

# **Biobehavioral Health Research:**

## **A nursing study of women with and without fibromyalgia**

**Carol A. Landis<sup>1)</sup>, Martha J. Lentz<sup>2)</sup>**

### **Biobehavioral Nursing Research**

Biobehavioral nursing research has been defined as "...the description of the relationships among biological, behavioral and social factors that affect health promotion, disease prevention and care during acute and chronic illness"(Cowan et al., 1993). This definition is consistent with the premise that better understanding of health and illness will occur with research that examines interactions among biological, behavioral, social and environmental dimensions affecting health outcomes.

Nursing educators and researchers have embraced a multivariate, biopsychosocial view of

human health and illness for many decades. As students in the 1960's we recall nursing care plans were organized around physical, psychological, and social 'needs' of patients. In the 1980's, nursing scholars began focusing on human responses to potential or actual health problems as one of the domains within nursing science. Shaver (1985) developed a biopsychosocial model of human health and vulnerability and along with colleagues at the University of Washington explicated a model that acknowledged the interaction of person and environmental factors in shaping human responses in health and illness (Heitkemper & Shaver, 1989; Mitchell et al., 1991). Human responses were cate-

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gorized into physiologic, pathophysiologic, experimental and behavioral aspects and viewed within a broad context of human ecology that emphasizes dynamic transactions between the person and the environment (Heitkemper & Shaver 1989; Mitchell et al., 1991; Shaver, 1985). In this model, 'risk' is attributed to environmental hazards and 'vulnerability' characterizes the individual or personal factors that interact with the environment to affect health (Rose & Killien, 1983). Person factors influence and, in part, determine individual vulnerability. For example, resistance and susceptibility to illness and altered function change over time as a function of age and development. Environmental factors establish the context, or risk, that challenges, supports or perturbs individual responses.

### HMR diagram

Basic knowledge about the processes or mechanisms that shape personal vulnerability is fundamental for understanding the nature of human responses, symptom expression, and relations among indicators of responses (e.g. physiological, experiential, behavioral) in health and illness. This knowledge is important for the development of new and for the appropriate use of existing therapies.

We conducted a study of fibromyalgia (FM) that is an example of biobehavioral nursing research framed, in part, within the individual human response model and focused on explicating processes and mechanisms that shape personal vulnerability, symptoms, and illness outcomes. This study was conducted in the late 1990's and the findings have been published in interdisciplinary journals and presented at scientific meetings. In this

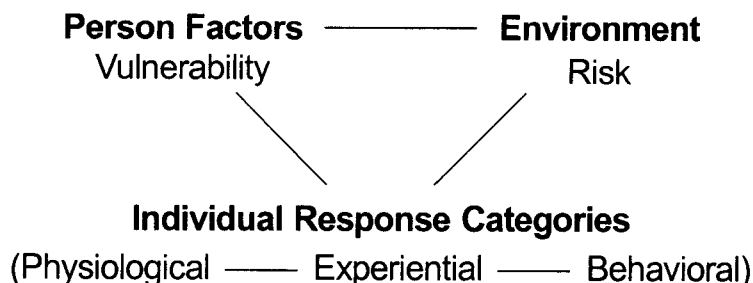


Figure 1. Individual Human Response Model modified from Heitkemper & Shaver, 1989; Mitchell, Gallucci & Faught, 1991. Individual responses are shaped by person factors that establish one's vulnerability and the environment or context, which is the source of risk. Individual responses are described by selected indicators within physiological, experiential and behavioral categories.

paper we provide a summary and review of the study findings framed from the perspective of the individual human response model and the specific conceptual framework developed from existing FM literature and our previous research. First, we provide background information about FM, an overview of the study framework and procedures. Second, we describe the findings from the study based on the main concepts in the conceptual framework. Finally, we review new findings that emerged during the course of the study and how those findings shaped are thinking to better understand the nature of sleep disturbance and the role that it plays in symptom expression in FM.

## **Fibromyalgia**

### Definition.

Fibromyalgia (FM) is a common cause of chronic, widespread pain. The case definition is a history of chronic, generalized aching of three months duration and the finding of pain (tenderness), during physical examination, in at least eleven out of eighteen discreet musculoskeletal points in nine paired regions of the body (Wolfe et al., 1990). Patients with FM also commonly report fatigue, sleep disturbance, and morning stiffness. FM is a chronic disabling disorder that tends to neither progress nor improve over time. Some individuals report improvement with pharmacological and behavioral therapies (Buchwald, 1996; Rossy et al., 1999; Whiting et al., 2002; Wolfe et al., 1997) but many continue to have significant complaints of pain and fatigue (Kennedy & Felson, 1996).

### Prevalence.

The prevalence of FM in the general adult population in the United States is estimated at 2-4 %, and the disorder also occurs in children and adolescents (Siegel, Janeway, & Baum, 1998). The prevalence is much higher in women and increases with age (Wolfe et al., 1995). A greater sensitivity to pain compared to men may render women more vulnerable to develop FM (Pillemer et al., 1997). Higher prevalence rates have been found among female offspring (Buskila et al., 1996) and relatives (Buskila & Neumann, 1997) of individuals with FM. FM has been described as an illness predominately of 'middle aged White women' (Buchwald, 1996), but this observation may reflect the population density of people in localities where a preponderance of research studies on FM have been conducted in the US and Europe (Croft et al., 1993; Hencriksson & Burckhardt, 1996; Wolfe et al., 1997).

### Associated Conditions.

Individuals with FM are likely to suffer from co-morbid conditions such as irritable bowel syndrome, multiple chemical sensitivity, temporomandibular joint disorder, myofascial pain syndrome, tension headache, Gulf War illness, chronic sinusitis, and interstitial cystitis (Clauw & Chrousos, 1997; Clauw & Crofford, 2003). Psychological distress, anxiety and depressed mood are common and a history of psychiatric disorders renders individuals more vulnerable for FM (Goldenberg, 1999). A specific polymorphism in the 5-HT<sub>2A</sub> receptor gene (Bondy et al., 1999) and the serotonin transporter gene (Offenbaecher et al., 1999) have been linked to FM, and may predispose individuals with FM to develop psychiatric symp-

toms (Gursoy et al., 2001).

### Pathogenesis and Pathophysiology.

The etiology and pathogenesis of FM is not known. In about 50% of those diagnosed, symptoms develop in the absence of any prior medical condition. However, symptoms of FM often follow an infection or traumatic psychological or physical event. A general model of the pathogenesis of FM has emerged in recent years that susceptible individuals have a predisposition or genetic background that renders them highly sensitive to 'triggering events' such as an illness or a psychological or physical trauma. This event or series of events activates mediators involving central nervous system (CNS) networks related to pain processing and modulation, along with neuroendocrine, autonomic, and immune systems such that symptoms of the primary illness persist, never completely resolve, or new symptoms develop (Clauw & Chrousos, 1997; Clauw & Crofford, 2003).

### **Conceptual Framework for Biobehavioral Nursing Study of FM**

Sleep disturbance is a particular troubling and disabling symptom in FM, but it is considered secondary to CNS mediated pain or dysregulated stress responses. Unlike most painful conditions, which are relieved by sleep, individuals with FM consistently report poor and nonrestorative sleep with intensified muscle aching upon awakening. The most commonly mentioned changes in sleep physiology are alpha wave (waking pattern) intrusion into delta (slow wave or deep) sleep (Moldofsky et al., 1975) and lighter, more frag-

mented sleep that reflects sleep state instability and used as evidence of arousal in sleep (Jennum et al., 1993; Molony et al., 1986; Shaver et al., 1997). The original framework for the study was based on a pathophysiological model of FM that postulated CNS changes lead to peripheral changes and symptoms (Figure 2). This model was based on evidence in the literature (as of the mid-1990's) and on our prior study of women with FM-like symptoms (Shaver et al., 1997). A low CNS level of serotonin (platelet model of central 5-HT) was postulated to lead to 'aroused sleep' as indicated by increased wakefulness, an alpha electroencephalograph (EEG) pattern, and fragmented NREM sleep. Dysregulation of nocturnal hormones (e.g., decreased GH, increased PRL, increased ACTH & reduced cortisol and melatonin) during sleep was thought to reflect altered circadian timing. Based on what was known about FM and the peripheral effects of these hormones on muscle and other peripheral tissues, it was postulated that these altered central changes would give rise to altered physiologic [e.g., low levels of urinary cortisol and serotonin (5 hydroxyindolacetic acid, 5-HIAA); altered immune function (e.g., hyperemia, natural killer cell activity)] and self-reported [e.g., pain (tender points), nonrestorative sleep, fatigue, psychological distress] outcomes (Shaver, Lentz, & Landis, 1995).

## FM-CF

### Synopsis of the Procedures and Findings from the Biobehavioral Nursing Study of FM

#### Procedures.

The details of the methods and procedures used in our study and the results have been published in a series of papers (Landis et al., 2001; Landis et al., 2003; Landis et al., 2004b; Landis et al., 2004c). In brief, we studied a group of symptomatic middle-aged women with FM (n = 37) recruited from a tertiary medical center setting and compared them to a

group of healthy sedentary women (n = 30) of similar age who were recruited from the community. All women completed a daily symptom diary for one month prior to and during the study. Women with FM were weaned from hypnotic, analgesic, or antidepressant medications and drug free for two weeks prior to the sleep study. All the women wore an actigraph for recording wake and sleep (activity) patterns for 3 days prior and 3 days during the laboratory study. They underwent psychiatric interviews, completed psychological instruments, had pain tender points assessed, and polysomnographic sleep recorded for 3 consecutive nights in a laboratory setting. Urine samples for 24 hours were obtained on day 2 blood samples were obtained the morning

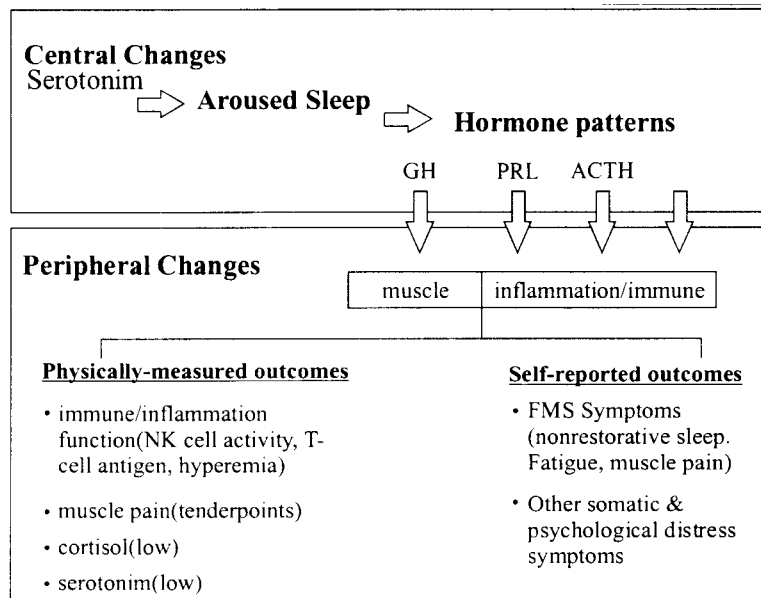


Figure 2. Conceptual Framework for the Nursing Study of Fibromyalgia. Changes in the central nervous system were thought to lead to changes in peripheral tissues and to symptoms. This figure was modified from Shaver et al., 1995. GH = growth hormone, PRL = prolactin, ACTH = adrenocortropin hormone, NK = natural killer.

after night 2, and before and during sleep on the third night for immune and hormone assays, respectively.

### Results.

As expected compared to women of similar age, women with FM reported more pain, sleep disturbance, fatigue and had higher psychological distress and depression scores (Landis et al., 2003; Landis et al., 2004c), and a higher mean (17 out of possible 18) number of positive tender points indicative of severe FM. Despite these differences in symptoms and mood, few differences in physiological outcomes were observed between groups. In particular, we found evidence for reduced circulating levels of GH and PRL (Landis et al., 2001), but we did not find evidence for dysregulation of hormones of the hypothalamic-pituitary-adrenal axis (HPA) during sleep. There were no group differences in nocturnal circulating levels of ACTH or cortisol (Landis et al., 2004a; Lentz et al., 1999b), or in the 24 hour urinary output of cortisol (Landis et al., 2004c). We failed to see obvious differences in the pattern of nocturnal hormones that indicated altered circadian rhythm timing as an important link to symptom expression. In addition, melatonin, platelet serotonin and urinary 5-HIAA levels were not different between groups (unpublished observations). Finally, we failed to find evidence of significant group differences in outcomes of altered immune function (e.g., hyperemia or natural killer cell function) (Landis et al., 2004c).

One of our main interests was in obtaining a better understanding of sleep disturbances with evidence of EEG arousal biomarkers and the role of arousal in symptom expression. Similar to our preliminary study of women with FM-like symptoms

(Shaver et al., 1997), we found no evidence for group differences in arousal biomarkers (e.g. EEG alpha activity during sleep), but we also did not find evidence for a fragmented sleep pattern during the first half of the night. Compared to control women, women with FM had slightly longer sleep latency, lighter stages of sleep, and were awake more during the night while in the sleep laboratory, but these changes in polysomnographic sleep in FM were modest compared to self-reported poor sleep quality (Landis et al., 2004c). Further, we found no differences between patients and controls in actigraphy derived wakefulness after sleep onset, sleep efficiency (total sleep time/time in bed), total sleep time or fragmentation index studied over 3 days at home (Landis et al., 2003). We found that self-reported sleep quality was directly related to actigraphy-derived indicators of total sleep time and inversely related to sleep fragmentation in the women with FM, but not in the controls. Furthermore, fatigue the next day was directly correlated with amount of wake after sleep onset and inversely related to sleep efficiency. Thus, disturbed sleep probably contributes to fatigue in FM and actigraphy may be a sensitive objective indicator of sleep quality.

### **Rethinking the Framework with New Findings**

In our original model, we postulated that altered central 'arousal' mechanisms from pain and dysregulated neuroendocrine activity were key factors in symptom expression in FM. We thought that biomarkers of arousal (e.g. serotonin deficiency, alpha activity in sleep EEG, fragmented sleep) along with altered timing of neuroendocrine hormone patterns during sleep, particularly ACTH and cortisol, the

hormones of the HPA axis, would be abnormal. However, we found no evidence for abnormal EEG arousal biomarkers or for dysregulation of neuroendocrine HPA hormones. Instead we found reduced amounts of sleep-related GH and PRL, which are secreted in higher amounts during sleep than during wakefulness in the daily cycle. The clinical significance of lower levels of sleep-related hormones, GH and PRL, in FM is not known. However, prolactin has anxiolytic behavioral effects and been shown to attenuate HPA responsiveness to stress activation (Torner et al., 2001). Activation of the stress response is usually thought to lead to sleep disturbance, but disturbed sleep with altered neuroendocrine during sleep could contribute to altered regulation of the stress response in FM. Thus, abnormalities of the HPA stress response that have been reported in FM (Clauw & Chrousos, 1997; Clauw & Crofford, 2003; Pillemer et al., 1997) may be influenced by dysregulation of sleep-related hormones.

Because we found no evidence for abnormal EEG arousal and because we found that actigraph-derived poor sleep was related to sleep quality and fatigue in FM, we looked for other biomarkers of abnormal sleep physiology. We chose to quantify sleep spindle activity, an EEG biomarker considered important for the induction and maintenance of NREM sleep (Steriade et al., 2000). We found that women with FM had more pain and fewer mean spindles per minute and per epoch of NREM stage 2 sleep compared to controls (Landis et al., 2004b), but we found no differences in delta or slow wave activity (Lentz et al., 2003). We also reported that pain pressure threshold predicted spindle incidence and time in NREM sleep, after controlling for age and depression, two variables associated with fewer sleep spindles. Reduced spindle activity also has

been reported in nondepressed patients with chronic low back pain (Harmon et al., 2002). It is plausible that reduced spindle activity could reflect altered pain processing at the level of the thalamus, which is a critical component of sleep continuity mechanisms. Rather than altered pain processing linked to altered 'arousal' mechanisms, as we originally maintained, deficits in 'sleep' mechanisms in the thalamus may be impaired in FM and in other chronic pain conditions. One practical implication of our findings for patients with FM is that sleep would be more easily disturbed both by endogenous and environmental stimuli. Sleep-related benefits associated or derived from the mechanisms underlying spindle activity also could be dampened. Since age is associated with reduced sleep spindle incidence and spindle power, older women with the pain of FM may be particularly vulnerable to sleep disturbing stimuli.

Pain, sleep disturbance, and fatigue are disabling symptoms in FM. Sleep disturbance is viewed as perpetuating FM symptoms of pain and fatigue, rather than as predisposing or precipitating factors that alter an individual's vulnerability to illness onset. Yet, in our sample about 50% of patients in our study associated the onset of FM symptoms after trauma, surgery, or an infectious illness when sleep is likely to have been disturbed. Griffins and Peerson (2005) recently reported nearly a doubling of insomnia symptoms three months after elective surgery and hospitalization that was associated with dysfunctional beliefs and attitudes about sleep and poor sleep hygiene. Whether persistent insomnia after trauma or an infectious illness places individuals at greater 'risk' to develop FM has not been reported in prospective studies and this is an important question for future studies.

## Concluding Comments

Based on the results of our biobehavioral study of FM, we maintain that changes in sleep mechanisms are an important aspect of altered CNS processing along with pain and neuroendocrine function that underlies symptom expression. Furthermore, changes in sleep mechanisms render individuals more vulnerable to the development of or to an exacerbation of FM symptoms. For many patients with FM, sleep disturbance coupled with reduced amounts of sleep related hormones renders them more vulnerable to environmental risks. Therapies targeted directly to improve sleep are likely to improve symptoms and health outcomes in FM.

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Abstract

## **Biobehavioral Health Research: A nursing study of women with and without fibromyalgia**

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Biobehavioral nursing research is focused on generating knowledge that examines relations among biological, behavioral, and social dimensions of health to improve outcomes. In this paper we review the findings of a biobehavioral nursing study of individuals with fibromyalgia (FM) that was framed from the perspective of an individual human response model, the FM literature, and our previous studies in midlife women. We were particularly interested in the studying the role of 'arousal' secondary to pain or to dysregulated hypothalamic-pituitary-adrenal (HPA) axis hormones during sleep and the impact on symptom expression. Unexpectedly, we did not find evidence of 'arousal' or abnormal amounts of HPA axis hormones but we did find reduced amounts of growth hormone (GH) and prolactin (PRL) and of sleep spindle activity, a biomarker of sleep maintenance. We discuss these new findings and how our thinking was re-shaped to better understand the role that disturbed sleep plays in symptom expression in FM. It is argued that disturbed sleep maintenance mechanisms coupled with dysregulated somatotrophic-growth hormone axis and sleep-related PRL render individuals vulnerable to the development of or exacerbations of FM symptoms.

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