provide training to the student investigator as a function of the dissertation process. In addition, the student investigator will conduct a trial run of the study prior to enrolling any participants. No other personnel are involved in this research.

III. CONFLICT OF INTEREST

Describe how the principal investigator and sub/co-investigators might benefit from the subject’s participation in this project or completion of the project in general. Do not describe (1) academic recognition such as publications or (2) grant or contract based support of VCU salary commensurate with the professional effort required for the conduct of the project

The researchers will not financially benefit from subjects’ participation or completion of this project. There are no conflicts of interest to report.

IV. RESOURCES

Briefly describe the resources committed to this project including: (1) time available to conduct and complete the research, (2) facilities where you will conduct the research, (3) availability of medical or psychological resources that

FIBROMYALGIA

participants might require as a consequence of the research (if applicable), and (4) financial support.

The student investigator will be conducting this research full time in fulfillment of her dissertation requirements. The Virginia Commonwealth University (VCU) Center for Sleep Medicine is the primary data collection site, and this study has received the full support of Dr. David Leszczyszyn, MD, PhD, the medical director of this facility. The student investigator has the resources of an appointed doctoral committee for advice and consultation on data collection, entry, data analysis, and preparation of results. The Center for Biobehavioral Clinical Research (CBCR) lab of the VCU School of Nursing is the site for the storage and analysis of blood samples. Lab data will be processed there using resources available to the PI.

V. HYPOTHESIS

Briefly state the problem, background, importance of the research, and goals of the proposed project.

Fibromyalgia (FMS) is a chronic pain syndrome characterized by diffuse musculoskeletal pain, non-restorative sleep, fatigue, and psychological distress¹. It affects approximately 5 million Americans², 90% of whom are women³. Most people are diagnosed in middle age⁴, and incidence increases with age; by age 80 nearly 8% of adults may be so classified⁵. The economic impact of this condition is substantial; individuals with FMS often have trouble maintaining long-term employment due to increasing disability⁶. It has been estimated that 10% of FMS patients are disabled, 30% are forced to change employment, and another 30% modify their jobs to remain employed⁷. Those who complain of significant fatigue are 6 times more likely to report being disabled⁸. Close to \$20 billion is spent annually in the US on diagnosis and treatment of FMS⁷. Mean annual healthcare expenditures per FMS patient have been reported to be more than \$10,000⁹. Over 75% of FMS patients internationally complain of two components of this disability, poor sleep quality and fatigue^{10;11}. These factors have been deemed critical in the treatment of FMS^{8;12;13}. Pain, disordered sleep, and fatigue have been ranked by FMS patients as symptoms having great impact on their quality of life^{14;15}. Current views of FMS suggest it may be a neuroimmunoendocrine inflammatory disorder exacerbated by stress¹⁶; although multiple hypotheses have been advanced for its etiology, there is no current consensus.

The relationships among autonomic nervous system (ANS) function, perceived stress, sleep quality (as measured by polysomnography [PSG] and patient self-report), fatigue, pain, and immune function (as measured by plasma cytokine levels) have not been explored together in a study of participants referred to a Sleep Center. Stress and its relationship to sleep in FMS has been studied¹⁷, and cytokine expression in FMS has been also been examined¹⁸. The relationships among ANS dysfunction, stress, sleep, and cytokines in FMS are undergoing increased scrutiny, but whether these variables correlate with pain and fatigue in FMS patients remains unexplored¹⁹.

Study Hypotheses

To study Aim 1, it is being hypothesized that the FMS group, in comparison to the non-FMS group, will demonstrate significantly: higher Composite Autonomic Symptom Scale (COMPASS) scores; lower heart rate variability (HRV); higher Perceived Stress Scores (PSS); higher Pittsburgh Sleep Quality Index (PSQI) scores; greater sleep disturbance as evidenced by an increased number of sleep arousals on PSG; an increased ratio of pro- to anti-inflammatory cytokines; and greater Brief Fatigue Inventory (BFI) scores.

For Aim 2, correlations among ANS activity (COMPASS and HRV), perceived stress (PSS), sleep quality (PSG and PSQI), immune function (17-plex cytokines), and fatigue (BFI) will be explored within each group. Also, within the FMS group, these variables will be correlated with pain, using the Brief Pain Inventory (BPI). It is being hypothesized that different correlation patterns will be observed in the FMS group than the non-FMS group.

To study Aim 3, it is being hypothesized that construct validity of the COMPASS will be demonstrated by meaningful correlations between COMPASS scores and HRV, as well as selected PSG sleep indices (number of arousals and sleep latency).

VI. SPECIFIC AIMS

Aim 1 of this proposal is to compare two groups, 25 women with and 25 women without FMS, on the following variables: ANS activity; perceived stress; sleep quality; immune function (17-plex cytokines); and fatigue.

Aim 2 is to explore the relationships among the above variables within each group of participants. Within the FMS

FIBROMYALGIA

group, these variables will also be correlated with pain.

Aim 3 is to assess the validity of the COMPASS by comparing it to measures of HRV and sleep indices (number of arousals and sleep latency). The clinical relevance of ANS function and the study of stress in FMS patients lies in the evidence that ANS stress responses are altered in FMS as compared to healthy individuals experiencing stress²⁰, but the underlying mechanisms are not well understood.

VII. BACKGROUND AND SIGNIFICANCE

Include information regarding pre-clinical and early human studies. Attach appropriate citations.

Psychoneuroimmunology (PNI) is the research framework being used to guide this proposed study. PNI is the term used to identify an interdisciplinary field of research related to investigating mind-body relationships, i.e., interactions of behaviors, brain function, the neuroendocrine and neuroimmune systems. The field of PNI was developed further within a biobehavioral framework by Dr. Nancy McCain and others in the VCU School of Nursing's Center for Biobehavioral Clinical Research (CBCR) (P20 NR008988, 2004-2009).

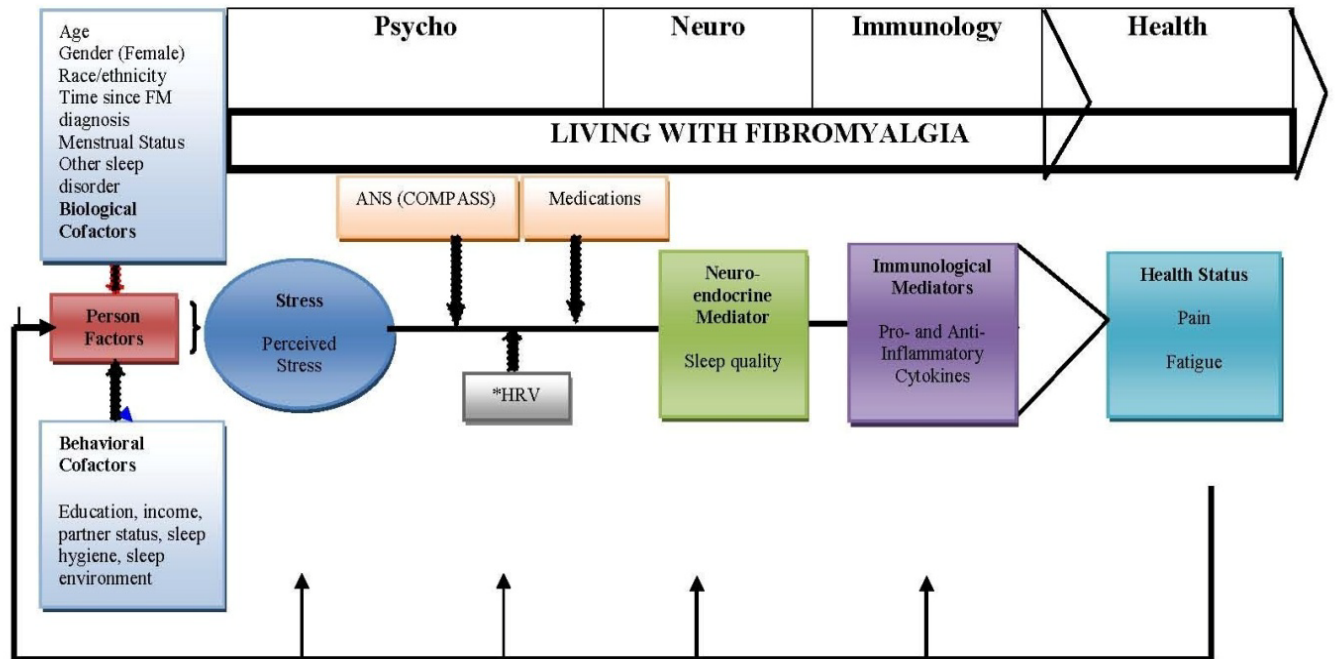
A basic goal of this biobehavioral research is translation of neuroimmune mechanisms into an understanding of clinically relevant mechanisms and outcomes²¹. PNI has been employed as a biobehavioral nursing model by researchers to explore interactions among psychosocial, behavioral, environmental, and biological variables in a holistic fashion²². Nursing research has used PNI as a framework to examine relationships among biological and behavioral correlates and their effects on patient outcomes²³. In particular, PNI has been used as a framework for exploring stress and coping mechanisms as they relate to health outcomes in various cohorts of chronically ill patients²⁴. The model for the proposed study (Figure 1) posits that particular biological and behavioral cofactors interact with the ANS in women with FMS to produce dysfunctional changes in the ANS response to perceived stress, which in turn alter sleep quality and cytokine expression. Poor sleep quality leads to cytokine changes; both interact with the ANS in a circular fashion, resulting in generalized pain and severe fatigue. Pain further diminishes sleep quality, leading to a vicious cycle of non-restorative sleep, fatigue, stress, and pain.

The extent to which expression of FMS symptoms accounts for cytokine changes independent of sleep quality is unclear. It is also unknown which particular aspects of sleep in FMS, such as length of sleep stages or number of arousals, may be predictive of cytokine changes and pain or resultant from them. Additionally, perceived stress has been implicated in worsening sleep quality, pain, and fatigue for FMS patients, but the degree to which it initiates or reflects ANS stress arousal remains unclear. This study seeks to shed light on these complex relationships in anticipation of formulating targeted clinical interventions for symptom management.

Figure 1: PNI-based Biobehavioral Model of Symptoms in FMS

FIBROMYALGIA

Program Director/Principal Investigator (McNallen, A):



PNI-based theoretical framework (McCain et al., 2005) adapted for fibromyalgia
 *HRV will be explored as a training goal.

ANS factors

Several lines of evidence support a physiologic basis for FMS. While etiology is unclear, disordered pain processing through central sensitization seems to play a role in symptom development^{16;25;26}. *N*-methyl-*D*-aspartate receptors may become activated, leading to central sensitization of nociceptive neurons in the dorsal horn of the spinal cord²⁷. FMS is thought by some investigators to result from ANS dysfunction, initiated by a genetically impaired stress response^{20;28}. Another example of ANS dysfunction being linked to FMS is provided by the prevalence of postural orthostatic tachycardia syndrome (POTS), in FMS patients. This common event experienced by FMS patients during tilt table testing is defined as a heart rate increase of more than 30 beats per minute after more than 3 minutes of standing upright²⁹.

First-degree relatives of FMS patients have an 8-fold increased risk of developing FMS in comparison to the general population³⁰ and display enhanced pain sensitivity to multiple stimuli³¹. A polymorphism of the catecholamine *o*-methyl transferase gene may predispose individuals under stress to have a hyperactive sympathetic nervous system (SNS) response, resulting in poor sleep and anxiety^{30;32}.

ANS dysregulation of pain modulatory systems may lead to prolonged interactions among the central nervous system (CNS), the peripheral nervous system, and the immune system, such that the characteristic of neuroplasticity enables a connection to be made among the SNS and nociceptive fibers. This is postulated to result in neuropathic pain²⁵. Implicated in this putative neuroplastic response is a stress response that induces sodium channels to up-regulate and initiate sympathetic sprouting in the dorsal root ganglia of the spinal cord through nerve growth factor overexpression³³. FMS has been associated with low serotonin levels and elevated Substance-P levels³²; it has been hypothesized that the combination of the 2 results in heightened pain perception³⁴.

Multiple sensory perceptions, including pressure and heat, may be altered for FMS patients; it has been reported that 20 FMS patients exhibited decreased noise tolerance compared to either 20 osteoarthritis patients or 20 controls³⁵. Other investigators found that 16 FMS patients displayed greater awareness of unpleasant odors and less awareness of pleasant ones than 15 matched controls³⁶. A neuroimaging study provided corroboration of those findings, evidenced by heightened activity in specific brain regions in response to pressure and heat in 9 FMS patients as compared to 9 controls³⁷. These instances of enhanced perception of unpleasant stimuli have been posited to be further evidence of CNS alteration,

FIBROMYALGIA

heightened response to sensory input, and a perceptual style of amplification, which has been termed generalized hypervigilance³⁵. Light et al.²⁵ reported that 54 FMS patients displayed altered adrenergic function as compared to 34 controls; they view the SNS as persistently hyperactive, yet paradoxically hypoactive to acute stressors due to receptor desensitization²⁰. They hypothesized that the stressed SNS is overwhelmed, and due to a ceiling effect, unable to respond to further stress; this, they speculated, might be related to the fatigue of FMS.

Stress and the ANS

Considered a state of threatened homeostasis²⁰, stress alters various immune mechanisms including lymphocyte production, natural killer cell activity, cytokine and antibody production, phagocytosis and oxidative stress²². The stress response system, comprised mainly of the ANS and the hypothalamic-pituitary adrenal (HPA) axis, operates dynamically to maintain this homeostasis. The ANS regulates essential involuntary functions such as vital signs and is activated by centers in the brain stem, the spinal cord, hypothalamus, and thalamus. It is the interface between the mind and body that alerts an organism to respond to a particular stressor. ANS effects include elevated blood pressure (BP), pulse and respiratory rate; pupil dilation; vasoconstriction; and shunting of circulation from intestines to skeletal muscles. Nilsen et al.³⁸ found lower diastolic BP and increased pain in response to stress in 23 FMS patients as compared to 35 controls.

Normal beat-to-beat HRV is the signature of a healthy ANS response to perceived changes in the environment, and appears to be a reliable biomarker of stress³⁹. FMS patients have been reported to display less HRV compared to controls^{30;38}. ANS hyporeactivity seems to be correlated with fatigue, low BP, dizziness, and faintness in FMS patients as well³⁹. It has been reported that women with FMS respond with altered cardiovascular dynamics to resistance exercise⁴⁰, and that resistance training can improve HRV in FMS patients⁴¹. However, in a recent meta-analysis of HRV and functional somatic disorders studies, including FMS, Tak et al. concluded that current evidence is insufficient to confirm this claim⁴². Sleep is also affected by the ANS; HRV changes are reported to precede arousals from deep sleep and the onset of REM sleep by up to 20 beats per minute³⁹. Therefore general ANS response patterns in FMS, as well as HRV specifically, are areas requiring continued investigation.

Perceived stress

Perceived stress is a person's cognitive appraisal of insufficient coping resources⁴³ and has been thought to increase SNS activity²⁰. FMS studies have detected stress intolerance or outright psychological distress⁴⁴ and increased basal SNS tone⁴⁵. Theadom & Cropley¹⁷ found that 83 FMS patients had significantly higher levels of perceived stress as compared to 83 controls. Their patients reported that pain was intensified by stress and this has been corroborated by other studies³¹. Level of perceived stress was found to account for the greatest amount of variance associated with FMS symptoms in a cross sectional survey of 201 individuals with FMS⁴⁶.

Stress perception is potentially unbounded by time; up to 64% of FMS patients report a history of childhood trauma, which was correlated to elevated evening cortisol levels in 85 FMS patients⁴⁷. Childhood abuse may be a chronic emotional stressor that dysregulates FMS patients' endocrine function into adulthood⁴⁸. Factors associated with the onset of FMS are infection (55%), physical trauma (14-23%), and emotional trauma or acute stress (14%); up to 65% of FMS patients report a history of sexual abuse²⁷. Cohen et al.⁴⁹ found that 57% of 77 FMS patients reported clinically significant post-traumatic stress disorder (PTSD) symptoms, including avoidance, hyperarousal, and re-experiencing events, as well as anxiety and depression.

The degree to which pain is experienced as a stressor may be heightened in FMS. Zautra et al.⁵⁰ found that 87 FMS patients displayed heightened stress responses to pain as compared to 39 patients with osteoarthritis. Positive affect as a coping mechanism for stress was diminished in patients with FMS as compared to those with osteoarthritis; stress-related increases in perceived pain were exacerbated by negative mood in the FMS group⁵⁰. Ablin et al.⁴⁸ reported that general coping styles of 77 FMS patients with or without PTSD varied from those of 48 controls. This may be associated with FMS patients being more vulnerable to stress than individuals with other chronic pain conditions^{47;51}. Perceived stress has been independently associated with poor sleep quality and increased nighttime arousals; ruminating about pain at bedtime predicted longer sleep onset latency and total duration of night arousals in 83 FMS patients as compared to 83 controls¹⁷.

Sleep quality and FMS

ANS activity drives many physiologic changes that occur during sleep⁵². Nearly 100% of FMS patients report poor sleep quality^{4;17;53}. FMS patients have scored significantly worse than controls on instruments measuring sleep quality in several studies^{17;54;55}; Osorio et al.⁵⁴ found that Pittsburgh Sleep Quality Index (PSQI) scores were 3 times higher

FIBROMYALGIA

in 30 FMS patients than 30 controls on all questionnaire components except sleep medications. FMS patients have reported sleeping an average of 4 to 6 hours per night and waking up unrefreshed^{17;34;54;55}. Sleep disturbances commonly reported have included difficulty falling asleep, nighttime arousals and fatigue upon arising^{17;54-56}.

These findings have been supported by PSG⁵⁶ and actigraphy¹¹, which suggest that FMS patients are more easily aroused from sleep^{4;4:17;56} and have higher levels of physical activity at night than controls^{11;17;56;57}. PSG studies have indicated that FMS patients have interrupted deep sleep, i.e., repeated arousals, due to insertion of rapid-eye-movement (REM) sleep, known as alpha wave intrusions or alpha-delta sleep^{34;56}. Other investigators noted that alpha intrusion during sleep can be of different patterns; phasic alpha sleep activity was the pattern they found better correlated with FMS symptoms⁵⁸. Abad et al.⁵⁹ found that 15 FMS patients displayed significantly shorter durations of stage 2 sleep than 15 controls, which was predictive of pain reports. Landis et al.¹¹ reported increased stage 1 non-rapid-eye-movement (NREM) sleep; sleep spindles in stage 2 sleep of 37 FMS patients were significantly decreased compared to 30 controls, which also correlated with increased sub-sequent pain. Rizzi et al.⁴ found that 45 FMS patients (vs. 38 controls) had a 29% increase in the rate of cyclic alternating patterns; this disturbance in sleep microstructure dynamics was closely correlated to FMS patients' experience of poor sleep quality. Other PSG findings reported in FMS include decreased total sleep time, decreased delta sleep, and decreased REM sleep percentages²⁷.

FMS patients also are highly prone to sleep-disordered breathing resulting in inspiratory airflow limitation; this was found in 27 of 28 FMS patients⁶⁰. Poor sleep has been strongly associated with greater pain^{55;61} and fatigue^{11;53} in FMS. Sleep quality was found to have a predictive relationship to pain in a longitudinal study of 492 FMS patients⁵⁵. Conversely, improving sleep quality has decreased pain and fatigue in FMS patients and has been viewed as a barometer for clinical symptom management^{16;34}. Rates of sleep apnea/hypopnea in women with FMS have been reported to be approximately 19 to 25%⁶². Yet identification and treatment of sleep disorders in FMS patients, such as obstructive sleep apnea (OSA) or upper airway resistance, has not consistently led to improvement in overall FMS symptoms³⁰. Additionally, the extent to which various sleep disorders may be considered a part of the underlying ANS dysfunction posited for FMS remains unknown. Other investigators have found that quantified-delta EEG power, auditory arousal thresholds, and urinary free cortisol largely failed to distinguish FMS and control subjects, but HRV analyses showed more promise, as they suggested both increased sympathetic activity and decreased complexity of autonomic nervous system function in FMS⁶³. Therefore, further investigation into the role of sleep microstructure in the predisposition to or onset of FMS symptoms is warranted.

Fatigue and FMS

Fatigue, defined as weariness caused by exertion, is a sensation of decreased vitality that disrupts activities of daily living⁶⁴. It can vary from general lethargy to a specific work-induced burning in particular muscles and may be physical and/or mental. Fatigue has been described in qualitative studies as a highly debilitating symptom of FMS and a constant, inescapable burden that isolated patients from family and community^{65;66}. Zautra et al.⁶⁴ found that 90 FMS patients reported significantly more pain and fatigue than 89 rheumatoid arthritis or 76 osteoarthritis patients. In studying predictors of fatigue in 105 FMS patients, Nicassio et al.⁸ reported that poor sleep quality accounted for a significant, positive relationship between pain and fatigue. FMS patients have described a vicious cycle of pain and non-restful sleep underlying their experience of fatigue^{65;67}.

Pain and FMS

Pain is central to the detection of FMS. The American College of Rheumatology guidelines for diagnosis of FMS require widespread aching for at least 3 months and 11 out of 18 possible tender points^{56;68}. Tender points are elicited by applying 4 kg manual pressure to those 18 predefined points³⁰. Functional magnetic resonance imaging (fMRI) studies have shown activation patterns in FMS patients' brains comparable to their reported pain, even if the stimulus was light pressure^{32;37;69}. Cook et al.³⁷ used fMRI to compare 9 FMS patients to 9 controls and found significantly greater activity in prefrontal, supplemental motor, insular, and anterior cingulate cortices. Wood et al.⁷⁰ studied 11 FMS patients as compared to 11 controls with fMRI and found that FMS patients exhibited an abnormal dopamine response to painful stimuli. They observed a positive relationship between amount of dopamine released in response to pain, and a patient's perceived pain intensity⁷⁰.

Julien et al.⁶⁸ hypothesized that FMS pain may be a deficit of endogenous pain inhibition, i.e., ineffective descending control mechanisms. They compared 30 FMS patients to 30 chronic low back pain patients and 30 controls; the FMS group differed significantly from the other groups in that their perception of pain did not diminish during the descending as compared to the ascending cold stimulation sessions. Stress has been viewed as a key variable in pain

FIBROMYALGIA

perception; low-grade mental stress significantly increased pain perception for 29 FMS patients in comparison to 35 controls in one study³⁸. The underlying mechanism is unknown but an animal-model study implicated the HPA axis in altered cell-signaling⁷¹. The investigators speculated that even relatively low-level mental stress might precipitate a long-lasting hyperalgesic reaction in FMS patients.

Cytokines and Sleep

Cytokines are polypeptides that act as chemical messengers between immune cells (among others); cytokines are critical to cell growth, repair, and modulation of pro- and antiinflammatory immune responses⁷. Interactions among the HPA axis, the SNS, and cytokines help regulate sleep, stress responses, pain perception, and fatigue⁷; they are also affected by sleep. Chronic insomnia was associated with a shift of IL-6 and tumor necrosis factor (TNF) secretion from patterns of nighttime to daytime elevations in 11 insomniacs compared to 11 controls⁷². Sleep deprivation was found to reduce natural killer cell activity in 45 volunteers in a within-subject study⁷³. It was found in a within-subject study ($n=30$) that sleep deprivation was associated with altered monocyte proinflammatory cytokine responses, and with significantly increased production of IL-6 and TNF- α ⁷⁴. A followup study by those researchers explored differences by gender; sleep loss was again associated with altered monocyte pro-inflammatory cytokine responses, with 11 females showing significantly more cellular immune activation than 15 males⁷⁵.

IL-1 and TNF- α have been related to symptoms associated with sleep deprivation, such as pain and fatigue⁷⁶⁻⁷⁸; both cytokines are somnogenic and enhance electroencephalograph (EEG) slow waves. IL-1 and TNF- α increase the duration of NREM sleep and reduce REM sleep, yet IL-1 also causes fragmentation of NREM sleep in a dose-dependent way⁷⁸. Suggested NREM-promoting substances are IL-2, acidic fibroblast growth factor, interferon (IFN)- α , epidermal growth factor, neurotrophins, nitric oxide, adenosine, prostaglandin P₂, and growth hormone releasing factor (GHRH); however, evidence for their role in sleep is still accumulating⁷⁶. Cytokines thought to inhibit NREM sleep include; IL-1, IL-4, IL-10, IL-13, insulin-like growth factor, transforming growth factor- β , the soluble IL-1, and TNF receptors^{59;76}. Research on the relationships among cytokine patterns and sleep patterns continues to develop and the proposed study has the potential to contribute to knowledge development in this area.

Cytokines and FMS

Alterations in various cytokine levels have been reported in FMS patients, but this is a rapidly developing field, with various study methods and contradictory results being reported¹⁹. Plasma IL-1 receptor antibody (IL-1ra) and IL-8 levels were significantly higher in 56 FMS patients as compared to 56 age- and gender-matched controls in an early pilot study¹⁸. Skin biopsies of 53 FMS patients were compared to those of 10 age- and gender-matched controls; IL-1 β (38%), IL-6 (27%) and TNF- α (32%) were detected in FMS patients but not in controls⁷⁹. Initial plasma TNF- α and IL-8 levels were elevated, but not IL-6, in 20 FMS patients compared to 80 controls in a longitudinal study⁸⁰. Those authors reported that IL-8 levels correlated with perceived pain intensity, but only at the end of a 6-month study, when it decreased along with pain reports; they did not find a significant difference in IL-10 levels. Higher IL-8 levels, but not IL-1 or IL-6, were seen in 81 FMS patients as compared to 32 controls⁸¹. Increased IL-6 levels in 6 FMS patients were found during a tryptophan depletion study, but those levels were decreased in 11 other FMS patients and all 17 controls⁸². They postulated the existence of a select subgroup of FMS patients; this might imply more than one etiology for FMS, or perhaps genetic variations in cytokine responses. Togo et al.⁸³ reported 3 significant findings; in contrast to 9 controls, 7 FMS patients had frank increases in nighttime antiinflammatory cytokine IL-10 secretion, they did not have compensatory bursting of pro-inflammatory cytokines IL-8, IL-1 β and TNF- α , and even during the day, the ratio of pro- to antiinflammatory cytokines was reduced relative to controls.

It has been suggested that there is an imbalance in FMS patients in favor of sleep-disturbing antiinflammatory cytokine responses during sleep⁸⁴. Yet, other researchers reported findings in contradiction to Togo et al.⁸³; in 40 patients with widespread pain, 26 of whom had FMS (vs. 40 age- and gender-matched controls), they found lower mRNA levels for the anti-inflammatory cytokines IL-4 and IL-10, no significant increase in proinflammatory cytokines, and no significant correlations among cytokine levels and fatigue in FMS patients⁸⁵. They also noted that cytokines are key elements in the induction and maintenance of pain, and posited that an imbalance of pro- and antiinflammatory cytokine levels may be a significant variable in FMS pain sensitivity⁸⁶.

The authors of a recent integrative review of cytokines in FMS concluded that there are discrepancies regarding whether pro- or antiinflammatory cytokines are elevated or reduced in FMS, and whether or not they correlate with FMS symptoms⁸⁷. They call for pursuing this potentially promising line of research, using multiplex cytokine measurement platforms, which might offer a more complete picture of the pro/anti inflammatory balance among cytokine levels.

FIBROMYALGIA

VIII. PRELIMINARY PROGRESS/DATA REPORT

If available.

Ms. McNallen has gained invaluable experience in working collaboratively with interdisciplinary teams through various exposures and experiences in research at the VCU School of Nursing. The study described below highlights her experiences in the design and implementation of a biobehavioral study, including data collection, measurement, database development, and dissemination of study results.

Actigraphy and Patient Movement

This was a substudy of a larger study, NIH/NINR R01 NR009506, entitled “Sedation effects in mechanically ventilated patients” (SAVE Study) with Dr. Grap, principal investigator (PI). The specific aim of this study was to evaluate, in a laboratory setting, actigraphic measures of a variety of simulated activity types (calm/sedated, restless, agitated states). A sample of 30 participants was drawn from volunteers 18 years of age or older who responded to posted brochures or flyers. Exclusion criteria included neuromuscular disorders that might result in abnormal movement (e.g., Parkinson’s disease) or decreased levels of movement (e.g., paralysis), severe sensory limitations, or inability to speak English. Data were collected to quantify the actigraphic pattern associated with different levels of observed movement. As a graduate research assistant (GRA) working for the SAVE study, Ms. McNallen developed and submitted the substudy protocol to the VCU Institutional Review Board (IRB), prepared all study measures and procedures, and wrote the operations manual. The study was approved by the VCU IRB on October 28, 2008; participant recruitment, enrollment and data collection were completed on May 15, 2009. The applicant set up and maintained the study database in collaboration with the SAVE study research team (M.J. Grap [PI]; V.A. Hamilton [project director]; J. Ketchum [Biostatistician]). Ms. McNallen performed all data entry and management and collaborated extensively in data analysis. This experience provided invaluable experience and skills building related to conducting and completing a research study as well as training in the use of instruments that may be used in her proposed study. Collaborative experience in research methodology and dissemination continues; an abstract on the SAVE actigraphy study was presented at the 2010 Southern Nursing Research Society conference. A manuscript (Grap, Hamilton, McNallen, Best, Ketchum, Wetzel, & Arief) has been accepted for publication in *Heart and Lung*.

Self-efficacy, Stress, Immunity, and Symptoms of Fibromyalgia

Ms. McNallen has worked as a GRA for this ongoing study since its inception in October 2009. She has worked closely with the PI, Dr. Victoria Menzies, and is responsible for participant recruitment, scheduling, study preparation, data collection, and data management to date. She developed the study Protocol Manual, internal documents, and procedures for the study used by the undergraduate research assistants assigned to the study. She has acquired extensive experience with the FMS population, made contacts within the FMS support community, and also acquired hands-on experience with administering many of the study measures she will use in this proposed study.

IX. RESEARCH METHOD AND DESIGN

Include a brief description of the project design including the setting in which the research will be conducted and procedures. If applicable, include a description of procedures being performed already for diagnostic or treatment purposes.

Using a single stage cross-sectional design, the primary aim of this study is to compare 2 groups, 25 women with and 25 women without FMS, who are referred for sleep studies at the VCU Center for Sleep Medicine on the following variables: ANS activity (COMPASS and HRV); perceived stress (PSS); sleep quality (PSG and PSQI); immune function (17-plex cytokines); and fatigue (BFI). A secondary aim is to explore the relationships among the above variables within each group of participants. Also, within the FMS group these variables will be correlated with pain (BPI). The third aim is to assess the validity of the COMPASS by comparing it to measures of HRV and sleep indices (number of arousals and sleep latency).

Table 1: Key study variables and their measures

Variable	Measure	Type
FMS	Demographic data	Questionnaire

FIBROMYALGIA

ANS activity	COMPASS Heart rate variability (HRV)	73- item scale Sleep study
Immune Function	Plasma 17-plex cytokines	8 ml blood sample
Stress	Perceived Stress Scale (PSS)	10-item scale
Sleep Quality	Pittsburgh Sleep Quality Index (PSQI) Polysomnography (PSG)	19-item scale Sleep study
Fatigue	Brief Fatigue Inventory (BFI)	10-item scale
Pain (in FMS only)	Brief Pain Inventory (BPI)	11-item scale

Setting

The VCU Center for Sleep Medicine is the setting for this study. All recording and monitoring equipment is enclosed in a centrally located control room separate from 5 testing bedrooms. The center has monitoring equipment and a computer system that allow completely digital sleep recordings. The control room is staffed by professional technicians who greet and prepare scheduled patients in the early evening, and monitor the sleep studies continuously through the night. Preparation of the patient for PSG normally takes approximately an hour for all monitoring equipment to be applied. Dr. David Leszczyn, the medical director of this facility (see letter of support) will assist with access to study participants. The VCU Center for Sleep Medicine saw 861 patients in 2007, with 52% (463) of these being female. The average female age was 50; 57% were African American, 41% Caucasian, and 2% Hispanic or other/unknown. Of these, 10% (46) may be estimated to have a diagnosis of FMS.

Sample

A total of 50 women, 25 with a recorded medical diagnosis of FMS, and 25 without such a diagnosis, will be recruited. The sample will include participants aged 35 to 65, without rheumatologic comorbidities, and not pregnant. The participants recruited who do not have a diagnosis of FMS will be queried for the presence of chronic widespread pain to avoid including undiagnosed FMS persons within the comparison group.

Table 2: Inclusion/exclusion criteria for proposed study

Inclusion Criteria	Exclusion Criteria
Aged 35 to 65	Pediatric patients
Female	Males
For FMS group:	Rheumatologic conditions, i.e. RA, SLE, or Sjogren's disease.
For Comparison group:	Chronic widespread pain or rheumatologic conditions that may be confounded with FMS.
Referral to Sleep Disorders Center	Pregnancy
English literacy Ability to complete questionnaires	Major communicative disorder
Able to participate in sleep study	Unable to sleep alone at sleep study

Measures

A demographic and health history questionnaire will be used to obtain information regarding age, height, weight, race/ethnicity, partner status, length of FMS diagnosis, education, socioeconomic status, psychiatric history, medical comorbidities, and medication history. This is completed by the potential participant upon arrival at the VCU Center for Sleep Medicine. Sleep environment, usual bedtime, symptom management measures employed by the participant, and blood pressure, pulse and respirations will also be recorded. History of any suspected or diagnosed sleep disorders will be obtained. Menstrual status, determined by the date of the last menstrual period, will be recorded since 72% of premenopausal women report worsening of FMS symptoms prior to menstruation. Pregnancy and menopause have also been reported to exacerbate symptoms⁸⁸.

ANS function will be measured with the Composite Autonomic Symptoms Scale (COMPASS), a 73-item multidimensional questionnaire that takes approximately 30 minutes to complete⁸⁹. It does not directly measure ANS function, but assesses orthostatic, secretomotor, sexual dysfunction, urinary, gastrointestinal, pupillomotor, vasomotor, reflex syncope, and sleep functions. Symptoms from these 9 domains have been found to be consistent with autonomic dysfunction. The highest possible score for women is 170. Mean score for the initial sample of healthy control women was 47.2 ± 11.6 ; women with neurogenic autonomic failure had a mean score of 57.4 ± 13.9 ⁸⁹. Since no validated self-report

FIBROMYALGIA

autonomic questionnaire existed prior to COMPASS, it could not be tested for concurrent validity; the authors tested it against the Composite Autonomic Scoring Scale (CASS) for criterion validity⁸⁹. The CASS has been reported to be sensitive and specific for detecting autonomic symptomatology⁹⁰.

The COMPASS has since been used to study FMS patients, where it was found to significantly correlate with the Fibromyalgia Impact Questionnaire²⁸. Mean score for FMS patients in that study (54.6 ± 20.9) differed significantly from healthy controls (9.5 ± 10.2). It has been used to study patients with primary Sjogren's syndrome in relation to HRV⁹¹. Those investigators found a modest correlation between COMPASS and decreased HRV that did not attain statistical significance. Patients with chronic fatigue syndrome (CFS) have also been studied with COMPASS and HRV measurements; those researchers found significantly higher COMPASS scores in CFS patients as compared to healthy controls⁹². They also reported a strong, significant correlation between low-frequency HRV and higher COMPASS scores.

ANS function will also be evaluated using HRV, derived from the continuous ECG recording that is a customary part of PSG throughout the night. Staud³⁹ stated that, "although not specific for FM(S), ANS dysfunction can be readily determined by HRV analysis requiring only computer analysis of ECG recordings by commercially available software". He concluded that ANS dysfunction as assessed by HRV analysis is a useful biomarker, and may even become part of FMS diagnostic criteria in the future. As noted earlier, FMS is characterized by persistent ANS hyperactivity at rest, yet hyporeactivity during stress (the ceiling effect). FMS patients have displayed higher resting heart rates and lower HRV than controls; in addition, power spectral analysis of their HRV variability was positively correlated with their perceived stress and pain⁴⁹. One clinical trial of HRV biofeedback in FMS patients indicated a trend suggestive of improvements in sleep and pain⁹³.

Perceived stress will be measured with the 10-item Perceived Stress Scale (PSS). It has been used for more than 16 years in a variety of patient populations and in many health-related contexts⁹⁴. It measures the frequency of stressful events over a month's time, perceived control, the degree to which situations are perceived to be stressful, and ability to cope¹⁷. Because it is a global measure of perceived stress, it does not measure the same concept as psychological distress. It has been reported to have a reliability coefficient for the 10-item version of $\alpha=0.91$ ⁹⁴. The authors also reported that the 10-item PSS met standards of construct validity and criterion-related validity and reflected a unidimensional construct of stress.

Sleep quality will be measured with the Pittsburgh Sleep Quality Index (PSQI), a 19-item questionnaire that assesses sleep quality and disturbances over a one-month interval. The items generate 7 component scores: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. Each of the component scores is weighted equally on a scale of 0 to 3, 0 indicating no difficulty and 3 indicating severe difficulty. The component scores are then summed to yield a global PSQI score, ranging from 0 to 21. Higher scores indicate worse sleep quality; a global PSQI score ≥ 5 is consistent with poor sleep quality. The overall PSQI global score correlation coefficient for test-retest reliability was reported to be 0.87; a global score >5 resulted in a sensitivity of 98.7 and specificity of 84.4 as a marker for sleep disturbances in insomnia patients versus controls⁹⁵. It has been used to assess sleep quality in FMS patients in several studies^{17;54}.

Sleep quality will also be measured with polysomnography (PSG), an array of physiologic measures to study sleep duration and quality, including central and occipital EEG, eye movement monitoring, muscle tension in several locations, ECG, airflow, respiratory rate, blood oxygen saturation, limb movements, and expired CO₂. PSG has been in use for sleep studies since 1968, and has continually developed and evolved with changes in technology⁹⁶. PSG is performed in an outpatient sleep laboratory overnight, with technicians monitoring patient status and equipment. The entire battery of tests is arrayed on a computer monitor and sleep stages (wake, stages 1-3 NREM, and REM) are visually scored for 30-second epochs according to the criteria of Rechtschaffen and Kales⁹⁶. A neurologist board-certified in sleep medicine reads and interprets results. PSG is a major diagnostic clinical tool and has been employed in many studies of FMS and sleep^{56;97}.

Fatigue will be measured using the Brief Fatigue Inventory (BFI)⁹⁸, a 9-item scale that taps into a single dimension of fatigue severity and the interference fatigue creates in daily life. The BFI is a clinically validated tool used to assess cancer-related fatigue and its impact on daily functioning. The BFI uses simple numeric rating scales from 0 to 10 that are easy to understand. On the BFI, severe fatigue can be defined as a score of 7 or higher. The BFI has demonstrated excellent reliability in clinical trials, ranging from 0.82 to 0.97⁹⁹. Estimated time for completion of the BFI is 5 minutes.

Pain will be measured using the Brief Pain Inventory (BPI)¹⁰⁰, an 11-item pain assessment tool that has well-established reliability and validity for adult patients with no cognitive impairment in trajectory studies of cancer and its symptoms¹⁰¹. The BPI assesses current pain, average severity of pain, the amount of pain in the past 24 hours, and the impact of pain on daily functions. Estimated time for completion of the BPI is 5 minutes. The arithmetic mean of the 4 severity items will be used as a measure of pain severity, and the arithmetic mean of the 7 interference items will be used

FIBROMYALGIA

as a measure of pain interference. In widespread testing, the Cronbach's α reliability has ranged from 0.70 to 0.91⁹⁹.

Cytokine samples will be collected via 8-milliliter blood samples obtained by venipuncture using CPT cell preparation tubes with sodium heparin for plasma assay. Samples will be analyzed using the Bio-Plex® Human 17-Plex (Bio-Rad: Hercules, CA) multiplex assay system. This system permits simultaneous analyses of up to 100 different biomolecules in a single microplate well. Daily system calibration and assay validation are performed using standardization methods developed by the manufacturer. Bio-Plex® offers greatly improved sensitivity (10 pg/ml), reliability, recovery, and reproducibility in comparison to conventional enzyme-linked immunosorbent assays (ELISAs). The standardized 17-Plex kit includes coupled beads, detection antibodies, and standards for the detection of IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), interferon-gamma (IFN- γ), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 β (MIP-1 β), and tumor necrosis factor alpha (TNF- α).

Procedures

Recruitment and enrollment. The student will conduct a preliminary test of all study procedures during fall 2010, prior to participant recruitment to ensure that all procedures, equipment and data collection techniques are operational. Potential participants will be pre-selected based on the VCU Center for Sleep Medicine database of women, both those diagnosed with FMS, and those without such a diagnosis. Those with a diagnosis of FMS will be screened for the presence of exclusion criteria, such as a concurrent diagnosis of SLE. Those women without a diagnosis of FMS will be screened for the presence of chronic widespread pain that might be indicative of an undiagnosed FMS condition. The student will make rounds at the VCU Center for Sleep Medicine to evaluate patients as potential study participants based on their medical and sleep histories, invite study participation from those who meet eligibility criteria, conduct all informed consent processes, and screen and enroll all participants who consent to participate in the study.

Data collection procedures. Psychometric data obtained for study purposes will not affect the participant's care; clinical data obtained from PSG or intake interviews will be used in clinical diagnosis and/or management of any sleep disorder detected, as per VCU Center for Sleep Medicine institutional protocol. Once the participant has been screened, consented, and is enrolled in the study, descriptive data concerning participant demographics will be collected from medical records and patient interviews using the demographic and health history form. All data collection will occur at the VCU Center for Sleep Medicine. Once included in the study, and after completion of the demographic and health history form, each participant will receive an appointment for the sleep study at the VCU Center for Sleep Medicine.

Each study participant will meet the student at the VCU Center for Sleep Medicine 90 minutes prior to her scheduled sleep study. For purposes of sleep study protocol, patients usually arrive at either 7:30 or 8:30 pm and stay until 6 am; therefore, for purposes of the proposed study, participants will be asked to arrive either at 6:00 p.m. or 7:00 p.m., depending upon their appointment time. During this time, the study participant will complete the COMPASS, the PSS, the PSQI, the BFI, and the BPI. After questionnaires have been completed, the student will perform venipuncture on a participant's accessible arm vein to collect an 8-milliliter blood sample into CPT cell preparation tubes with sodium heparin. Following completion of study data collection, each participant will be compensated for their time with a \$25 gift card.

VCU Center for Sleep Medicine staff managing patient care will evaluate the patient's comfort and stability in a routine manner while conducting the sleep study. The sleep study will not vary in any way from established VCU Center for Sleep Medicine institutional protocols. Technicians initiate and monitor the PSG throughout the night; a neurologist, board certified in sleep medicine, interprets PSG findings at a later time. If patients require treatment during the night, such as use of a continuous positive airway pressure (CPAP) machine for sleep apnea, treatment will be initiated per VCU Center for Sleep Medicine protocol. Evaluation, diagnosis and treatment based on sleep study results will be conducted by the participant's physician.

The blood sample will be placed in an appropriate cold-pack biohazard container for transport to the CBCR laboratory at the VCU School of Nursing, where it will be stored and analyzed. All blood samples will be centrifuged for separation of plasma; specimens will be aliquoted, frozen, and stored at -70° C until all samples have been collected.

X. PLAN FOR CONTROL OF INVESTIGATIONAL DRUGS, BIOLOGICS, AND DEVICES.

For investigational drugs and biologics: IF IDS is not being used, attach the IDS confirmation of receipt of the management plan.. See item #11 on Initial Review form.

For investigational and humanitarian use devices (HUDs): Describe your plans for the control of investigational

FIBROMYALGIA

devices and HUDs including: (1) how you will maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s); (2) plan for storing the investigational product(s)/ HUD as specified by the sponsor (if any) and in accordance with applicable regulatory requirements; (3) plan for ensuring that the investigational product(s)/HUDs are used only in accordance with the approved protocol; and (4) how you will ensure that each subject understands the correct use of the investigational product(s)/HUDs (if applicable) and check that each subject is following the instructions properly (on an ongoing basis).

N/A

XI. DATA ANALYSIS PLAN

For investigator-initiated studies.

Data analysis plan

Statistical analyses will be performed using JMP 8.0 or higher, and significance set at $\alpha \leq 0.05$. Descriptive statistics of the 2 groups will be reported and compared, with means and standard deviations for continuous data, and frequency distributions and percentages for ordinal or categorical data. The normality for all continuous variables will be examined to assess the need for a transformation (e.g., the cytokines are typically log-transformed). For the demographic variables, differences between the groups will be assessed using 2-sample *t*-tests for continuous data and Chi-square for ordinal or categorical data.

To test the Aim One hypotheses, 2-sample *t*-tests will be used to test for significant group differences in the study variables, ANS activity (COMPASS and HRV), perceived stress (PSS), sleep quality (PSG and PSQI), immune function (17-plex cytokines), and fatigue (BFI). The normality for all continuous variables will be examined to assess the need for transformations. It is expected that the cytokines will be analyzed following log transformations.

To test the Aim Two hypotheses, Pearson's correlation coefficients will be calculated to determine the relationships among ANS activity (COMPASS and HRV), perceived stress (PSS), sleep quality (PSG and PSQI), immune function (17-plex cytokines), and fatigue (BFI) within each group. Also, within the FMS group, these above variables will be correlated with pain (BPI). For Pearson's correlation coefficient to be used, several conditions must be met: variables must be quantitative with no restriction on their level of precision; the variables must have a linear relationship; and the variables must be normally distributed¹⁰². The normal distribution of all the above continuous variables will be examined to assess the need for a transformation to meet these assumptions. Linearity will also be assessed.

To test the Aim Three hypothesis, Pearson's correlation coefficients will be calculated to determine the relationships among COMPASS scores, HRV, and selected sleep indices (number of arousals and sleep latency).

XII. DATA AND SAFETY MONITORING

- **If the research involves greater than minimal risk and there is no provision made for data and safety monitoring by any sponsor, include a data and safety-monitoring plan that is suitable for the level of risk to be faced by subjects and the nature of the research involved.**
- **If the research involves greater than minimal risk, and there is a provision made for data and safety monitoring by any sponsor, describe the sponsor's plan.**
- **If you are serving as a Sponsor-Investigator, identify the Contract Research Organization (CRO) that you will be using and describe the provisions made for data and safety monitoring by the CRO. Guidance on additional requirements for Sponsor-Investigators is available at <http://www.research.vcu.edu/irb/wpp/flash/X-2.htm>**

Data and Safety Monitoring Plan

The proposed project is an observational study, not a clinical trial. The study investigator is available 24 hours a day by cell phone; this number is provided to participants. The study investigator will meet monthly with the PI (dissertation chair) to monitor for safety issues. In addition, the study process will be reviewed for unexpected occurrences or alterations in clinical conditions. Any changes will be examined for their relationship to the project protocol. Reports of these chair meetings will be reviewed at the full progress meetings of the Dissertation Committee.

Because the planned project involves minimal risk, no adverse events are expected to occur as a direct result of participant participation. However, should any event occur that might be related to study participation, the study

FIBROMYALGIA

investigator will assume responsibility for notification of the designated care providers and any referral for recommended treatment, as well as notification of the VCU IRB. Adverse event reporting forms and procedures are available on-line at: <http://www/orsp.vcu.edu/irb>.

XIII. MULTI-CENTER STUDIES

If VCU is the lead site in a multi-center project or the VCU PI is the lead investigator in a multi-center project, describe the plan for management of information that may be relevant to the protection of subjects, such as reporting of unexpected problems, project modifications, and interim results.

N/A

XIV. INVOLVEMENT OF NON-VCU INSTITUTIONS/SITES (DOMESTIC AND FOREIGN)

1. Provide the following information for each non-VCU institution/site (domestic and foreign) that has agreed to participate:

- Name of institution/site
- Contact information for institution/site

N/A

2. For each institution, indicate whether or not it is “engaged” in the research (see OHRP’s guidance on “Engagement of Institutions in Research” at <http://www.hhs.gov/ohrp/humansubjects/guidance/engage08.html>.)

N/A

3. Provide a description of each institution’s role (whether engaged or not) in the human subjects research, adequacy of the facility (in order to ensure human subject safety in the case of an unanticipated emergency), responsibilities of its agents/employees, and oversight that you will be providing in order to ensure adequate and ongoing protection of the human subjects. You should only identify institutions that have agreed to participate. If additional institutions agree to participate at a later time, they must be added by amendment to the protocol.

N/A

4. For each institution that is “engaged” provide an OHRP Federalwide Assurance (FWA) # if: (1) the research is not exempt, AND (2) the research involves a DIRECT FEDERAL award made to VCU (or application for such).

NOTE: Additional guidance at <http://www.research.vcu.edu/irb/wpp/flash/XVII-6.htm>, and <http://www.research.vcu.edu/irb/wpp/flash/XVII-11.htm>.

N/A

XV. INVOLVEMENT OF INDEPENDENT INVESTIGATORS

INDEPENDENT INVESTIGATOR: an individual who is acting independently and not acting as an agent or employee of any institution or facility while carrying out his or her duties in the research protocol. Additional guidance at <http://www.research.vcu.edu/irb/wpp/flash/XVII-15.htm>.

ENGAGEMENT IN RESEARCH: An independent investigator becomes "engaged" in human subjects research when he/she (i) intervenes or interacts with living individuals for research purposes; or (ii) obtains individually identifiable private information for research purposes [45 CFR 46.102(d)-(f)]. See OHRP’s guidance on “Engagement of Institutions in Research” at <http://www.hhs.gov/ohrp/humansubjects/guidance/engage08.html>.

FIBROMYALGIA

1. Provide a list of independent investigators.
2. For each independent investigator indicate whether or not he/she is “engaged” or “not engaged” in the research
3. For each independent investigator who is “engaged”: (1) describe his/her role with human subjects/identifiable human data, AND (2) describe YOUR oversight of his/her involvement.

N/A

NOTE: If an independent investigator is “engaged,” and the research is (1) not exempt AND (2) involves a DIRECT FEDERAL award made to VCU (or application for such), the independent investigator must sign a formal written agreement with VCU certifying terms for the protection of human subjects. For an agreement to be approved: (1) the PI must directly supervise all of the research activities, (2) agreement must follow the ORSP template, (3) IRB must agree to the involvement of the independent investigator, AND (4) agreement must be in effect prior to final IRB approval.

XVI. HUMAN SUBJECTS INSTRUCTIONS (Be sure to use the sub-headings under A-I)

ALL sections of the Human Subjects Instructions must be completed with the exception of the section entitled “Special Consent Provisions.” Complete that section if applicable.

A. DESCRIPTION

Provide a detailed description of the proposed involvement of human subjects or their private identifiable data in the work.

The study will involve 50 female participants ages 35 or older, 25 with fibromyalgia and 25 without fibromyalgia. Participants must meet the study criteria outlined below. They will be recruited using study advertisements and participant referrals. Eligible participants will be asked to sign the consent, complete demographic and psychosocial measures, and allow a one-time venous blood draw, the evening of their scheduled sleep study at the VCU Center for Sleep Medicine.

B. SUBJECT POPULATION

Describe the subject population in terms of sex, race, ethnicity, age, etc., and your access to the population that will allow recruitment of the necessary number of participants. Identify the criteria for inclusion or exclusion of any subpopulation and include a justification for any exclusion. Explain the rationale for the involvement of special cases of subjects, such as children, pregnant women, human fetuses, neonates, prisoners or others who are likely to be vulnerable. If you plan to allow for the enrollment of Wards of the State (or any other agency, institution, or entity), you must specifically request their inclusion and follow guidance on Wards and Emancipated Minors in the VCU IRB Written Policies and Procedures (specifically WPP#: XV-3) available at <http://www.research.vcu.edu/irb/wpp/flash/XV-3.htm>.

The sample will consist of 50 female participants, 25 diagnosed with fibromyalgia and 25 without fibromyalgia, who meet inclusion criteria and complete the study.

Inclusion Criteria: a) ages 35 and older; b) female; c) diagnosis of fibromyalgia confirmed by the patient’s primary physician by half the sample; d) no known major psychiatric or neurological conditions that would interfere with study participation; e) able to speak and read standard English; f) a minimum of a 6th grade education level; and g) an ability to understand and sign the consent form and understand and complete the pencil and paper assignments.

Exclusion Criteria: are (a) presence of other systemic rheumatologic conditions such as rheumatoid arthritis, systemic lupus erythematosus, and/or Sjogren's Disease; (b) history of epilepsy; (c) any present psychiatric disorder involving a history of psychosis (e.g., schizophrenia, schizoaffective disorder; schizophreniform disorder, delusional disorder, etc.); (d) being immunocompromised; (e) receiving corticosteroid treatments; or (f) being pregnant.

C. RESEARCH MATERIAL

Identify the sources of research material obtained from individually identifiable living human subjects in the form of specimens, records, or data. Indicate whether the material or data will be obtained specifically for research purposes or whether use will be made of existing specimens, records, or data.

Data will be collected from research instruments given to the study participants by the study investigator. In addition, FMS

FIBROMYALGIA

participants will be asked to provide documentation confirming FMS diagnosis unless this is already in the VCUHS data base. The results of the sleep study will be obtained by the study investigator. Blood samples will be collected by the study investigator via venipuncture into 8-milliliter CPT cell preparation tubes with sodium heparin. All data will be obtained specifically for research purposes.

D. RECRUITMENT PLAN

Describe in detail your plans for the recruitment of subjects including: (1) how potential subjects will be identified (e.g., school personnel, health care professionals, etc), (2) how you will get the names and contact information for potential subjects, and (3) who will make initial contact with these individuals (if relevant) and how that contact will be done. If you plan to involve special cases of subjects, such as children, pregnant women, human fetuses, neonates, prisoners or others who are likely to be vulnerable, describe any special recruitment procedures for these populations.

Participants will be recruited using study advertisements (flyers and brochures) distributed in print (see Appendix C) at the VCU Center for Sleep Medicine. Dr. David Leszczyszyn, MD, PhD, the medical director (see letter of support, Appendix D) will assist with access to the project settings.

Participants may self-identify as potential participants by responding to advertisements and calling the study investigator at her office telephone number or contacting her through an email address (each identified in advertising materials). The study investigator will explain the study to the potential participant who will be screened based upon inclusion and exclusion criteria. If she meets the study criteria and desire to participate, an appointment will be made for her to meet with the study investigator at a convenient time. At this initial meeting, the study investigator will review the study, obtain informed consent, and conduct and conduct the data collection visit. The data collection visit will be conducted in a private room at the VCU Center for Sleep Medicine. Following consent and enrollment, the data collection visit, which includes administration of the measurement tools and collection of the blood sample, should take no longer than 90 minutes.

E. POTENTIAL RISKS

Describe potential risks whether physical, psychological, social, legal, or other and assess their likelihood and seriousness. Where appropriate, describe alternative treatments and procedures that might be advantageous to the subjects.

Venipuncture involves potential small risk of ecchymosis or infection at the site. As the questionnaires do not involve any sensitive data, no risk to the subjects is anticipated related to completion of questionnaires.

F. RISK REDUCTION

Describe the procedures for protecting against or minimizing potential risk. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse events to the subjects. Also, where appropriate, describe the provisions for monitoring the data collected to ensure the safety of subjects.

As part of the process involved in obtaining written informed consent, participants will be given a copy of the informed consent form. Venipuncture will be performed by the study investigator using aseptic technique. The PI and the study investigator are both licensed, registered nurses. Because the nature of the survey questions is not sensitive, this poses almost no risk to participants. Contact information for the PI and the study investigator is provided on the consent form.

G. ADDITIONAL SAFEGUARDS IF ANY PARTICIPANTS WILL BE VULNERABLE

Describe any additional safeguards to protect the rights and welfare of participants if you plan to involve special cases of subjects, such as children, pregnant women, human fetuses, neonates, prisoners or others who are likely to be vulnerable. Safeguards to protect the rights and welfare of participants might relate to Inclusion/Exclusion Criteria: (“Adults with moderate to severe cognitive impairment will be excluded.” “Children must have diabetes. No normal controls who are children will be used.”) Consent: (“Participants must have an adult care giver who agrees to the participant taking part in the research and will make sure the participant complies with research procedures.”

FIBROMYALGIA

“Adults must be able to assent. Any dissent by the participant will end the research procedures.”) Benefit: (“Individuals who have not shown benefit to this type of drug in the past will be excluded.”).

All participants shall be able to understand English and able to assent to participate. Any dissent or withdrawal of consent by the participant will end the research procedure.

H. CONFIDENTIALITY

Describe how the confidentiality of data collected as part of this project will be protected including pre-screening data (e.g., physical controls on the data; access controls to the data; coding of data; legal controls, such as a Federal Certificate of Confidentiality; statistical methods; or reporting methods).

Confidentiality of participant data is the primary safety-related issue in this study. Participants’ identities will be protected. Each data record will be assigned an arbitrary code number by the study investigator and then identifying information will be removed from the data record and attached to the consent form, which will be kept in a locked file accessible only by the study personnel. All laboratory data and sleep study results will be blindly and anonymously coded.

I. PRIVACY

Describe how the privacy interests of subjects will be protected where privacy refers to persons and their interests in controlling access to themselves, and assess their likely effectiveness. Identify what steps you will take for subjects to be comfortable: (1) in the research setting and (2) with the information being sought and the way it is sought.

Study participants and information will only be accessible to the study investigator and the PI who will maintain participant privacy and ensure clinical acumen. Each study visit will be conducted in a private room to ensure participants’ privacy.

J. RISK/BENEFIT

Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and in relation to the importance of the knowledge that may reasonably be expected to result. If a test article (investigational new drug, device, or biologic) is involved, name the test article and supply the FDA approval letter.

This study has the potential to make a significant contribution to the literature in the areas of chronic illness and symptom management, healthcare research, and to provide scientific support for relationships among psychoneuroimmunological parameters in persons diagnosed with FMS. If it is found that there are significant correlations among cytokine production patterns, ANS symptoms, perceived stress, and symptoms of pain, fatigue, and sleep disturbance, this information will help in the design of nursing interventions for managing sleep disturbance and other symptoms related to this disorder, using both self-report and objective measures to capture outcome data. There is no cure on the horizon for FMS and there is limited research on symptom management in persons with this disorder. The literature is especially limited when examining this issue from the PNI perspective. Using the PNI model that includes both subjective and objective measures to explore key variables, data from this study may be important in the development of nonpharmacological or other interventions for management of sleep disturbance and other symptoms in women diagnosed with FMS.

K. COMPENSATION PLAN

Compensation for subjects (if applicable) should be described, including possible total compensation, any proposed bonus, and any proposed reductions or penalties for not completing the project.

Upon completion of the study visit and assessment and determination of patient safety, a \$25 gift card will be provided to the participant as compensation for their time and effort.

L. CONSENT ISSUES

1. CONSENT PROCESS

Indicate who will be asked to provide consent/assent, who will obtain consent/assent, what language (e.g., English, Spanish) will be used by those obtaining consent/assent, where and when will consent/assent be obtained, what steps

FIBROMYALGIA

will be taken to minimize the possibility of coercion or undue influence, and how much time will subjects be afforded to make a decision to participate.

Informed consent will be obtained in a private setting. Potential participants can take as much time as needed to read or discuss the consent with the study investigator, family or friends before making their decision. Furthermore, explanation of the study will be provided verbally and in writing. Patients will be allowed to ask questions or call the study investigator to discuss any concerns at any time.

2. SPECIAL CONSENT PROVISIONS

If some or all subjects will be cognitively impaired, or have language/hearing difficulties, describe how capacity for consent will be determined. Please consider using the VCU Informed Consent Evaluation Instrument available at <http://www.research.vcu.edu/irb/guidance.htm>. If you anticipate the need to obtain informed consent from legally authorized representatives (LARs), please describe how you will identify an appropriate representative and ensure that their consent is obtained. Guidance on LAR is available at <http://www.research.vcu.edu/irb/wpp/flash/XI-3.htm>.

N/A

3. If request is being made to **WAIVE SOME OR ALL ELEMENTS OF INFORMED CONSENT FROM SUBJECTS OR PERMISSION FROM PARENTS**, explain why: (1) the research involves no more than minimal risk to the subjects, (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects, (3) the research could not practicably be carried out without the waiver or alteration; AND (4) whether or not subjects will be debriefed after their participation. Guidance is available at <http://www.research.vcu.edu/irb/wpp/flash/XI-1.htm>. **NOTE:** Waiver is not allowed for FDA-regulated research unless it meets FDA requirements for Waiver of Consent for Emergency Research (see below).

N/A

4. If request is being made to **WAIVE DOCUMENTATION OF CONSENT**, provide a justification for waiver based on one of the following two elements AND include a description of the information that will be provided to participants: (1) the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Subject will be asked whether they want documentation linking them with the research, and each subject's wishes will govern; or (2) the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. Guidance is available at http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#XI-2.htm

N/A

5. If applicable, explain the **ASSENT PROCESS** for children or decisionally impaired subjects. Describe the procedures, if any, for re-consenting children upon attainment of adulthood. Describe procedures, if any, for consenting subjects who are no longer decisionally impaired. Guidance is available at <http://www.research.vcu.edu/irb/wpp/flash/XV-2.htm> and <http://www.research.vcu.edu/irb/wpp/flash/XVII-7.htm>.

N/A

6. If request is being made to **WAIVE THE REQUIREMENT TO OBTAIN ASSENT** from children age 7 or higher, or decisionally impaired subjects, explain why: (1) why some or all of the individuals age 7 or higher will not be capable of providing assent based on their developmental status or impact of illness; (2) the research holds out a prospect of direct benefit not available outside of the research; AND/OR (3) [a] the research involves no more than minimal risk to the subjects, [b] the waiver or alteration will not adversely affect the rights and welfare of the subjects, [c] the research could not practicably be carried out without the waiver or alteration; AND [d] whether or not subjects will be debriefed after their participation. Guidance is available at <http://www.research.vcu.edu/irb/wpp/flash/XV-2.htm>

N/A

FIBROMYALGIA

7. If request is being made to waive consent for emergency research, see guidance at <http://www.research.vcu.edu/irb/wpp/flash/XVII-16.htm>.

N/A

8. If applicable, address the following issues related to **GENETIC TESTING**:

a. FUTURE CONTACT CONCERNING FURTHER GENETIC TESTING RESEARCH

Describe the circumstances under which the subject might be contacted in the future concerning further participation in this or related genetic testing research.

N/A

b. FUTURE CONTACT CONCERNING GENETIC TESTING RESULTS

If planned or possible future genetic testing results are unlikely to have clinical implications, then a statement that the results will not be made available to subjects may be appropriate. If results might be of clinical significance, then describe the circumstances and procedures by which subjects would receive results. Describe how subjects might access genetic counseling for assistance in understanding the implications of genetic testing results, and whether this might involve costs to subjects. Investigators should be aware that federal regulations, in general, require that testing results used in clinical management must have been obtained in a CLIA-certified laboratory.

N/A

c. WITHDRAWAL OF GENETIC TESTING CONSENT

Describe whether and how subjects might, in the future, request to have test results and/or samples withdrawn in order to prevent further analysis, reporting, and/or testing.

N/A

d. GENETIC TESTING INVOLVING CHILDREN OR DECISIONALLY IMPAIRED SUBJECTS

Describe procedures, if any, for consenting children upon the attainment of adulthood. Describe procedures, if any, for consenting subjects who are no longer decisionally impaired.

N/A

e. CONFIDENTIALITY

Describe the extent to which genetic testing results will remain confidential and special precautions, if any, to protect confidentiality.

N/A

APPENDICES

Appendix A Advertising Materials

Flyer
Brochure

Appendix B Letter of Support

Dr. David Leszczyszyn

Appendix C Consent

Appendix D Instruments

Demographic and Health History Questionnaire
Pittsburgh Sleep Quality Index (PSQI)
Composite Autonomic Symptoms Scale (COMPASS)

FIBROMYALGIA

The Brief Fatigue Inventory (BFI)
Perceived Stress Scale (PSS)
The Brief Pain Inventory (BPI)

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FIBROMYALGIA

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Chapter Four

FIBROMYALGIA

Biobehavioral Correlates in Fibromyalgia

Fibromyalgia (FMS) is a chronic pain syndrome characterized by diffuse musculoskeletal pain, non-restorative sleep, fatigue, and psychological distress (Schaefer, 2003). The American College of Rheumatology guidelines for diagnosis of FMS require widespread aching for at least three months and the presence of 11 out of 18 possible tender points (Shah, Feinberg, & Krishnan, 2006; Wolfe et al., 1990). It affects approximately five million Americans (Lawrence et al., 2008), 90% of whom are women (Bennett, Jones, Turk, Russell, & Matallana, 2007). The economic impact of this condition is substantial; individuals with FMS often have trouble maintaining long-term employment due to increasing disability (Birtane, Uzunca, Tastekin, & Tuna, 2007). Pain, disordered sleep, and fatigue have been ranked by people with FMS as symptoms having great impact on quality of life (Theadom, Cropley, & Humphrey, 2007; Smith, Harris, & Clauw, 2011).

The primary aim of this study was to compare two groups, 25 women with FMS and 25 without FMS, on the following variables: autonomic nervous system (ANS) activity; perceived stress; sleep quality; immune function (17-plex cytokines); and fatigue. A secondary aim was to explore the relationships among the above variables within each group of participants. A third aim was to assess the construct validity of the Autonomic Symptoms Profile (ASP) in FMS research by comparing it to measures of heart rate variability (HRV) and sleep indices (number of arousals and sleep latency).

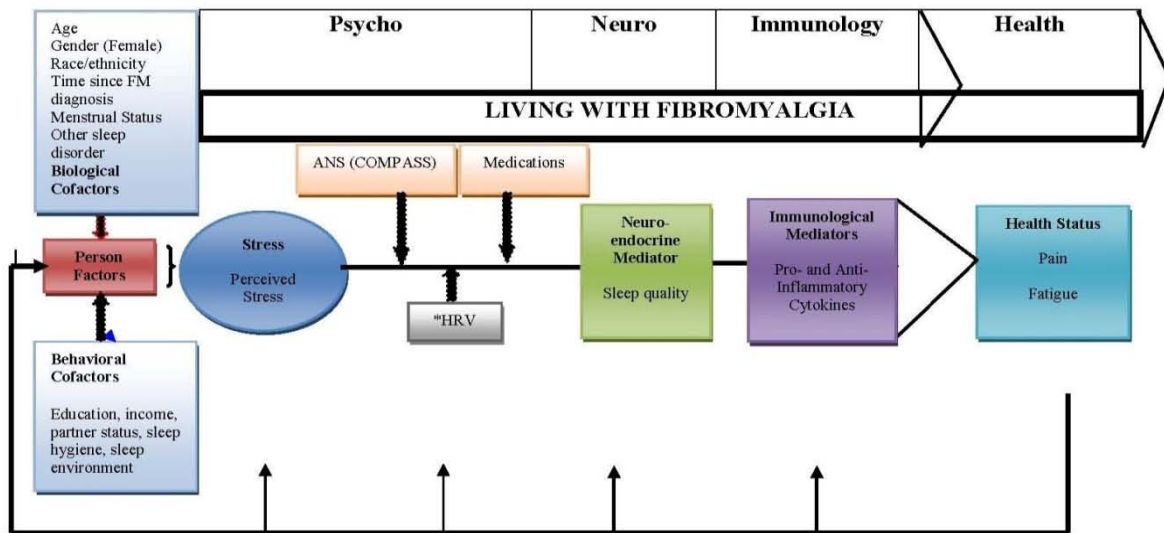
Psychoneuroimmunology (PNI) has been used as a framework to examine relationships among biological and behavioral correlates and their effects on patient outcomes (McCain, Gray, Walter, & Robins, 2005). Within that framework, this study posited that biological and behavioral cofactors interact with the ANS in women with FMS to produce dysfunctional changes in the ANS response to perceived stress, which in turn might alter sleep quality and

FIBROMYALGIA

cytokine expression. Poor sleep quality also leads to cytokine changes (Vgontzas et al., 1997); both perceived stress and poor sleep quality interact with the ANS in a circular fashion, which may result in generalized pain and fatigue. The conceptual framework for this research is displayed in Figure 1.

Figure 1

PNI-based biobehavioral model of symptoms in FMS (adapted from McCain et al., 2005)



The extent to which expression of FMS symptoms is associated with cytokine changes independently of poor sleep quality has been unclear. It is unknown which particular aspects of sleep in FMS, such as length of sleep stages or number of arousals, may be predictive of cytokine changes or resultant from them. Additionally, perceived stress has been implicated in worsening sleep quality, pain, and fatigue for people with FMS, but the degree to which it initiates or reflects ANS stress arousal remains uncertain.

Background

Disordered pain processing through central sensitization appears to play a role in the development of FMS symptoms (Light et al., 2009). FMS is thought to result from ANS dysfunction initiated by a genetically impaired stress response (Martinez-Lavin, 2007; Solano et

FIBROMYALGIA

al., 2009). ANS dysregulation of pain modulatory systems may lead to prolonged interactions among the central nervous system, the peripheral nervous system, and the immune system, such that neuroplasticity establishes a connection among the sympathetic nervous system (SNS) and nociceptive fibers. This is postulated to result in neuropathic pain (Light et al., 2009). In this view the SNS is persistently hyperactive, yet paradoxically hypoactive to acute stressors due to receptor desensitization. Thus the SNS is overwhelmed and due to a ceiling effect, unable to respond appropriately to further stress (Martinez-Lavin, 2007).

Normal beat-to-beat HRV is the signature of a healthy ANS response to changes in the environment, and HRV alteration may be a biomarker of stress (Staud, 2008). Consistent with the premise that perceived stress increases SNS activity (Martinez-Lavin, 2007), participants with FMS have displayed higher resting heart rates (Cohen et al., 2000) and decreased HRV as compared to healthy controls (Dadabhoy, Crofford, Spaeth, Russell, & Clauw, 2008; Nilsen et al., 2007; Lerma et al., 2011). Theadom and Cropley (2008) found that study participants with FMS had significantly higher levels of perceived stress as compared to controls, which was associated with intensified pain. Study participants with FMS also displayed greater stress response to pain as compared with participants with osteoarthritis who reported similar pain levels (Zautra et al., 2005). Perceived stress also has been independently associated with poor sleep quality and increased nighttime arousals in persons with FMS (Theadom & Cropley, 2008).

Nearly 100% of individuals with FMS report poor sleep quality (Rizzi et al., 2004). They have endorsed sleeping an average of four to six hours per night and arising unrefreshed (Osorio, Gallinaro, Lorenzi-Filho, & Lage, 2006). Sleep disturbances commonly reported have included difficulty falling asleep, nighttime arousals, and fatigue upon arising (Bigatti, Hernandez, Cronan, & Rand, 2008). These findings have been supported by polysomnography (PSG) and

FIBROMYALGIA

actigraphy, which suggest that study participants with FMS are more easily aroused from sleep (Rizzi et al., 2004; Landis et al., 2003) and have higher levels of physical activity at night than controls (Shah et al., 2006). People with FMS have been shown to experience protracted sleep latency, reduced sleep efficiency, reduced slow wave and REM sleep, increased motor activity during sleep, and increased alpha EEG activity during non-REM sleep (Moldofsky & MacFarlane, 2005). Study participants with FMS have displayed significantly shorter duration of non-REM stage 2 (N2) sleep than controls, which was predictive of pain (Landis et al., 2003). Other PSG findings in patients with FMS have included decreased total sleep time and decreased delta sleep (Harding & Hawkins, 2005). Restless leg syndrome (RLS) and periodic limb movement disorder (PLMD) are reported to occur in 20% of people with FMS as opposed to 5 to 10% in the general population (Moldofsky & MacFarlane, 2005).

Poor sleep also has been associated with greater pain (Bigatti et al., 2008) and fatigue (Hamilton et al., 2008) in persons with FMS. Conversely, improved sleep quality has been associated with decreased pain and fatigue and is viewed as a barometer for clinical symptom management among those with FMS (Perrot, Dickenson, & Bennett, 2008; Peterson, 2007). No systematic studies have shown that treating RLS, PLMD, or obstructive sleep apnea (OSA) improves the poor sleep, fatigue, and pain typically experienced by those with FMS (Moldofsky & MacFarlane, 2005). The extent to which various sleep disorders may be considered a part of the underlying ANS dysfunction posited for FMS remains unknown.

Cytokines are polypeptides that act as messengers between immune cells (among others); they are critical to cell growth, repair, and modulation of pro- and anti-inflammatory immune responses (Wallace, 2006). Interactions among the hypothalamic-pituitary-adrenal (HPA) axis, the SNS, and cytokines help regulate sleep, stress responses, pain perception, and fatigue

FIBROMYALGIA

(Wallace, 2006). The pro-inflammatory cytokines interleukin 1-beta (IL-1 β) and tumor necrosis factor-alpha (TNF- α) have been related to symptoms associated with sleep deprivation, such as pain and fatigue (Krueger, 2008; Opp, 2006). IL-1 and TNF- α have been shown to enhance EEG slow waves, increase the duration of NREM sleep, and reduce REM sleep (Imeri & Opp, 2009).

Alterations in various cytokine levels have been reported in study participants with FMS, but this is a developing field, with varying study methods and contradictory results (Menzies & Lyon, 2010). It has been suggested that there may be an imbalance in persons with FMS in favor of sleep-disturbing anti-inflammatory cytokine responses during sleep (Togo et al., 2009). Yet in 40 study participants with widespread pain, 26 of whom had FMS (vs. controls), no significant increase in pro-inflammatory cytokines, and no significant correlations among cytokine levels and fatigue in those with FMS were found (Uceyler et al., 2006). From an integrative review of cytokines in FMS, Menzies and Lyon (2010) concluded that there are discrepancies regarding whether pro- or anti-inflammatory cytokines are elevated or reduced in FMS, and whether they correlate with FMS symptoms. The same group later reported that fatigue in participants with FMS was found to negatively correlate with IL-1 β , IL-10, and granulocyte colony-stimulating factor (G-CSF) (Menzies, Lyon, Elswick, Jr., Montpetit, & McCain, 2011). However, in a recent meta-analysis of cytokine research in FMS, other authors concluded that the majority of investigated cytokines were not found to differ significantly between study participants with FMS and controls (Uceyler, Hauser, & Sommer, 2011). Given this current degree of uncertainty, more research has been called for to clarify what role cytokine levels may play in the etiology of or immunological response to FMS. This study adds to the growing body of evidence concerning cytokine alterations in relation to FMS.

FIBROMYALGIA

Research Design and Methods

A university sleep center was the setting for this study. Using a single stage cross-sectional design, a total of 50 women, 25 with a recorded diagnosis of FMS, and 25 without that diagnosis, were recruited. All the women had been referred to the sleep center for evaluation of their sleep complaints. The sample was designed to include English-speaking women aged 35 to 65, without rheumatologic comorbidities, and not pregnant. Participants without a diagnosis of FMS were queried for the presence of chronic widespread pain to avoid including persons with undiagnosed FMS in the comparison group. Study measures are outlined in Table 1.

Table 1

Study Measures

Variable	Measure	Type
FMS	Demographic data	Questionnaire
ANS activity	Autonomic Symptom Profile (ASP)	73- item scale
	Heart rate variability (HRV)	Sleep study ECG
Immune Function	Plasma 17-plex cytokines	8 ml blood sample
Stress	Perceived Stress Scale (PSS)	10-item scale
Sleep Quality	Pittsburgh Sleep Quality Index (PSQI)	19-item scale
	Polysomnography (PSG)	Sleep study
Fatigue	Brief Fatigue Inventory (BFI)	10-item scale

ANS function was measured with the Autonomic Symptom Scale (ASP), a multidimensional questionnaire that assesses orthostatic, secretomotor, sexual, urinary, gastrointestinal, pupillomotor, vasomotor, reflex syncope, and sleep symptoms. The highest possible score for women is 170. Higher ASP scores have been significantly positively correlated with the Fibromyalgia Impact Questionnaire (FIQ) (Solano et al., 2009). Lerma et al. (2011) reported mean ASP scores of 53.6 ± 18.2 for participants with FMS as compared to 13.5 ± 10.6 for healthy controls ($p < 0.0001$).

FIBROMYALGIA

HRV time-domain measures were used to explore ANS function; these were obtained from the ECG recording that is part of the PSG in the sleep center. Time domain HRV measures are based on the mean interval between normal sinus beats on ECG, referred to as RR intervals (also known as NN intervals). These are computer analyzed to acquire additional variables such as SDNN (standard deviation of NN intervals); SDANN (mean standard deviation of average NN intervals calculated over 5 minutes); pNN50 (percentage of pairs of successive NN intervals differing by >50 milliseconds); and SDNN index (the mean of all the 5-minute standard deviations of NN). SDNN and SDANN are indicative of overall HRV; pNN50 evaluates the number of large beat to beat fluctuations (Bilchick & Berger, 2006).

Perceived stress was measured with the 10-item Perceived Stress Scale (PSS), which indicates self-reported frequency of stressful events over a month's time, perceived control, the degree to which situations are perceived to be stressful, and ability to cope (Cohen & Williamson, 1988). It has a reliability coefficient for the 10-item version of $\alpha = 0.91$ (Mitchell, Crane, & Kim, 2008).

The Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality and disturbances over a one month interval. Its components yield a global score from 0 to 21. The PSQI global score correlation coefficient for test-retest reliability was reported to be 0.87; a global score >5 resulted in a sensitivity of 98.7 and specificity of 84.4 as a marker for sleep disturbance in patients with insomnia versus controls (Backhaus, Junghanns, Broocks, Riemann, & Hohagen, 2002).

Sleep duration and quality were also measured with polysomnography (PSG), an array of physiologic measures to study sleep duration and quality, including central and occipital EEG, eye movement monitoring, muscle tension in several locations, ECG, airflow, respiratory rate,

FIBROMYALGIA

oxygen saturation, limb movements, and expired CO₂. The PSG was performed in an outpatient sleep laboratory overnight with sleep technologists. The entire battery of tests is arrayed on a computer monitor and sleep stages (wake, N1, N2, N3, and REM) are visually scored for 30-second epochs according to the criteria of Rechtschaffen and Kales (Berry, Geyer, & Carney, 2005). The PSG is the primary means of diagnosing obstructive sleep apnea (OSA). Apnea is defined as the cessation of airflow for at least 10 seconds; a decrease but not total cessation of airflow that lasts 10 seconds is considered hypopnea. Apnea-hypopnea index (AHI) is the average number of hourly apnea and hypopnea episodes found on PSG; an AHI greater than five events per hour is indicative of obstructive sleep apnea (OSA). Mild OSA is characterized by an AHI between 5 to 15 events per hour. Moderate OSA is diagnosed when AHI values range from 15 to 30. Severe OSA occurs when the AHI is above 30 (Guilleminault & Bassiri, 2005).

Fatigue was measured using the Brief Fatigue Inventory (BFI), which assesses fatigue severity and interference in daily life. It uses numeric rating scales from 0 to 10. Severe fatigue is a score of 7 or higher (Mendoza et al., 1999). The BFI has demonstrated reliability in clinical trials, ranging from 0.82 to 0.97 (MD Anderson website, 2010).

Cytokine samples were collected via peripheral venous blood samples obtained by sterile venipuncture using cell preparation tubes with sodium heparin. Plasma samples were analyzed using the Bio-Plex Plus® Human 17-Plex (Bio-Rad: Hercules, CA) multiplex magnetic bead assay system. The standardized 17-Plex kit includes coupled beads, detection antibodies, and standards for the detection of IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), interferon-gamma (IFN- γ), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 β (MIP-1 β), and TNF- α .

FIBROMYALGIA

Potential participants were recruited from the VCU Center for Sleep Medicine schedule of patients following initial screening for inclusion/exclusion criteria. Women who met the study criteria were given a verbal and a written explanation of the study. Those who agreed to participate met the investigator at the sleep center 90 minutes prior to the scheduled clinical sleep study. The participants consented in writing after a verbal review of the study, completed the study psychosocial measures, and then had a blood sample collected. After data collection, participants were compensated for their time with a \$25 gift card. Technologists conducted the PSG; a neurologist board certified in sleep medicine interpreted the PSG findings. If patients required titration of continuous positive airway pressure (CPAP) for sleep apnea, it was initiated per protocol. The blood sample was transported in a cold-pack biohazard container to the laboratory. All blood samples were centrifuged for plasma separation; specimens were aliquoted, frozen, and stored at -70° C until all samples had been collected and they were batch processed using standard procedures performed by a highly experienced technician.

Descriptive statistics of the demographic variables for the two groups were compared with means and *SEs* for continuous data and frequency distributions and percentages for categorical data. For the demographic variables, differences between the groups were assessed using two-sample *t*-tests for continuous data and Chi-square for categorical data. In Aim 1, it was hypothesized that the FMS group as compared to the non-FMS group would demonstrate significantly more autonomic symptoms, stress, fatigue, and sleep disturbance; lower HRV and sleep quality; and an altered ratio of pro- to anti-inflammatory cytokines. For Aim 2, Pearson's correlations among ANS activity, perceived stress, sleep quality, immune function (cytokines), and fatigue were explored within each group. It was hypothesized that different correlation patterns would be observed in the FMS group than the non-FMS group. To study Aim 3,

FIBROMYALGIA

construct validity of the ASP was explored by examining Pearson's correlations between ASP scores and HRV, arousals, and stages of sleep. Statistical analyses were performed using JMP 9.0, and significance set at $\alpha \leq 0.05$.

The two groups were compared on the basis of AHI. These data were not normally distributed and thus were log transformed. The groups differed significantly on the basis of log AHI, with 20% of the FMS group having OSA (mean = 0.95, $SE = 2.53$), while 80% of the non-FMS group had OSA (mean = 2.33, $SE = 0.28$, $p = 0.0008$). Hence, AHI was factored into ANCOVA testing by using log AHI, group, and group by AHI as model effects initially, then using only group and log AHI if the interaction between those two variables was not significant. Log AHI also was used as a covariate in the models used to test for significant group differences in ANS activity, perceived stress, sleep quality, immune function, and fatigue.

Findings

A demographic questionnaire was used to obtain information regarding age, height, weight, race/ethnicity, partner status, education, medical history, and socioeconomic status. As shown in Table 2, the two study groups did not differ significantly on the basis of age, weight, BMI, menstrual status, marital status, or income. The prevalence of hypertension and diabetes mellitus was not significantly different between the groups. There was a significant difference between the groups in their racial proportions. The non-FMS group was significantly more likely to have African American members. The FMS group women were significantly more likely to be disabled, and the non-FMS group was more likely to be employed.

FIBROMYALGIA

Table 2

Demographic Data

Demographic characteristic	Total N = 50	Non-FMS group	FMS group	Statistics
Age (Range 35-65)	52 (CI = 49-54)	52 (CI = 48-55)	52.5(CI = 49-56)	$p = 0.7$
Weight	200 (CI = 187-214)	208 (CI = 188-228)	193 (CI = 174-213)	$p = 0.27$
BMI	34 (CI = 32-36)	35.9(CI = 33-39)	32 (CI = 29-35)	$p = 0.09$
Race/ethnicity				
Caucasian	20	5	15	<i>Pearson's</i> $p = 0.0039^*$
African American	30	20	10	
Menstrual status				
Premenopausal	9	7	2	<i>Fisher's</i> $p = 0.138$
Postmenopausal	41	18	23	
Marital status				
Divorced	17	6	11	<i>Pearson's</i> $p = 0.1369$
Partnered	17	9	8	
Single	12	6	6	
Widowed	4	4	0	
Education				
8 th grade	8	6	2	<i>Pearson's</i> $p = 0.30$
High school	18	8	10	
College	24	11	13	
Work status				
Employed	38	12	7	<i>Pearson's</i> $p = 0.0316^*$
Unemployed	12	8	4	
Disabled	19	5	14	
Income				
Below 15,000	22	11	11	<i>Pearson's</i> $p = 0.96$
15,000-44,999	14	7	7	
45,000-89,999	7	4	3	
Above 90,000	7	3	4	
Hypertension	32	16	16	<i>Pearson's</i> $p = 1.0$
Diabetes	11	6	5	<i>Pearson's</i> $p = 0.73$

FIBROMYALGIA

Study Aim 1

The FMS group had significantly higher ASP scores than the non-FMS group. The mean ASP score was nearly twice as high for the FMS group (mean = 42, *SE* = 3.48, *CI* = 34.99-49) than the non-FMS group (mean = 23.8, *SE* = 3.48, *CI* = 16.79-30.81) ($p = 0.029$). No significant difference between the two groups was found on the basis of total PSS ($p = 0.26$). Both groups had elevated stress as compared to established norms. PSS mean score norms are 12.8 (*SD* = 6.2) for whites and 14.7 (*SD* = 7.2) for African Americans; for women in general the mean score is 13.7 (*SD* = 6.6) (Cohen, 1994). In the current study, the mean PSS for the FMS group was 21.9 (*SD* = 8.0, *CI* = 18.6-25.2); it was 19.1 (*SD* = 6.3, *CI* = 16.5-21.7) for the non-FMS group.

Both groups reported poor sleep quality but the FMS group had significantly higher PSQI scores (mean = 15.08, *SE* = 0.68, *CI* = 13.7-16.45) than the non-FMS group (mean = 11.24, *SE* = 0.68, *CI* = 9.86-12.61) ($p = 0.0011$). The FMS group also had significantly higher BFI scores (mean = 66.24, *SE* = 3.75, *CI* = 58.69-73.78) than the non-FMS group (mean = 44.92, *SE* = 3.75, *CI* = 37.37-52.46) ($p = 0.0006$). However, the groups did not differ significantly on the basis of sleep stages derived from PSG data, as reported in Table 3.

Table 3

Sleep by group

	FMS group			Non-FMS group			<i>p</i> -value
	Mean	<i>SE</i>	<i>CI</i>	Mean	<i>SE</i>	<i>CI</i>	
Total Wake Time	50.1	9.9	29.6-70.6	61.4	8.4	44-78.8	0.39
Total Sleep Time	627.7	240.9	130.4-1125	387.3	17.9	350.3-424.3	0.20
Non-REM: N1	20.8	2.4	15.9-25.7	25.4	2.6	19.9-3.9	0.40
N2	192.3	13.6	164.3-220.3	208.5	10.1	187.5-229.5	0.58
N3	106.4	12.5	80.6-132	314.6	240.4	-181.6-810.8	0.52
REM	68.2	7	53.7-82.7	74	6.7	60.2-87.9	0.35

FIBROMYALGIA

Arousals were scored according to the rules of the American Academy of Sleep Medicine (1992). As indicated in Table 4, arousals were not found to be significantly different on the basis of group status. Mean hourly arousal norms for healthy individuals aged 41 to 60 range from 14.9 to 16.2 (Bonnet & Arand, 2007). In this sample total arousals ($p = 0.002$) and respiratory arousals ($p = 0.0001$) were found to be elevated when increased Log AHI was high, however.

Table 4

Arousals by group

	FMS group			Non-FMS group			<i>p</i> -value
	Mean	<i>SE</i>	<i>CI</i>	Mean	<i>SE</i>	<i>CI</i>	
Total arousals	93	11.83	69-116	129	11.83	106-153	0.39
Spontaneous arousals	45	4.94	35-55	43	4.94	33-53	0.81
Limb-movement arousals	17	5.69	6-29	19	5.69	8-31	0.45
Respiratory arousals	31	9.84	11-51	67	9.84	47-87	0.57
Hourly arousals	15	2.14	11-19	20	2.14	16-25	0.42

Cytokine data were log transformed as they were not normally distributed. Of the 17 cytokine levels assayed, only IL-1 β and TNF- α varied significantly between the groups. The IL-1 β levels per group were not significantly different when log AHI was less than 1.6 ($p = 0.195$), but at 1.6 (equivalent to AHI of 5, the cut-off point for diagnosis of OSA), the non-FMS group had significantly higher IL-1 β levels than the FMS group ($p = 0.0486$). When log AHI was greater than 1.6, the difference was even more pronounced ($p = 0.00096$). For TNF- α , the FMS group had significantly higher log TNF- α values (mean = 0.907, $SE = 0.5047$, $CI = -0.11-1.925$) than the non-FMS group (mean = -0.436, $SE = 0.4721$, $CI = -1.389-0.516$) ($p = 0.0116$).

The FMS group demonstrated significantly lower SDNN as compared to the non-FMS group, as indicated in Table 5. However, SDNN had a significant group by Log AHI interaction such that SDNN declined as Log AHI increased in the non-FMS group.

FIBROMYALGIA

Table 5

HRV by group

	FMS group			Non-FMS group			<i>p</i> -value
	Mean	SE	CI	Mean	SE	CI	
RR interval	885.7	27.8	828.4-943	868.8	30.8	805.1-932.4	0.42
SDNN	97.4	14.3	67.8-126.9	148.6	46.3	53-244	0.014*
SDANN	136.3	24.9	84.8-187.7	78.5	12.7	52.3-104.8	0.133
pNN50	12.8	3.6	5.3-20.3	16.9	2.8	11-22.7	0.088
SDNN index	46.4	5.5	34.9-57.8	51	6	38.5-63.6	0.81

Study Aim 2

Pearson's correlation coefficients were calculated to determine if there were significant relationships among ANS activity, perceived stress, sleep quality, immune function (cytokines), and fatigue within each group. As displayed in Table 6 for the FMS group, the BFI was positively correlated with the PSS, the ASP, and TNF- α ; the PSS was also positively correlated with the ASP. AHI was correlated with total arousals and was negatively correlated with IL-1 β .

Table 6

FMS Group Correlations

	BFI	PSS	AHI	Arousal	RR	SDNN	PSQI	IL-1 β	TNF- α
PSS	0.4495*								
AHI	-0.1653	-0.0975							
Arousal	-0.2283	-0.3420	0.4008*						
RR	0.0645	-0.0395	-0.1595	-0.2478					
SDNN	0.1390	0.2570	0.1007	-0.1417	0.0762				
PSQI	0.0083	0.2052	-0.3041	-0.0537	0.0904	0.2554			
IL-1 β	-0.0672	0.0814	-0.4445*	-0.3347	-0.3297	-0.0093	0.4089		
TNF- α	0.4512*	0.2837	0.1809	0.3287	0.0079	0.3631	0.1781	-0.1525	
ASP	0.4122*	0.6628**	-0.2487	-0.3590	0.0286	-0.0647	0.1687	0.2926	0.1051

* $p \leq 0.05$. ** $p \leq 0.001$.

FIBROMYALGIA

In the non-FMS group (Table 7), the PSQI was positively correlated with the BFI and both were positively correlated with IL-1 β . IL-1 β was positively correlated with TNF- α . Total arousals were correlated with AHI and negatively correlated with mean RR interval. SDNN was correlated with RR interval and negatively correlated with AHI.

Table 7

Non-FMS Group Correlations

	BFI	PSS	AHI	Arousals	RR	SDNN	PSQI	IL-1 β	TNF-a
PSS	0.3505								
AHI	0.1583	0.0175							
Arousals	0.3666	0.0359	0.4511*						
RR	-0.0904	0.1638	-0.5876*	-0.4175*					
SDNN	-0.1033	0.2345	-0.6551**	-0.2605	0.7346**				
PSQI	0.4315*	0.2048	0.1277	-0.0889	0.0819	-0.0774			
IL-1 β	0.4980*	0.2195	0.2723	0.2186	0.0585	-0.1241	0.4274*		
TNF- α	0.2897	0.0417	0.3610	0.1903	-0.0927	-0.1907	0.2995	0.8462**	
ASP	0.3587	0.1145	0.1095	0.0698	0.0932	-0.1495	0.2526	0.3135	-0.0274

* $p \leq 0.05$. ** $p \leq 0.001$.

Table 8 displays the significant correlations contrasted for the two groups. Only the positive correlation of total arousals with AHI was shared by both groups. All other FMS group variables that were significantly correlated were different than the significant correlations found in the non-FMS group.

FIBROMYALGIA

Table 8

Significant correlations by group

Correlations	FMS	Non-FMS
PSS by BFI	0.4495*	0.3505
Arousals by AHI	0.4008*	0.4511*
RR by AHI	-0.1595	-0.5876*
RR by arousals	-0.2478	-0.4175*
SDNN by AHI	0.1007	-0.6551**
SDNN by RR	0.0762	0.7346**
PSQI by BFI	0.0083	0.4315*
IL-1 β by BFI	-0.0672	0.4980*
IL-1 β by AHI	-0.4445*	0.2723
IL-1 β by PSQI	0.4089	0.4274*
TNF- α by BFI	0.4512*	0.2897
TNF- α by IL-1 β	-0.1525	0.8462**
ASP by BFI	0.4122*	0.3587
ASP by PSS	0.6628**	0.1145

* $p \leq 0.05$; ** $p \leq 0.001$.

Study Aim 3

Pearson's correlation coefficients were calculated to determine the relationships among ASP scores, HRV, and sleep stages for each group. As noted above, the ASP did not have any significant correlations with Log AHI, total arousals, SDNN, or RR interval in either group. No significant correlation of the ASP with any HRV measure, arousal, or stage of sleep was detected, as indicated in Table 9.

FIBROMYALGIA

Table 9

ASP correlations by group

Variable	FMS	Non-FMS
SDANN	-.1448	0.0381
SDNN index	-0.1214	0.1584
pNN50	0.0920	0.1684
Spontaneous arousals	-0.2674	-0.0912
Hourly arousals	-0.3774	-0.1147
Non-REM: N1 sleep	-0.1649	0.2867
N2 sleep	-0.1004	0.1738
N3 sleep	0.2014	-0.0405
REM sleep	0.2178	0.2869

In summary, findings of this study indicated that the FMS group had significantly worse sleep quality, more autonomic symptoms, and greater fatigue than the non-FMS group; they also had higher TNF- α levels. The non-FMS group was significantly more likely to have OSA. Non-FMS participants who had OSA also had significantly higher IL-1 β values than the FMS group. Study variables that significantly correlated with each other in the FMS group differed from those seen in the non-FMS group, with the exception of the positive correlation of total arousals with AHI in both groups. In the FMS group, fatigue was positively correlated with perceived stress, autonomic symptoms, and TNF- α ; stress was positively correlated with autonomic symptoms; and AHI was negatively correlated with IL-1 β levels as well as the above noted correlation with total arousals. In the non-FMS group, sleep quality was positively correlated with fatigue, and sleep quality and fatigue were positively correlated with IL-1 β . IL-1 β also positively correlated with TNF- α . Total arousals were significantly correlated with AHI and significantly negatively correlated with mean RR interval. SDNN was significantly correlated

FIBROMYALGIA

with RR interval and significantly negatively correlated with AHI. The hypothesis tests related to construct validity of the ASP indicated no significant supportive correlations.

Discussion

Menzies et al. (2011) found that perceived stress significantly positively correlated with fatigue in their study of 50 participants with FMS. The results from this study are in accord with that finding. The additional strong positive correlation of fatigue and stress with autonomic symptoms in the FMS group adds additional support for the PNI framework characterized by those authors. Specifically, the type and degree of autonomic symptoms present in persons with FMS may be markers that reflect increases in perceived stress and fatigue, but the direction of any possible effect remains unknown.

In this study there was a significantly higher level of TNF- α in the FMS group as compared to the non-FMS group. This finding was unexpected because a previous meta-analysis found no significant differences in TNF- α levels between study participants with FMS and controls (Uceyler et al., 2011). Plasma levels of TNF- α have been consistently found to be elevated in the presence of OSA (Alberti et al., 2003; Sahlman et al., 2010; Vgontzas et al., 1997) and positively correlated with AHI in one study (Ciftci, Kokturk, Bukan, & Bilgihan, 2004). The positive interaction between TNF- α and Log AHI complicates this picture and cannot be accurately interpreted because this study lacked a normal control group.

There was a positive correlation with TNF- α and fatigue in the FMS group. This is also a unique finding; no significant correlations between FMS-related fatigue and TNF- α were found in at least two other studies (Menzies et al., 2011; Uceyler et al., 2006). No association between TNF- α and fatigue was found in the non-FMS group, which had lower TNF- α levels and less fatigue than the FMS group. It is therefore plausible that the increased TNF- α in the FMS group

FIBROMYALGIA

may be directly related to their greater experience of fatigue, independent of sleep quality as suggested by the lack of correlation in this group between sleep quality and fatigue.

It is unclear why the non-FMS group in the setting of higher AHI displayed significantly higher IL-1 β values than the FMS group. No significant differences in plasma IL-1 β between people with OSA and healthy controls have been found by some investigators (Alberti et al., 2003; Vgontzas et al., 1997). However, one study reported significantly lower serum concentrations of IL-1 β among people with mild OSA (AHI between 5 and 15) as compared to control participants, and in the participants with OSA, lower IL-1 β was associated with higher AHI (Sahlman et al., 2010). No differences in levels of IL-1 β have been previously reported in persons with FMS as compared to controls (Uceyler et al., 2006). In the current study IL-1 β significantly positively covaried with TNF- α , sleep quality, and fatigue in the non-FMS group even though fatigue and TNF- α were not significantly correlated with each other. IL-1 β was found to significantly negatively correlate with AHI in the FMS group, which is contrary to the findings in the non-FMS group, even though the non-FMS demonstrated higher AHI.

Four of the five HRV comparisons between the two groups did not display a significant difference in this study, in contrast to consistent findings of decreased HRV in study participants with FMS as compared to healthy controls in previous studies (Dadabhoy et al., 2008; Nilsen et al., 2007; Lerma et al., 2011; Chervin et al., 2009). However, SDNN, a marker of overall HRV, was significantly lower in the FMS group; this was found despite confounding of increased AHI in the non-FMS group in association with lower SDNN. Non-significant HRV findings for the FMS group also may be related to the high incidence of OSA in the non-FMS group. In healthy subjects nighttime EEG arousals are preceded by an increase in heart rate (HR). This effectively lowers the HRV as HR increases (Versace, Mozzato, De Min, Cavallero, & Stegagno, 2003).

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One might expect that increased numbers of arousals of any kind would therefore raise overall HR and decrease HRV. Patients with OSA have displayed decreased time- and frequency-domain HRV measures as compared to healthy individuals during wake time (Balachandran et al., 2012). The literature on this topic is inconsistent, however, with some studies indicating greater nighttime HRV in OSA, and others reporting no significant differences (Sforza, Pichot, Cervena, Barthelemy, & Roche, 2007).

Mean RR intervals did not negatively covary with arousals in FMS participants, as they did in the non-FMS group; this may support the notion of a defect in ANS activity in FMS. Both groups did display a similar arousal response to apnea episodes, as indicated by the significant association of total arousals with AHI. Interestingly, in the non-FMS group fatigue was correlated with poor sleep quality, but this was not found in the FMS group. In the FMS group, a heightened presence of autonomic symptoms (i.e., faintness, palpitations, GI instability, and blurred vision) was correlated with fatigue and highly associated with perceived stress. Perceived stress has been implicated in worsening sleep quality and fatigue for people with FMS, but the degree to which it initiates or reflects ANS stress arousal remains unclear; there was not a significant group difference in perceived stress detected in this study. It is still unknown which particular aspects of sleep in FMS, such as length of sleep stages or number of arousals, may be predictive of cytokine changes or resultant from them. Objective sleep measures did not capture any significant differences that might account for the poorer sleep quality reported by participants with FMS. This is consistent with the findings of Chervin et al. (2009), who found no objective markers of sleep disturbance specific for FMS.

These findings suggest a need to refine the postulated biobehavioral model of FMS as a response to a dysfunction of the ANS. Specifically, it may be that genetic predisposition,

FIBROMYALGIA

psychosocial experience, and behavioral cofactors interact in women with FMS to produce ANS changes that alter response to perceived stress and increase SNS predominance during sleep.

There is evidence that poor sleep quality may precede the onset of other FMS symptoms although this is highly controversial (Gupta et al., 2007; Mork & Nilsen, 2012). The SNS is viewed as persistently hyperactive, yet paradoxically hypoactive to stressors such as nighttime arousals, which may affect cytokine expression. Autonomic symptoms, including poor sleep quality, and perceived stress may lead to additional cytokine changes, all of which interact with the ANS in a circular fashion, resulting in generalized fatigue.

Conclusion

The implications for nursing research are that this study may shed light on the complex relationships of these variables in FMS in anticipation of formulating targeted nursing interventions for sleep symptom management. There is no regimen that alleviates FMS sleep symptoms consistently. Medications such as minalcipran, duloxetine, amitriptyline, and pregabalin have provided limited pain relief for some patients with FMS, which helps promote better sleep but is often not tolerated due to side effects (Hauser, Wolfe, Tolle, Uceyler, & Sommer, 2012). Sodium oxybate, a sleep agent approved for use in narcolepsy, was not approved by the FDA in 2011 for treatment of poor sleep quality in FMS, despite its reported efficacy in clinical trials.

Complementary and alternative therapies such as guided imagery are modalities that have been explored for FMS treatment in pilot studies and have shown promise for sleep symptom management (Menzies, Taylor, & Bourguignon, 2006). It is anticipated that such research efforts will continue. Future directions for research include randomized controlled trials of the effects of alternative modalities such as guided imagery or Reiki on autonomic symptoms as

FIBROMYALGIA

measured by the ASP, frequency-domain as well as time-domain HRV measures, and sleep quality in women with FMS.

Limitations

As a correlational study, inferences regarding causality cannot be made. A cross-sectional design does not capture changes that occur as a result of environment or other events that occur over time. The FMS group was not compared to healthy controls, but to individuals who had reported poor sleep quality, thus the differences between the two groups in this study are likely related to the high incidence of OSA in the non-FMS group (80%) as opposed to the FMS group (20%). The small subset of women who had both FMS and OSA may have unique characteristics not common to either group, but a detailed analysis of such a small number ($n = 5$) was not possible. This confounding factor must be addressed in future studies by the addition of a healthy control group. The use of any medications or continuous positive airway pressure (CPAP) therapy was not controlled because this was an observational study. Only one blood draw for cytokines was performed, and this was prior to the PSG; a second blood draw in the morning may have revealed more information. Finally, use of frequency-domain HRV measures in addition to time-domain measures in future studies might be more revealing as these have been reported to be more sensitive in differentiating persons with sleep fragmentation related to respiratory events (Sforza et al., 2007).

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Vita

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