

ABSTRACT OF DISSERTATION

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SLEEP DISTURBANCES AND SLEEP QUALITY IN WOMEN WITH
FIBROMYALGIA

ABSTRACT OF DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Nursing
at the University of Kentucky

By Suzette L. Scheuermann

Lexington, Kentucky

Director: Dr. Lynne Hall, Professor of Nursing

Lexington Kentucky

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The purpose of this dissertation was to explore the complaint of poor sleep quality in women suffering with fibromyalgia. Up to 80% of people with fibromyalgia complain of poor sleep quality in addition to musculoskeletal pain, fatigue, and other somatic symptoms. Using limb actigraphy and sleep diaries, an examination of sleep quality and circadian rhythm was performed with 50 women volunteers over at least one week. Impact from fibromyalgia was measured using the Fibromyalgia Impact Questionnaire. While the sleep times of these women were not grossly disturbed, their complaints of poor sleep quality, difficulty falling asleep, and difficulty staying asleep are indicative of insomnia. Results suggest that women with fibromyalgia may be altering their circadian rhythm to adapt to their disease.

KEYWORDS: Fibromyalgia, Fibromyalgia Impact Questionnaire, Actigraphy, Sleep Diaries, Circadian Rhythm

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Director of Dissertation

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This dissertation is dedicated to my husband, Jim Scheuermann, and my sons Brian and Cory Sewell, who unconditionally supported me through this pursuit of knowledge. With their encouragement, I have overcome mountainous obstacles and found my way.

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CHAPTER ONE

Introduction

The purpose of this dissertation was to explore the complaint of poor sleep quality in women with fibromyalgia. Although remarkable progress has been made in understanding sleep, the assessment of sleep disturbances in medical conditions like fibromyalgia remains symptom based. Fibromyalgia (FM) is a common musculo-skeletal disorder characterized by widespread non-articular pain, tender points, stiffness, and fatigue (Wolfe, Ross, & Anderson, 1995). It is the second most common disorder seen by rheumatologists (Rooks & Katz, 2002) and affects approximately 2% - 4% of the population in the United States (Puttick, 2001; Schachter, Busch, Peloso, & Sheppard, 2003). Almost 80% of patients with FM report un-refreshed sleep, sleep disturbance, or insomnia (Klerman, Goldenberg, Brown, Maliszewski, & Adler, 2001; Landis et al., 2003; Menefee et al., 2000; Wolfe et al., 1995). Although sleep disturbance is not considered part of the diagnostic criteria for FM (Landis, Lentz, Rothermel, Buchwald, & Shaver, 2004), this symptom is mentioned frequently as a concurrent problem in these persons (Hakkinen, Hakkinen, Hannonen, & Alen, 2001; Ramsay et al., 2000; Rooks & Katz, 2002; Schachter et al., 2003; Schaefer, 1995; Shaver, Lentz, & Landis, 1997). Poor quality sleep can result in muscle aches, fatigue, trouble with concentration and other somatic complaints, similar to those found in people with circadian rhythm disturbances (CRSD) like jet lag or night shift work (Klerman, Gershengorn, & Kronauer, 2002; Klerman et al., 2001; Schaefer, 2003). It is possible that sleep disturbances are linked to the widespread pain and fatigue of FM and that improvement in sleep efficacy would result in a reduction of these symptoms (Schaefer, 2003).

Sleep disturbance and FM contribute to social and economic issues that have a major impact on quality of life (Annemans et al., 2003; Huber, Suman, Biasi, & Carli, 2008). Care of patients with FM creates diagnostic and treatment challenges for health care professionals and consequently, care may be more costly and time consuming (Robinson et al., 2003; Rutledge, Jones, & Jones, 2007). Even though persons with FM are frequent users of medical services, their symptoms remain stable over time (Dobkin et al., 2003). One study conducted in 1996 showed that the direct medical cost per patient exceeded \$2,200 per year (Wolfe et al., 1997a). This amount increased to \$5945 in 2003 (Robinson et al., 2003). In this study, the economic cost of FM was twice as much as that of the typical beneficiary (\$2486). Other research has shown a decrease in family income for persons with FM with the same sample receiving aid from social security greater than that of the US population (Martinez, Ferraz, Sato, & Atra, 1995). Other reports have shown that as many as quarter of patients have FM associated disability (Wolfe et al., 1997b). Hidden cost of disability and the lost productivity to employers and individuals greatly increases the burden of FM. Research has shown that employees with FM had more claims than those with osteoarthritis for psychiatric diagnoses, chronic fatigue, and pain conditions, but the prescription drug use was similar (White et al., 2008). Often, the person suffering from FM may frequently present to their health care provider over a long period with various symptoms before the actual diagnosis of FM is made (Annemans et al., 2003).

FM is associated with psychosocial distress as well as physical distress, which may be a manifestation of depression or anxiety (Callahan & Blalock, 1997; Verbunt, Pernot, & Smeets, 2008). Co morbid depression may contribute to fatigue and sleep

disturbance, which in turn may cause persons with FM to have more severe impairment of their health status (Bergman, 2005; Niccassio, Moxham, Schuman, & Gevirtz, 2002). Verbunt, Pernot, and Smeets (2008) found that quality of life and perceived disability in persons with FM was influenced by their mental health condition and that their psychological distress was higher compared to persons with complex regional pain syndrome or chronic low back pain.

Others have pointed out that depression itself may be the cause of FM symptoms like fatigue, pain, and poor sleep quality (Russell, 2001). However, this conclusion may not be defensible in that not all patients with FM meet the diagnostic criteria for depression despite the majority of them having poor sleep quality and other somatic symptoms. Patients with depressive symptoms and body pain experience significantly more complaints of pain than those with pain alone (Greenberg, Leong, Birnbaum, & Robinson, 2003). One study estimated that FM is experienced by 22 – 45% of current depression sufferers (Epstein, et al, 1999).

Even though depression and fibromyalgia share similar presentations like reduced concentration, pain, headaches, and insomnia, etc., neither depression or FM may be diagnosed immediately due to the multiple physical and psychiatric symptoms that the person presents to their healthcare provider. Further, people with FM and depression may fail to seek specific treatment for their condition until it affects their quality of life, social and physical relationships, and physical function, which in turn adds to their economic burden.

There are several reasons for this. Individuals may not realize that they need treatment. They may consider that their symptoms are a consequence of aging or they

may not be able to afford treatment. They may deny the need for treatment due to stigmatization, or they may believe that it will not help them, especially if they have had several visits with their healthcare provider without the symptoms improving. However, until standard guidelines for the treatment of FM are established, a positive diagnosis and effective symptom management are the only mechanisms that can help reduce physical distress, psychological distress, sleep disturbance, and possibly decrease healthcare utilization related to this condition (Carville, et al., 2007).

Research on sleep disturbance in persons with FM has focused mostly on alterations in sleep stage, specifically, disturbance in non-rapid eye movement (NREM) sleep by alpha wave intrusion measured during polysomnography (PSG) (Anch, Lue, McClean, & Moldofsky, 1991; Moldofsky, Scarisbrick, & England, 1975). Moldofsky and Lue (1980) proposed that sleep disturbances in FM occurred from alpha wave intrusion on delta sleep (slow wave sleep) resulting in the participant not reaching phases of non-rapid-eye-movement sleep (NREM). Alpha waves are brain-generated electrical activity noted on electroencephalograms (EEG) conducted during PSG (sleep study), that are associated with wakefulness after sleep onset. Their presence is postulated to interrupt NREM sleep and reduce rapid-eye-movement (REM) sleep. During normal sleep, NREM cycles occurs over 90 –110 minutes with REM sleep increasing with each cycle (Beck, 1988). Adequate NREM sleep is theorized to improve physiological restoration, where as REM sleep appears important for restoration of mind and emotions (Schaefer, 1995).

Jennum et al. (1993) concluded that subjects with FM have higher rates of sleep arousal related to alpha intrusion, compared to that of normal controls. These vigilant

arousals, according to investigators, were associated with daytime feelings of un-refreshed sleep including musculo-skeletal stiffness, pain, and fatigue. Other research, however, has challenged these findings as a cause of sleep disturbance exclusive to FM as it was noted that healthy research participants with alpha delta sleep also reported musculo-skeletal aching, stiffness, and un-refreshed sleep (Lentz, Landis, & Rothermel, 1999; Paiva & Branco, 2002; Schneider-Helmert, Whitehouse, Kumar, & Lijzenga, 2001). It is possible that hypersomnolence and sleep fragmentation is related in some manner to more severe FM symptoms, although evidence of this has been limited.

Hypersomnolence is the experience of being sleepy during the day and experiencing the desire to take a nap or sleep longer than the usual eight hours due to sleepiness, tiredness, or fatigue (Punjabi, et al., 1999). The Multiple Sleep Latency Test (MSLT) is the most commonly used diagnostic test used to evaluate daytime sleepiness. In the absence of sleep disordered breathing (SDB), sleep disruption and sleep fragmentation have been shown to produce daytime sleepiness. Daytime sleepiness in persons with FM has been linked to greater severity of symptoms from FM (Sarzi-Puttini, Rizzi, & Andreoli, 2002). This research showed that persons with hypersomnolence and FM had significantly greater nocturnal arousals per hour (10 versus 6, $p = .01$), more tender points (15 versus 12, $p = .01$), higher pain scores (72 versus 52, $p = .05$), and greater fatigue (80 versus 62, $p = .05$) compared to the FM group without hypersomnolence. Decreased sleep efficiency, reduced total sleep time, reduced time in stage III & IV, and higher percentages of periodic breathing characterized the FM group complaining of hypersomnolence. While nocturnal arousals were associated with hypersomnolence in these patients, their frequency was much lower than that

demonstrated in sleep disordered conditions frequently associated with SDB, e.g. obstructive sleep apnea, upper airway resistance syndrome. This finding may be explained several ways.

One perspective is that the usual criteria applied to patients with SDB may not be applicable in sleep-disturbed persons with FM. Typically, respiratory effort related arousals (RERA) noted on polysomnography are associated with increasing respiratory effort and progressively more negative esophageal pressure terminating in an arousal that lasts longer than 10 seconds (ASDA/SRS, 1992; Kushida et al., 2005). Moderate frequency of apneic episodes is those occurring greater than 15 per hour (Sewell-Scheuermann & Phillips, 2006). However, body pain may also cause arousals and periodic breathing that do not meet this criteria and yet have the same fragmenting impact on sleep. Another perspective may be that persons with FM may over report symptoms of sleep disturbance and under-estimate their actual sleep time, which has been reported in the literature as sleep time misconception (Edinger & Fins, 1995). Unfortunately, previous research has not provided sufficient information to resolve this distortion. Even though self-reported sleep estimates were lower than actual sleep times, up to 20% of the participants produced overestimates of their actual sleep time (Sarzi-Puttini, Rizzi, & Andreoli, 2002). It is possible that other underlying disorders may be causing sleep fragmentation resulting in an experience of non-refreshing sleep by persons with FM (Sewell-Scheuermann & Phillips, 2006).

According to Schneider-Helmert et al. (2001), sleep disturbances are classified into two types: trouble falling asleep (prolonged sleep latency) and trouble staying asleep (wakeful arousals after sleep onset); both resulting in a reduction of estimated sleeping

time. Carette et al. (1995) found that subjects with FM had a significantly longer sleep latency time than that of nine control subjects. Cote (1997) however, found no significant differences in sleep latency in subjects with FM compared to controls; but subjects with FM reported having higher incidences of insomnia, pain, fatigue, and mood disturbance over that of controls.

Epidemiological and clinical research has demonstrated that a relationship exists between normal sleep and physiological homeostasis (Drewes, 1999; Perlis, Giles, & Bootzin, 1997). Correspondingly, sleep fragmentation and disturbances in sleep structure like these may relate to increased morbidity of FM; and possibly influence the impact of FM and other diseases (Smith, Perlis, & Smith, 2000). What still remains unclear from these investigations is whether trouble falling asleep and trouble staying asleep are the only classifications of sleep disturbance in persons with FM and whether current criteria for SDB are applicable for sleep disturbances experienced by persons with FM.

Sleep logs and polysomnography (PSG) have demonstrated sleep fragmentation with hypersomnolence in persons with FM, but research using the less invasive actigraphy has not been used as frequently and may not be a sensitive marker to these difficulties. It is unknown whether complaints of disturbed sleep in FM are associated with a sleep structure problem, perceived poor sleep quality (sleep state misconception), or a circadian rhythm sleep disturbance (CRSD) or whether actigraphy is sensitive enough to determine the source of these complaints.

Several different methodologies exist in the determination of sleep times: the actigraph, sleep logs, and PSG. Polysomnography collects information on multiple variables including electrocardiography (ECG); electroencephalography (EEG);

electrooculography (EOG); electromyography (EMG) including chin movement, limb movements, and respiratory effort (thoracic and abdominal motion); percutaneous oximetry (SPO2); body position; nasal pressure and airflow; and sound recording of snoring (snorogram). Polysomnography requires the participant to sleep in a sleep laboratory overnight, which may potentially alter the routine or schedule of the person being studied. The results require scoring by an expert in sleep medicine to determine the sleep times and pertinent events that may point to alterations in sleep architecture and pathophysiology (Sewell-Scheuermann & Phillips, 2006).

Sleep diaries collect sleep times by participant self-report and require the participant to remember to complete the diary daily and accurately. Participants may also be less than adherent to completing the diary and either not complete it or complete it right before presenting it to their healthcare professional. While sleep diaries are easy to use, the diary may not accurately reflect the actual number of awakenings at night, the time it takes for the participant to fall asleep, or actual time spent asleep.

Actigraphy uses algorithms that estimate the same sleep times determined by sleep diaries and PSG, but does so using sophisticated algorithms that convert limb motion into measures of sleep/wake. Actigraphy is non-invasive and does not require the participant to sleep in a lab or give up their routines. However, it may not be able to determine when someone is laying quietly awake versus being asleep or when someone is moving but still asleep. All the methods have been used previously in the study of persons with FM. The examination of sleep in persons with FM requires a sensitive measure to solve the mystery of poor sleep quality in FM.

Purpose, Specific Aims, and Hypotheses

The purposes of this dissertation were to: (1) explore the subjective and objective experience of poor sleep quality in women diagnosed with FM; (2) review the general principles of circadian rhythm sleep disturbance and discuss the accumulated evidence about circadian rhythm sleep disturbance, assessed using limb actigraphy, in persons with fibromyalgia; (3) evaluate the psychometric properties of the Fibromyalgia Impact Questionnaire; (4) determine the degree of concordance of sleep times estimated over 7 days using actigraphy versus a sleep diary; (5) compare four statistical methods for quantitatively determining average circadian period; and (6) to identify factors that predict the impact of fibromyalgia.

Overview of Dissertation

The review of literature presented in chapter two pertains to the exploration of circadian rhythm sleep disturbance and its assessment in persons with FM using actigraphy. The growing literature on the use of actigraphy has led to its inclusion as a guideline measure according to the American Academy of Sleep Medicine (AASM), for determination of sleep duration and specific types of circadian sleep patterns (Carvalho-Bos, Waterhouse, Edwards, Simon, & Reilly, 2003; Morgenthaler et al., 2007). Despite these recommendations, few publications on the procedural issues of using limb actigraphy to determine circadian rhythm and periodicity exist (Sack et al., 2007a, 2007b). In this review, the types of CRSD are discussed and issues related to the reliability of sleep logs and actigraphy to examine circadian rhythm are discussed. In addition, various methods of determining circadian period quantitatively are summarized.

Chapter three is devoted to a literature review of existing research and an examination of the psychometric properties of the primary instrument used to measure impact from fibromyalgia, the Fibromyalgia Impact Questionnaire. The factor structure of the Fibromyalgia Impact Questionnaire is explored using principle components analysis and convergent validity is examined.

Chapter four examines the discrepancies that may exist in estimates of sleep times obtained from actigraphy compared to sleep diaries. Cronbach's alpha was used to examine internal consistency of the sleep times obtained using the sleep diary and actigraphy. Pearson's correlation and paired sample *t* testing was used to evaluate stability and the level of agreement between the two methods.

Data analysis in circadian rhythm physiology involves an examination of both graphical and numerical data that are used to characterize the mean or mesor, amplitude (peak oscillation), acrophase (timing of peak), and period of the circadian biorhythm (Refinetti, 1993). Chapter five provides an illustration of these parameters and compares the products obtained by four methods for quantifying circadian period (Cugni, 1993).

Chapter six identifies factors that predict FM impact. Lastly, chapter seven concludes with a summary of this research, the results of hypotheses testing, and the contributions of this dissertation to the science of sleep.

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CHAPTER TWO

Actigraphy and Circadian Rhythm Sleep Disturbance (CRSD) in Persons with Fibromyalgia (FM)

Fibromyalgia (FM) is a disorder of unknown etiology affecting approximately 7 million Americans or 2-4% of the population (Hughs, 2006). Fibromyalgia is a pain syndrome characterized by widespread non-articular pain and other clinical manifestations such as fatigue, migraines, sleep disturbance and irritable bowel syndrome (Bennet, 2005). Diagnostic criteria established by the American College of Rheumatology (ACR) define FM as pain for at least three months involving three or more quadrants of the body including an axial distribution. Fulfillment of these criteria require 11 of 18 specified tender points to be painful using a pressure of 4 kg (Wolfe et al., 1990) (See Table 2.1).

FM may represent an altered function of the central nervous system that influences pain sensitivity, musculoskeletal and neuroendocrine functions, and mechanisms of sleep. Non-restorative sleep has been proposed as a hallmark of FM with as many as 78% of patients with FM reporting sleep disturbance (Schaefer, 2003; Wolfe, Ross, Anderson, Russell, & Herbert, 1995). Many of the symptoms experienced by persons with FM are similar to those observed in persons with sleep disturbances related to circadian rhythm disorders, e.g. jet lag or shift work (Klerman, Goldenberg, Brown, Maliszewski, & Adler, 2001).

Circadian rhythm sleep disorders (CRSD) are shifts in the timing of onset of sleep and the onset of wakefulness that are accompanied by symptoms of sleepiness, impaired concentration, cognitive dysfunction, and other somatic symptoms (Sack et al., 2007a).

Circadian rhythm disorders should be considered in persons who present with symptoms of insomnia, early awakenings, or hypersomnia when other conditions have been ruled out (Lu, Manthena, & Zee, 2006).

Widespread pain and enduring fatigue associated with FM may be a response to a chronic sleep disturbance or may initiate sleep problems that result from CRSD. This relationship remains unknown. Prolonged symptoms or somatic complaints should prompt a search for underlying sleep, psychiatric, or neurological disorders. Therefore, the purposes of this paper are to review the general principles of CRSD and to discuss the accumulated evidence of CRSD assessed using activity based actigraphy in persons with fibromyalgia.

Although remarkable progress has been made in understanding sleep and circadian rhythms, both biologically and behaviorally, clinical assessment and treatment of sleep disturbances in medical conditions like FM remains symptom based. Management of sleep complaints in FM typically involves a three-prong approach: medication to reduce symptoms and induce sleep, physical therapy to increase exercise, and cognitive therapy to improve sleep hygiene and decrease or eliminate bad habits like smoking, overeating, and using excessive caffeine (Schaefer, 2003).

Sleep disturbance and FM contribute to social and economic issues that have a major impact on quality of life. Care of patients with FM creates diagnostic and treatment challenges for health care professionals and consequently, care may be more costly and time consuming (Robinson et al., 2003). Even though persons with FM are frequent users of medical services, their symptoms remain stable over time (Dobkin et al., 2003). The hidden cost of disability and the lost productivity to employers and individuals

greatly increases the burden of FM (Martinez, Ferraz, Sato, & Atra 1995). One study showed that employees with FM had more claims than those with osteoarthritis for psychiatric diagnoses, chronic fatigue, and pain conditions, but the prescription drug use was similar (White et al., 2008). FM is associated with psychosocial distress as well as physical distress and may be a manifestation of depression or anxiety (Callahan & Blalock, 1997; Verbunt, Pernot, Smeets, 2008). Underlying depression may contribute to fatigue and sleep disturbance, which in turn may cause persons with FM to have more severe impairment of their health status (Bergman, 2005; Niccassio, Moxham, Schuman, & Gevirtz, 2002; Russell, 2001). A constellation of symptoms and complaints including poor sleep quality characterize the person suffering from FM.

Research on sleep quality in persons with FM has focused mostly on disturbances in sleep stage, specifically, disturbance in non-rapid eye movement (NREM) sleep by alpha wave intrusion (Anch, Lue, McClean, & Moldofsky, 1991; Moldofsky, Scarisbrick, & England, 1975). Alpha waves are brain-generated electrical activity noted on electroencephalograms conducted during polysomnography (sleep study), that are associated with wakefulness after sleep onset. Their presence is postulated to interrupt NREM sleep and reduce rapid-eye-movement (REM) sleep. Other research, however, has challenged these findings as a cause of sleep disturbance exclusive to FM as it was noted that healthy research participants with alpha-delta sleep also reported musculo-skeletal aching, stiffness, and un-refreshed sleep (Lentz, Landis, & Rothermel, 1999; Paiva & Branco, 2002; Schneider-Helmert, Whitehouse, Kumar, & Lijzenga, 2001). Sleep fragmentation and disturbances in sleep structure like these may relate to increased morbidity of FM, however, it remains unknown whether complaints of disturbed sleep

in FM are associated with a sleep structure problem, perceived poor sleep quality (sleep state misconception), or a circadian rhythm sleep disturbance (CRSD) (Smith, Perlis, & Smith, 2000).

Objective measures have been used to quantify circadian rhythm and sleep structure, most commonly, polysomnography (PSG) and actigraphy. Other measures used to assess circadian rhythm include circadian phase markers like core body temperature (CBT), melatonin, or cortisol which are secreted into the blood in a circadian pattern or fluctuate in 24-hour patterns (Benloucif et al., 2005; Klerman, Gershengorn, & Kronauer, 2002). Subjective measures including surveys, diaries or sleep logs have been used and represent a guideline for assessment of insomnia and CRSD according to the American Academy of Sleep Medicine (AASM) (Morgenthaler, Alessi et al., 2007). These measures and recommendations for their use in evaluation of CRSD are shown in Table 2.2 (Morgenthaler, Lee-Chiong et al., 2007). The AASM has classified these methodologies based on the level of evidence published on their use. Four classifications exist for use of these methodologies in diagnosis and treatment of CRSD based on these recommendations: standard recommendation, guideline recommendation, optional recommendation, or not recommended. Definitions of these classifications are published in the *Practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders* (Morgenthaler, Lee-Chiong et al., 2007).

Even though PSG remains the gold standard for assessment of most sleep disorders--especially for those lethal conditions involving airway disease (obstructive sleep apnea [OSA] or upper airway resistance syndrome [UARS]) or restless leg syndrome (RLS), it is less useful with measurement of the circadian rhythm due to its

artificial setting. Polysomnography collects information on multiple variables including electrocardiography (ECG); electroencephalography (EEG); electrooculography (EOG); electromyography (EMG) including chin movement, limb movements, and respiratory effort including thoracic and abdominal motion; percutaneous oximetry (SPO2); body position; nasal pressure and airflow; and sound recording of snoring (snorogram) usually over one night or cycle. Polysomnography requires the participant to sleep in a laboratory overnight, which may alter the routine or schedule of the person being studied. The results require scoring by an expert in sleep medicine to determine the sleep times and pertinent events that may point to alterations in sleep architecture and pathophysiology (Sewell-Scheuermann & Phillips, 2006). Currently, no recommendation for its routine use in CRSD exists.

Actigraphy is a unidimensional measure of limb activity with which highly sensitive algorithms are used to estimate the same parameters as those obtained by PSG (Ancoli-Israel et al., 2003). Actigraphy allows study in the person's own environment over multiple cycles. It has also been useful for documenting inconsistencies between objective and subjective measures of sleep. Sleep research in FM using actigraphy has shown that the factors reported by research participants about their quality of sleep were often inconsistent with the findings of diagnostic or behavioral testing (Landis et al., 2003). This discrepancy may be a sign of a sleep state misconception, which is a perception that sleep is poor, but at the same time objective recordings when performed reveal normal sleep (Tranjanovic, Radivojevic, Kaushanasky, & Shapiro, 2007). Sleep misconception may be common in persons complaining of insomnia and may also be present in persons with FM and CRSD. Actigraphy is considered a guideline by the

AASM for the study of CRSD due to its ability to capture objective information about sleep schedule over multiple cycles or nights.

Circadian phase markers have been identified and may be sensitive measures of circadian rhythm, but require frequent sampling of body fluids or invasive techniques (rectal temperature) to measure them accurately, making their use not as feasible in the clinical or field setting if collection is performed by the participant (Mayer, Leonhard, Krieg, & Meier-Ewert, 1998). Further study will be necessary to revise their use in the routine diagnosis of CRSD as a standard or guideline. Their use is considered optional for assessment of CRSD.

Overall, the numerous studies that used sleep logs or sleep quality surveys reflect the need to study people over multiple sleep cycles or in other circumstances where traditional PSG was impractical (Lee & Gay, 2004; McCrae et al., 2005; Wright, Valdimarsdottir, Erblich, & Bovbjerg, 2007). Sleep diaries collect sleep times by participant self-report and require the participant to remember to complete the diary daily. Participants may also be less than adherent to completing the diary and either not complete it or complete it right before presenting it to their healthcare professional making it less reliable. While sleep diaries are easy to use, the diary may not accurately reflect the actual number of awakenings at night, the time it takes for the participant to fall asleep, or actual time spent asleep. Sleep diaries are considered a guideline for assessment of CRSD according to the AASM.

Sleep logs, actigraphy, and PSG have been used to examine sleep times in persons with FM, but research using the less invasive actigraphy has not been used in the study of circadian rhythm in persons with FM. Several studies comparing actigraphy and PSG in

the estimation of sleep parameters like total sleep time or wake after sleep onset (WASO) also included measurements of circadian rhythmicity including mesor, amplitude, and acrophase but were conducted in samples other than persons suffering with FM (Beau, Lurisci, Beau, & Levi, 2007; Chevalier, Monmont, Cure, & Chollet, 2003; Edinger, Wohlgemuth, Krystal, & Rice, 2005; Fontana et al., 2003; Pati, Parganiha, Soni, Roy, & Choudhary, 2007). However, based on these results, actigraphy appears to be a useful tool for measuring sleep patterns over time or multiple cycles. This growing literature on the use of actigraphy has led to its inclusion as a guideline measure for determination of sleep duration and specific types of circadian sleep patterns (Carvalho-Bos, Waterhouse, Edwards, Simon, & Reilly, 2003; Morgenthaler, Alessi et al., 2007). The examination of sleep and circadian rhythm in persons with FM requires a sensitive measure to solve the mystery of poor sleep quality in FM.

Definition of Circadian Sleep Rhythm and Overview of Circadian Rhythm Sleep Disorders

Circadian rhythms are 24-hour cycles of rest and wakefulness regulated by the biological clock or circadian pacemaker in the suprachiasmatic nucleus (SCN) of the hypothalamus (Martin et al., 2006). The circadian pacemaker influences many physiological and neuroendocrine functions including melatonin secretion and the activity of the hypothalamic-pituitary-adrenal (HPA) axis, both having been studied previously in persons with FM (Klerman et al., 2001). Sleep/wakefulness usually alternate within or about a 24-hour frame in humans. The typical cycle in humans is seven to eight hours of sleep and 16 – 17 hours of wakefulness. These cycles also respond to environmental events or zeitgebers (German for time giver) such as daytime

light, meals, or exercise which may stabilize or regularize circadian rhythm (Lu, Manthena, & Zee, 2006). This response is known as entrainment and daytime light is considered the most powerful synchronizer of circadian rhythm in humans (Buysse, 2005; Painnain & Cauter, 2007).

According to the International Classification of Sleep Disorders (ICSD-2), CRSD is a persistent or recurring pattern of sleep disturbance due to alterations in the circadian (24-hr) time keeping system that affects timing or duration of sleep (AASM, 2005). These alterations can result from endogenous (internal propensity for sleep) or exogenous factors (lifestyle or demands of society) or both. The above diagnostic criteria include reference to impairment or sensitivity to the mal-aligned circadian rhythm with disturbances resulting in higher symptom burden or patient complaints. Another important consideration of the diagnostic criteria include that this diagnosis be used only when the disorder cannot be better explained by another primary sleep disorder (e.g., insomnia, OSA, RLS, etc.) (Sack et al., 2007a, 2007b).

Circadian science and sleep research have identified six types of CRSD that result from at least two possible mechanisms: those disorders that occur after a voluntary or imposed shift in timing and those thought to involve altered endogenous and exogenous mechanisms affecting the circadian rhythm itself. Jet lag disorder (JLD) and shift work disorder (SWD) are examples of the former, which result from travel across different time zones or shift in the timing of wakefulness for evening/night shift work. These diagnoses are dependent on recent history of travel or change in work habits that may have shifted the sleep wake cycle. The other disorders associated with CRSD include: advanced sleep phase disorder (ASPD), delayed sleep phase disorder (DSPD), free-

running disorder (FRD), and irregular sleep wake rhythm disorder (ISWD). According to the AASM, characteristics of these disorders are shifts in the timing of onset of sleep and wakefulness that are mal-aligned to the individual's desired sleep schedule (Sack et al., 2007a).

ASPD is a sleep schedule that occurs when sleepiness or sleep onset occurs several hours earlier than the person's conventional or desired sleep time. Characteristics of ASPD include sleepiness and sleep onset in the early evening hours (17:00 – 19:00) with awakenings from sleep occurring in the early morning hours (02:00 – 04:00) (ASA, 2002). The rare diagnosis of ASPD considers the degree of difficulty the person experiences conforming to a desired sleep schedule and the exclusion of other primary sleep disorders. These individuals are commonly referred to as "larks" as they retire early and awaken early. Larks also tend to be "morning" types who are energetic early in the morning (Kripke et al., 2008). A shortening of the circadian period (<24 hours) has been demonstrated in ASPD but requires further validation (ASA, 2002; Sack et al., 2007a). DSPD is characterized as a sleep schedule that occurs when sleepiness or sleep onset is later than the conventional or desired sleep time. Characteristics of DSPD include a later bedtime (1 – 4 am) and a later wake up time in the morning (10 a.m. – 12 p.m.) (ASA, 2002). These individuals described as "owls" that stay up late, considered "evening" types whose energy may increase late in the evening (Kripke et al., 2008). Sleep onset insomnia and difficulty arising early in the morning may occur when sufferers attempt to conform to an early morning work/school schedule. This disorder is common in adolescents and socially active individuals. If symptomatic, DSPS may be a cause of academic failure. This diagnosis is associated with a longer than circadian period (>24

hours), is familial and associated with unipolar depression, although further research is needed to confirm these findings (Kripke, et al. 2008; Sack et al., 2007a).

FRD is known as a non-24-hour sleep-wake syndrome. It has been proposed to reflect a failure of entrainment to environmental cues. Entrainment is alignment to an external rhythm, for example the daily light-dark cycle. Research on this syndrome has been limited and its occurrence is rare in sighted people. As much as 50% of blind people have this disorder (ASA, 2002). Persons diagnosed with this rhythm disturbance have cycles that mimic time-free environments without cues to encourage sleep like darkness. Characteristics of this disorder include cycles that are longer than 25 -26 hours with individual extremes of this disorder being awake for 48 hours or more alternating with 24 hours of sleep (ASA, 2002).

ISWD is characterized by the relative absence of any pattern to the sleep wake cycle (Sack et al., 2007a). Total sleep time may be comparatively normal because bouts of sleep that occur randomly distributed throughout the day and night. This disorder is characterized by frequent episodes of sleep (3 – 4 naps) alternating with wakefulness instead of one main period of sleep and one period of wakefulness (ASA, 2002). Cases of ISWD are usually associated with mental disease, dementia, or brain injury (Sack et al., 2007b). This disorder may also occur in acutely ill patients cared for within intensive care units where essential medical care does not permit a continuous bout of sleep. Sleep logs and actigraphy have face validity in documenting shifts like these in the sleep schedule and the associated inability to sleep at a conventional time (Ancoli-Israel et al., 2003; Morgenthaler, Lee-Chiong et al., 2007).

Several studies have demonstrated that human wrist activity has very robust rest/awake patterns but is also strongly influenced by homeostatic drive for sleep, as well as other factors that may obscure or mask the underlying circadian signal, e.g. decreased physical activity, work schedule, other health conditions (Buysse, 2005; Pati, Parganiha, Soni, Roy, & Choudhary, 2007). Circadian research conducted in children has noted that family socioeconomic status (SES) was a significant contributor to sleep/wake pattern variation. In this research, children in families with higher SES tended to be out of bed earlier in the morning, spent less time in bed during the night, and had less nocturnal waking, higher sleep efficiency, and longer continuous sleep bouts. Variability from night to night was lower, on average, in families with higher SES for bedtimes, sleep start times, and sleep period times. It was likely that parents in higher SES groups may be more likely to keep scheduled bedtimes for their children but were unable to avoid waking them early due to their work related schedule (Acebo & LeBourgeois, 2006).

Children diagnosed with attention deficit hyperactive disorder (ADHD) with sleep onset insomnia (SOI) were noted to have DSPD using actigraphy. In this study, sleep onset insomnia occurred in 70% of the children before three years of age indicating that the patterns were not precipitated by the pressure of an early morning school schedule outside the home. The etiology of this phase shift in these children remains unknown (Van der Heijden, Smits, Van-Someren & Gunning, 2005). Actigraphic research with adolescents with chronic pain compared to controls found that adolescents across both groups were receiving restricted sleep of about seven hours per night, although optimal developmental sleep requirements for adolescents have been estimated at nine hours per

night (Palermo, Toliver-Sokol, Fonareva, & Koh, 2007). These findings suggested that self-reported poor sleep quality was most likely associated with depressive symptoms and presleep arousal which was complimented by the data obtained by actigraphy and which may serve as targets for behavioral intervention.

Actigraphy has been frequently used to examine circadian rhythm in oncology to assess fatigue and guide the timing of treatments. In a study with in-patient cancer patients, actigraphy demonstrated disruption of the circadian rhythm with a dampening of the amplitude of activity, a lowering of the mean activity (mesor), and sleep phase advancement compared to controls, but both the cancer patients and the controls demonstrated a prominent 24-hour circadian rhythm (Pati et al. 2007). Other studies have showed that cancer patients are less active during the day, more active at night, and had less pronounced circadian rhythm compared to controls (Fernandes, Stone, Andrews, Morgan & Sharma, 2006). Actigraphy used in heart failure patients showed frequent early morning awakenings that may reflect the circadian phase advance common in the elderly (early bedtime and early morning awakenings) or they may be a consequence of early morning chest pain in patients with cardiovascular disease (Redeker & Stein, 2006). Inpatients with cancer or heart failure have impairments in their sleep and circadian rhythm that are likely to have significant effects on their quality of life.

Research conducted with airline pilots using actigraphy demonstrated a disruption in the pilots' circadian rhythm related to their work schedule (Petrilli, Roach, Dawson, & Lamond, 2006). Using sleep diaries, duty rosters, and actigraphy, it was noted that the pilots readjusted to their normal rhythm after an extended night of sleep upon return from scheduled flights (Eriksen & Akerstedt, 2006). Although results from actigraphy

generally agree with sleep/wake reported on sleep logs, it nonetheless raises the question of whether sleep logs are as good as actigraphy in determining circadian rhythm.

Sleep diaries require participants to record sleep times and other times including sleep latency (time to fall asleep), total hours of sleep, and number of awakenings after sleep onset. Participants are fairly reliable in recording their total time in bed and percentage of time asleep (sleep efficiency), but tend to overestimate the time it takes to fall asleep and underestimate the number of times they awoke at night (Menefee, et al., 2000; Wilson, Watson, & Currie, 1998). Sleep diaries are inexpensive and easily administered, but it is possible that participants may not be compliant in their completion of the daily diary and may even make up entries on logs they turn in. Thus, it may not be as accurate as objective methods like actigraphy in determining sleep latency and number of nocturnal awakenings.

Correspondingly, actigraphy is more sensitive for detecting sleep than it is for detecting wakefulness; so it may overestimate sleep and underestimate wakefulness (Ancoli-Israel, et al., 2003). Despite these limitations, there is substantial evidence that data from sleep diaries and data from actigraphy are both strongly correlated to PSG measures of sleep and circadian phase markers (Ancoli-Israel, et al., 2003; Lockley, Skene, & Arendt, 1999; Kushida, et al., 2001). It is recommended that a combination of self-report measures and actigraphy be used to collect information about physical activity, sleep, and circadian rhythm (Kos, et al., 2007).

Circadian Rhythms, Actigraphy, and Fibromyalgia

Measurement of circadian rhythms in FM using circadian phase markers like dim-light melatonin onset (DMLO) or cortisol has received some attention in the literature

(Bellamy, Sothorn, & Campbell, 2004; Bonifazi et al., 2006; Crofford et al., 2004; McLean et al., 2005; Qin & Guo, 2006; Weissbecker, Floyd, Dedert, Salmon, & Sephton, 2006). However, studies using actigraphy to measure circadian rhythm in the FM population have been scarce despite its recommendation by the AASM. Only three studies were noted using actigraphy to evaluate sleep in participants with FM and these studies did not include circadian rhythm analysis (Table 2.3).

Research with actigraphy and circadian phase markers has reported significant results in other populations including nursing home patients, college students, and in-patients . Research in older adults (without FM) noted significant correlations between actigraph identified bedtime, wake time, mesor, and acrophase compared to the acrophase of urinary 6-sulphatoxymelatonin secretion (Youngstedt, Kripke, Elliott, & Klauber, 2001). Similar results were reported with individuals diagnosed with DSPD and adolescents in the home setting (Carskadon, Acebo, Richardson, Tate, & Seifer, 1997; Cole, Smith, Alcala, Elliott, & Kripke, 2002). However, these studies also showed that activity rhythms were less stable than melatonin and core body temperature, and masking of rhythm could occur with voluntary behavior. Carskadon et al. (1997) found correlations ranging from .39 - .82 between actigraph identified sleep onset time at home and salivary DMLO time. This masking effect and its impact on measures of circadian rhythm may be substantial and true of actigraphy in general. Nevertheless, it is a useful tool for field study of circadian rhythm disorders and should be used for investigations of sleep disorders in FM.

Actigraphy does not measure sleep as it is defined by PSG nor does it measure the subjective experience of sleep as do sleep logs and questionnaires. Like circadian

markers, it measures patterns over time but it is not confined to a lab or require frequent sampling by the participant. All these measures are subject to their own limitations or measurement errors that add to the variability or masking of circadian rhythms.

Therefore, it is important that measurement of circadian rhythm procedures consider influences that result in its variability. These influences may be due to four different mechanisms: the circadian pacemaker itself, the intrinsic variability of the measure (actigraphy) relative to the pacemaker, the method of analysis, and the reliability of the device or instrument to measure what it says it measures (Table 2.4). Systematic discrepancies occur with PSG and sleep logs too. So in the absence of literature using actigraphy to determine circadian rhythm and periodicity in persons with FM, several technical areas for its use in determining circadian rhythm are discussed here instead.

Discussion

Activity is a standard marker of circadian rhythm in studies of non-human mammals, but it still requires further validation to achieve this status in humans (Ancoli-Israel et al., 2003). Obviously, because the environment of a laboratory animal is controlled and the masking or influences on activity that will add to the variability of the measurement can be reduced, a laboratory creates an ideal environment for study. Unfortunately, this environment cannot be created in the study of human circadian rhythms (unless institutionalized), and it would be unrealistic to measure it this way if we could.

As noted above, four areas contribute to the variability of the measurement of circadian rhythms and must be acknowledged within each study using actigraphy. These areas and examples of their influence are noted in Table 2.4. To determine whether a

CRSD exists, influences on the circadian pacemaker that occur endogenously or exogenously must be investigated. A thorough history of sleep and activities leading up to the development of sleep complaints may help determine the impact of these influences. It is extremely important to collect as much information about physiological and social activities of the person under study so that these influences can be adjusted statistically rather than trying to control them in the field setting. Some behavioral influences can be controlled (bed time, awake time), others like hormonal secretions cannot. However, it is likely that actigraphy could be used to determine what influences, e.g., work schedule or shift work, are affecting circadian rhythm and help with diagnosis of CRSD if more emphasis is placed on assuring that other areas are not over influencing the results e.g. removal of the device or non-adherence to completing the sleep diary.

Few standards exist to guide the investigator on procedural issues involving actigraphy. For example, is it better to use the times written in the sleep log or the actigraphic marks placed on the actogram by the subject at bedtime and wake time? Bedtime and sleep onset, while not the same, may be more reliably measured by actigraphy markers pushed at the time by the research participant than by times written (possibly inaccurate) in the sleep log. Other methods for ascertaining bedtime and awake time may be through the measurement of light or illumines, an option available on some actigraphs. Although, this latter technique may be affected if the partner of the participant continues light even after the participant has retired. Research conducted previously with actigraphy and sleep logs in FM has used both the sleep diary times and actigraphic markers for determining sleep parameters like sleep onset and total sleep time

(Korzun, 2002; Landis et al., 2003), but it is unknown which is the best method and therefore a combined approach may be preferred.

Other issues involve the cleaning and analysis of data and methodologies using algorithms for sleep parameter determination and rhythmicity. For example, data from participants that do not complete the sleep log, complete it retrospectively, or do not complete the study. These instances result in missing or inaccurate data. Is it better to exclude these data, use the mean of the individual times, or the mean of the group? The same is true for those individual results that are not characteristic of the group and represent outliers in the data, is it better to exclude them from analysis or just acknowledge their existence? To compare actigraphy results on circadian rhythm, the procedures used by each investigator to deal with missing data and outliers should be shared in the methods section so that results can be compared.

Additionally, information about the sample should also be shared including whether participants were inpatients or outpatients as these settings may influence the characteristics of the circadian rhythm because of the influence of the environment. Inpatients are in a more controlled environment, but are also disturbed by the essential medical care that is provided on a 24-hour basis. Outpatients are in a lesser controlled environment, but their sleep patterns are more likely to reflect their actual behavior which may affect their circadian periodicity.

Calculation of circadian periodicity can be performed several different ways. Selection of a method depends on whether quantitative calculation or qualitative descriptions are desired. Within this review, at least 10 different methods for calculation of circadian period and rhythm were noted in the literature as summarized in Table 2.5.

This list is not exhaustive, but does beg the question of which way is the best way to analyze circadian rhythms for determination of the period. The most common method for calculating the circadian period is Cosinor Analysis, however, several sources related that activity data may not ideally be fit by a cosine waveform (Ancoli-Israel, et al., 2003; Pati, et al., 2007) and other methods may be more suitable (Griefahn, Grob, & Robens, 2007). Research comparing these methods will help determine the ideal procedure for determining the circadian period, mesor, and other components of the activity biorhythm.

In addition, emphasis should be placed on whether data were visually inspected in determining sleep/wake cycles, whether the results were automated by the software, and whether a full diurnal cycle is used in the observations. Visual examination of actograms may reveal disturbances in circadian rhythm that quantitative measurement of the period may miss. This is also possible when averaging multiple days of data that contain less than full cycles versus using daily measures over 24 hours that are then averaged. For example, the first day and last day of the study may not contain full 24 hours of actigraphy due to the timing of the device being applied and removed. Statistical procedures that use averaging on the group results reduces the homogeneity of the standard error but may also obscure individual differences in the results.

Lastly, another recommendation is for investigators to address methods for dealing with artifact including first and last day artifact associated with different study start and stop times or removal of the device by the participant versus the appearance of taking a nap during the day both noted as a decrease in limb activity. Some investigators have addressed the issue of daytime naps by rescored epochs scored as sleep during the waking hours as wake if epochs closely surrounding them are also scored as wake

(Ancoli-Israel, et al., 2003). It would be helpful if these criteria were standardized for use in actigraphic studies.

Conclusion

It is hoped that these recommendations will encourage future research using actigraphy and assist investigators with results that can be replicated and compared. Conduct of additional research in FM using actigraphy and its use in other sleep-disturbed populations will help further clarify the relative and unique contributions of actigraphy in the diagnosis of circadian rhythm sleep disorders.

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Table 2.1 Tender Points and Their Bilateral Location in Fibromyalgia

- Occiput – located at the base of the skull beside the spinal column
- Low Cervical – located at the base of the neck in the back
- Trapezius – located on the top of the shoulder toward the back
- Second Rib – located on the breastbone
- Lateral Epicondyle – located on the outer edge of the forearm about 2 cm below the elbow
- Supraspinous – located over the shoulder blade alongside the spine
- Gluteal – located on the outside of the hip
- Greater Trochanter – located at the posterior to the greater trochanter prominence
- Knee – located on the fat pad over the knee

Reference: Wolfe et al. 1990

Table 2.2 Circadian Rhythm Disorders and Potential Evaluation Tools

Type	Sleep Diary	Actigraphy For Diagnosis	Actigraphy For Treatment Effect	Phase Markers	PSG
Shift Work					
Disorder	Useful	Useful	Useful	Optional	Not Useful
Jet Lag					
Disorder	Useful	Optional	Useful	Optional	Not Useful
Advanced Sleep					
Phase Disorder	Useful	Useful	Useful	Optional	Not Useful
Delayed Sleep					
Phase Disorder	Useful	Useful	Useful	Optional	Not Useful
Free Running					
Disorder	Useful	Useful	Useful	Optional	Not Useful
Irregular Sleep					
Wake Disorder	Useful	Useful	Useful	Optional	Not Useful

Reference: Sack 2007a, 2007b

PSG = Polysomnography

Table 2.3 Studies Using Actigraphy to Evaluate Sleep Quality in Persons with Fibromyalgia

<u>Author</u>	<u>Sample</u>	<u>Study Purpose</u>	<u>Measures Used</u>
Edinger 2005	<i>N</i> = 47 Participants with FM Randomized Controlled Trial	Compared CBT, sleep hygiene instructions, and usual care	Polysomnography Sleep logs Actigraphy Questionnaires
Landis 2003	<i>N</i> = 45 23 Women with FM 22 Women Controls (without FM)	Compared self- reported sleep quality, fatigue, between women with and without FM	Sleep diary Actigraphy Questionnaires
Korzun 2002	<i>N</i> = 59 16 Persons with FM 6 with FM/Depression 9 with Depression 28 Healthy Controls	Compared levels of activity and sleep in FM patients with & without depression to depressed persons & healthy controls	Actigraphy using Event Markers

FM = Fibromyalgia CBT = cognitive behavioral therapy

Table 2.4 Contributors to Variability of Circadian Rhythm Measurement

- Circadian pacemaker itself
 - Internal propensity to sleep after extended wakefulness
 - Entrainment
 - Lifestyle (night shift or time zone travel)
 - Behaviors (Poor Sleep Hygiene)
 - Medications (Sedative effects)
 - Occupational influences
- Actigraph relative to the pacemaker
 - No standards exist for setting start and stop times of the sleep wake periods when using actigraphy including whether to use event markers or entries on sleep diaries.
 - No standards exist for determining the level of sensitivity necessary for differentiation of sleep/wake from rest/active.
- Strategy
 - A variety of algorithms for sleep estimation and rhythmicity exist.
 - Technical details related to administration and scoring of actigraphy.
 - Description of procedure used in visual inspection of data, handling of missing data.
 - Variety of statistics used to determine shape of wave
- Reliability of the device
 - Few comparisons of different devices exist for evaluation of reliability

Table 2.5 Methods of Circadian Rhythm Analysis (Ancoli-Israel, 2003; Refinetti, 1993)

Cosinor Analysis	One of the most popular methods is a Cosinor model with a period of 24hr that is fit to the data by the least squares method to determine acrophase (time of peak activity), amplitude (peak to nadir) and mesor (mean) of the fitted curve.
Cosinor Analysis	A five parameter Cosinor model that also determines circadian minimum, alpha (width of the rhythm), and beta (steepness of the fitted curve).
Autocorrelation	Performs correlation between activity values at specific time lags of interest. High autocorrelations at or near 24 hour indicates a robust circadian rhythm.
Interdaily stability	Measurement of the coupling of a rhythm to an environmental zeitgeber based on the chi-square periodogram.
Circadian quotient	Ratio of the amplitude/mesor that is used to characterize the strength of the circadian rhythm by providing a normalized value that allows comparison between individuals.
Circadian quotient	Similar procedure for quotient using a normalized variable but does not rely on the assumption of a cosine fit. (Procedure uses the difference between the most active 10-hour interval and the least active 5-hour interval of the day).
Ratio of Activity	Ratio of nighttime activity to daytime activity or ratio of daytime activity to total activity, standard deviation of sleep onset time, and intradaily variability using spectral analysis and waveform education.

Table 2.5 (continued)

Dichotomy indices	Actimetry data is analyzed using two dichotomy indices, which compare the adjustment of activity during the sleeping and waking periods to changed rest-activity schedules. Dichotomy index 1 was defined as the percentage of “outofbed counts” that was greater than the median “in-bed count” (% OB > IB) and dichotomy index 2 was defined as the percentage of in bed counts that was less than the median out of bed count (% IB < OB).
Actimetry indices	Activity counts were ranked from the lowest to the highest value separately for the in bed and out of bed times. The following were calculated: 90 th percentile of activity counts during the in bed time (90% sleeping threshold) the 95% sleeping threshold, the 50% waking threshold and the 90% and 95% waking thresholds (both analogously defined).
Waveform education	Performed by calculating an average waveform for some period. If 24 hour is chosen, successive activity levels at similar times of the 24-hour day are averaged. Continuous bouts of sleep and wakefulness are clustered into periods that are circadian.

Reference: Ancoli-Israel, 2003; Refinetti, 1993

CHAPTER THREE

Psychometric Properties of the Fibromyalgia Impact Questionnaire in Sleep Disturbed Women

The purpose of this study was to examine the psychometric properties of the Fibromyalgia Impact Questionnaire (FIQ), an instrument used to measure health status, progress, and outcomes in persons with fibromyalgia (FM). The FIQ was designed to measure the components of health status believed to be most affected by FM, i.e., physical impairment, feeling good, missing work, doing work, pain, fatigue, restfulness, stiffness, anxiety, and depression (Burckhardt, Clark, & Bennet, 1991). The FIQ includes items from the Arthritis Impact Measurement Scale (AIMS) and the Health Assessment Questionnaire (HAQ). It has been used extensively in research with sufferers of FM and has been translated into at least 16 languages (Garcia-Campayo et al., 2006; Rosado, Pereira, da Fonseca, & Branco, 2006; Zijlstra, Taal, van de Laar, & Rasker, 2007). The instrument has published evidence of reliability, construct validity, and responsiveness to change (Bae & Lee, 2004; Perrot, Dumont, Guillemin, Pouchot, & Coste, 2003; Sarzi-Puttini et al., 2003). In this study, the instrument's reliability and validity were assessed in 50 women with FM and self reported sleep disturbance.

Review of Literature

Although the original instrument has been used in a variety of studies (e.g., Gursoy, et al., 2008; Gowans, DeHeuck, Voss, Abbey, & Reynolds, 2001; Fallon, Bujak, Guardino, & Weinstein 1999 ; Gowans, DeHeuck, Voss & Richardson 1999) published evidence on reliability assessment of the instrument is reported in only about a third of the studies using it. Most investigators cite the results of the reliability assessment

reported with the original research, but not reliability of the tool in their sample (Martinez-Lavin, Lopez, Medina, & Nava, 2003). Results of a MEDLINE review for available online reports on reliability published after 2000 using the FIQ are shown in Table 3.1. The majority of these studies reporting evidence on reliability used translated versions of the instrument not the original instrument. The translated versions of the FIQ had evidence of strong internal consistency ($\alpha > .80$) and strong test retest reliability ($r > .70$) in a variety of samples. Several studies using the FIQ were conducted with persons with other diseases or conditions, such as Lyme disease, Gaucher's disease, rheumatoid arthritis, or chronic musculoskeletal pain (Birtane, Uzunca, Tastekin, & Tuna, 2007; Brautbar et al., 2006; Burckhardt & Jones, 2005; Huber, Suman, Biasi, & Carli, 2008). Despite large sample sizes in several studies and enrollment of both men and women in the majority of the studies, the demographics of these samples consisted of predominantly middle-aged women with FM. Studies comparing the FIQ on men and women with FM were limited (Buskila, Neumann, Alhoashle, & Abu-Shakra, 2000). Other studies reported results using the FIQ that did not use or translate certain items of it because they were not considered applicable to the participants being sampled, i.e., items related to professional work were not considered if participants did not work outside of the home (Marques, Ferreira, Matsutani, Pereira, & Assumpcao, 2005; Tastekin, Birtane, & Uzunca, 2007). No studies were noted that reported the results of a factor analysis of the instrument. Ideally, reliability and validity assessment should be reported with every investigation using the original or modified instrument.

Burckhardt (1991) reported good internal consistency with a Cronbach's alpha of 0.80 in the original research with a sample of 64 women diagnosed with FM according to

the American College of Rheumatology guidelines. In the original research, test-retest reliability of the FIQ was 0.56–0.95. The FIQ has been compared to Arthritis Impact Measurement Scale (AIMS) and the Health Assessment Questionnaire (HAQ), two well-known instruments used in evaluation of patients with rheumatoid diseases. In the original research, it was concluded that the FIQ had sufficient test-retest reliability and could be a valuable outcome measure in FM patients (Burckhardt & Jones, 2005).

Several reports using translated versions of FIQ showed strong internal consistency. Buskila and Neuman (1996) reported Cronbach's alpha of .93 for the translated Hebrew version of the FIQ in 100 women with FM. Rosada et al. (2006) reported a Cronbach's alpha of .81 in 68 patients taking the Portuguese version of the FIQ. Rivera and Gonzalez (2004) reported a Cronbach's alpha of 0.82 in women taking the Spanish version of the FIQ ($n = 102$). Sarmer et al. (2000) reported internal consistency of .72 with a version of the FIQ translated into Turkish and used with 51 women with FM. Sarzi-Puttini et al. (2003) reported internal consistency of .90 for the Italian version of the FIQ ($n = 60$). Other FM studies involving medications and treatments using the original instrument reported similar findings of consistency as these (Huber et al., 2008; Jones et al., 2008).

It would be helpful if all investigations involving the FIQ briefly reported the results of reliability assessment in their summaries. Reports about validity and reliability of the instrument obtained in different samples improve the instrument by increasing its sensitivity to discriminate differences across samples and random errors within the results.

Therefore, the objective of this study was to evaluate the reliability and validity of the original FIQ in a sample of sleep-disturbed women with FM. The specific aims were to evaluate the internal consistency and stability of the FIQ; examine the relationship between socioeconomic characteristics and FIQ scores; examine of the dimensionality of the FIQ using factor analysis; and evaluate convergent validity of the FIQ through comparisons to two other fatigue measures and a pain scale: daily fatigue visual analogue scale scores (Fatigue VAS), scores from the 13-item Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue), and a daily pain visual analogue scale (Pain VAS).

Method

Design and Sample

The cross-sectional data for this psychometric assessment of the FIQ were collected from a volunteer, community-based sample of 50 women with a previous diagnosis of FM using an institutional review board (IRB) approved flyer that was posted in physician's offices and on the internet. Women with FM and perceived sleep disturbances were recruited in person, by phone, and by mail. These women self-reported their prior diagnosis of FM that was provided to them by a physician. The participants were not examined physically nor were the American College of Rheumatology diagnostic criteria for the number of tender points verified. Instead, to estimate the number of tender points, the women were asked to note painful areas on a body map and the percentage of body pain and tender points were estimated using procedures previously published (Margolis, Tait, & Krause, 1986). Exclusion criteria included not having a diagnosis of FM, a previous diagnosis or treatment of sleep apnea,

or working a night shift occupation. These criteria were verified with each participant in person, by phone or by email before enrollment. When asked if they get restorative sleep, 86% indicated that they did not.

The women were allowed to continue their daily medications and continue their usual level of activity during the study. Using a detailed questionnaire, a list of routine and as needed medications including their dosages were collected and categories were established based on the indication for the medication (pain medication, anti-inflammatory, sleep aid, antidepressant). Screening continued until at least 50 women meeting criteria were enrolled.

Instrument Descriptions

Fibromyalgia Impact Questionnaire

The FIQ is a self-administered questionnaire that takes approximately five minutes to complete and is composed of 20 items. The FIQ developed by Burckhardt et al. (1991) was created to evaluate FM patients. Higher scores on the scale indicate increased limitations suffered over the previous week. The only subscale of the instrument is related to physical functioning/impairment and consists of the first 11 items rated on a 4-point Likert-type scale ranging from 0 - 3. Because some of the participants may not do some of the tasks listed, e.g. do shopping, laundry, prepare meals, wash dishes, vacuum, etc., they are given the option of not completing these items and they are deleted from scoring. In order to obtain a valid summary score for questions 1 through 11, the scores for the items that the person has rated are summed and divided by the number of items rated (e.g., if the patient completed only 10 items at a score of 3 for each, the final score would be $10 \times 3/10 = 3$). An average raw score between 0 and 3 is

obtained in this manner. Items 12 and 13 ask the person to circle the number of days they felt well (0-7) and the number of days that they were unable to work due to their symptoms (0-7). Items 14 -20 are anchored horizontal linear scales marked into 10 - 1cm increments on which the patient rates work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety, and depression.

To score the instrument, the ratings of the first 11 items are summed and the sum divided by the number of questions answered to yield an average score from 0 -3. This score is multiplied by 3.33 to transform the score to a range of 0 – 10. Item 12 is reverse scored so that a higher number indicates more days feeling poorer. Raw scores range from 0-7 for items 12. Item 13 is scored directly and ranges from 0 -7. Both of these scores are also transformed by multiplying each by 1.43 to transform the score to a range of 0 -10. Items 14 – 20 are measured to within 0.5 cm increments with a range from 0 - 10 (If the person marks between two vertical lines, the item's score includes 0.5). Scores for the physical functioning/impairment subscale, the individual items, and total score can be derived. If one or more of the items are missed or not answered, the final summative score needs to be multiplied by $10/x$ (x =number answered). The range of the subscale physical impairment and the individual item scores is 0 - 10, with 0 indicating no impairment and 10 indicating maximum impairment. The overall score for the total FIQ score ranges from 0-100 such that the higher the score, the greater the impact. In addition to the data obtained using the FIQ, data from three other instruments were collected: the FACIT –Fatigue (13-item) completed at the end of the study, the Fatigue VAS, and the Pain VAS that was completed daily using a diary and the scores averaged.

Functional Assessment of Chronic Illness Therapy - Fatigue

The FACIT-Fatigue is a stand-alone subscale of the Functional Assessment of Chronic Illness Therapy measurement system, which measures health-related quality of life (QOL) among persons with cancer and chronic illness (Cella, 1993). The FACIT-Fatigue subscale is a 13-item questionnaire that assesses fatigue and its impact on function. The response format consists of a 5-point Likert scale to assess fatigue during the preceding week. FACIT-Fatigue scores range from 0 to 52, with higher scores representing lower levels of fatigue. It is easy to complete in five minutes or less and is written at the 4th grade reading level (9-10 years old).

The raw scores are transformed by subtracting each of the results from items, 1 – 6 and 9 -13 from 4 and by adding the results of 7 and 8 to 0. The sum of these transformed results forms the FACIT - Fatigue Score. The lower the total score the greater the fatigue. Scores < 30 are considered indicative of clinically significant fatigue (Cella, 1997; Haggell et al., 2006). Internal consistency of the FACIT-Fatigue evaluated in two samples of 50 men and 50 women with cancer was supported by alpha's of .93 and .94, respectively (Cella, Eton, Lai, Peterman, & Merkel, 2002). The instrument demonstrated strong internal consistency with a coefficient alpha range of .93 - .95 in 50 people with cancer and > .90 in persons ($n = 118$) with Parkinson's disease (Haggell et al., 2006). Discriminant analysis and convergent validity revealed a significant relationship with other fatigue measures (Yellen, Cella, Webster, Blendowski, & Kaplan, 1997). The FACIT's ability to differentiate cancer-associated fatigue from fatigue experienced by the general population was assessed across three different groups of people: anemic cancer patients ($n = 2369$ patients), non-anemic cancer patients ($n = 113$

patients), and the general population ($n = 1010$ persons). These results revealed that it was sensitive to fatigue in cancer patients with related anemia, but it did not differentiate fatigue associated with cancer in the absence of anemia when compared to ratings by the general population (Cella, Lai, Chang, Peterman, & Slavin, 2002). Internal consistency of the FACIT-Fatigue in 135 psoriatic arthritis patients was strong with an alpha coefficient of .96; test-retest intraclass coefficients of $r = .95$ supported the stability of the measure (Chandran, Bhella, Schentag, & Gladman, 2007). See the appendix for scoring guidelines of the instrument.

Fatigue Visual Analogue Scale

The Fatigue VAS is a simple 1-item instrument used to assess daily fatigue of participants during the weeklong study. This instrument consists of a 100 millimeter (mm) anchored horizontal line that the research participant marked to indicate the severity of their fatigue. Measured with a standard metric ruler, the result has a range of 0-100 mm with fatigue being greater at higher numbers. The daily scores when averaged form a final score for comparisons. Research conducted using a 1-item instrument for fatigue revealed high correlations with the FACIT – Fatigue ($r = -.75, p < .001$) in 640 patients with cancer (Temel, Pirl, Recklitis, Cashavelly, & Lynch, 2006).

Pain Visual Analogue Scale

Like the Fatigue VAS, the Pain VAS is also a simple 1-item instrument used to assess daily pain of participants during the weeklong study. This instrument consists of a 100 millimeter (mm) anchored horizontal line that the research participant marked to indicate the severity of their pain and has been used in study with fibromyalgia patients (Babu, Mather, Danda, & Prakash, 2007; Marques, Ferreira, Matsutani, Pereira, &

Assumpcao, 2005; McVeigh, et al., 2007) and in a variety of other settings to measure pain (Boonstra, Schiphorst Preuper, Reneman, & Posthumus, 2008; Camacho-Alonso & Lopez-Jornet, 2008; Loos, Hourterman, Schelting, & Roumen 2008). Measured with a standard metric ruler, the result has a range of 0-100 mm with pain being greater at higher numbers. The daily scores when averaged form a final score for comparisons.

Sleep Measures

To examine sleep characteristics in these women with Fibromyalgia, the participants were asked to complete a diary and wear an actigraph. Once a day, the participant completed the diary by responding to questions about various sleep times (bedtime, wake time, time to fall asleep, number of times awake after sleep onset, and number of times out of bed), any special medication use, and other questions regarding symptoms of their fibromyalgia. The diary included the Fatigue VAS and the Pain VAS instruments, in addition to the information collected on sleep.

The actigraph is a wristwatch like device worn on the wrist or ankle to measure limb movement (Buysse, 2005; DeSouza et al., 2003). It contains a miniature motion-based sensor that translates movement into a numerical activity count. Using sophisticated algorithms, the software of the device converts these raw activity counts to epochs of sleep or wake (Carvalho-Bos, Waterhouse, Edwards, Simon, & Reilly, 2003; Pollak, Tryon, Nagaraja, & Dzwonczyk, 2001). The women wore the device constantly for at least seven days. The device was configured to sample activity every minute (epoch length) during the time that the device was the participant's non-dominant wrist. The actigraph device used was the Minimitter Actiwatch 16 ® (Mini Mitter Company, 2004).

Procedures

The study was IRB approved by the University of Kentucky and the participants consented to share information about their FM symptoms and sleep quality. Study materials including a detailed medical history, the study questionnaires, daily sleep diary, and study watch were provided in person or were mailed to the research participant once criteria for enrollment were met and written consent was obtained. Enrolled women completed the FIQ at the start of the study and again at the end of the weeklong study. The same instructions were provided to each participant and no clarification or assistance was provided on ways for participants to answer any of the questions. Demographic information including socio-economic status, co morbidities, and medication use was collected using an extensive survey in addition to the standardized questionnaires. Statistical analysis was performed using SPSS 13.0 Windows Graduate Student Program.

The internal consistency of the FIQ was assessed using Cronbach's alpha for the total scale and the subscale physical impairment. Test-retest procedures on the two FIQ administrations were performed using Pearson's r . Statistical differences between the administrations were assessed using paired sample t tests. The dimensionality of the instrument was examined using factor analysis. To be interpreted as significant, factor loadings had to be at least $> .40$; and loadings of at least this magnitude would be expected with them loading on more than one factor if the instrument measures multiple factors (Stevens, 2002). Convergent validity was examined by comparing the FIQ scores to the Fatigue VAS, the FACIT-Fatigue and the Pain VAS.

Results

The demographic characteristics for the sample are summarized in Table 3.2. The sample was female, mostly Caucasian (90%) with a mean age of 47.6 ± 10.7 years, and diagnosed with FM for at least 4.1 ± 5.5 years. According to the participants, 44% were diagnosed by their family physician, 28% by a rheumatologist, and 24% by another specialist, e.g. neurologist, chiropractor. The mean duration of their symptoms was 7.3 ± 7.6 years; their mean body mass index (BMI) was 30.2 ± 7.2 ; 21% currently smoked cigarettes; and 72% of these women were employed in some capacity. The entire sample had at least a high school education and 34% of the sample were college graduates. The socioeconomic and health characteristics of the cohort are shown in Table 3.3 and 3.4.

Eighty-eight percent of the sample self-reported that they had trouble falling asleep or staying asleep. Fifty-seven percent of the sample indicated that they wake up in the early hours unable to fall back asleep. The participants rated their sleep latency or the time it takes them to fall asleep as a mean of 46 minutes (SD 41 minutes) or more. They indicated that their actual sleep time is 6.87 hours (2.33). Almost half of the participants indicated that they used an alarm clock to awaken themselves. When asked to rate their overall sleep quality (0 = refreshed, 1 = somewhat refreshed, and 2 = fatigued), 31% indicated their sleep was somewhat refreshed and 65% indicated that they were fatigued. Only 3.5% indicated that they felt they had refreshing sleep.

Ninety percent of the women used pain medication daily for their fibromyalgia pain, 74% used medication nightly to help them sleep, and 70% were prescribed anti-depressants. Eighty percent indicated that they exercised every day, although the type of exercise and intensity was not collected. Using the body pain map, the average number

of tender points rated by the participants was estimated at 10 (\pm 4) (slightly less than diagnostic criteria) and the average total percentage of body pain was 37.5% (\pm 25%).

Using the actigraph and sleep diaries, the women were in bed an average of eight hours and 21 minutes with their falling asleep taking at least 31 minutes. The mean actual sleep time for the group was six hours and 19 minutes. Activity data captured throughout the night indicated that the women had an average of 23 wake bouts after sleep onset lasting approximately two minutes each.

Reliability Assessment

Descriptive statistics and internal consistencies for the total FIQ and its subscale are shown in Table 3.5. A Cronbach's alpha of .85 for the total score indicated strong internal consistency of the FIQ. An alpha coefficient of .52 for the subscale physical impairment indicated questionable consistency. Test – retest reliability of total FIQ scores and subscale physical impairment scores collected at the beginning and at the end of the study were evaluated. Test retest reliability evaluated using Pearson's r was .74, $p < .001$ for the total score and .71, $p < .001$ for the subscale. Paired sample t tests indicated significant differences between the sets of FIQ scores (59.1 versus 54.0) completed by the participants [t (49) = 2.99, $p = .004$].

Construct Validity

A variety of procedures were used to investigate the construct validity of the FIQ. The relationships between the various socio-demographic characteristics and the FIQ total score were examined. Independent t tests revealed no significant differences in FIQ scores by with ethnicity, educational level, marital status, occupational status, sleep medication use, pain medication use, menopausal status, or exercise habits, however, there were significant differences in the FIQ scores of smokers and non smokers [t (46) =

-3.71, $p = .001$]. The FIQ was weakly correlated with age ($r = .29$, $p = .04$) otherwise, no significant correlations were noted between FIQ scores and other characteristics: BMI; disease duration; number of caffeinated beverages consumed per day; average peak activity, average actual sleep time; average wake bouts; average sleep latency; or average sleep efficiency.

Factor analysis was used to evaluate the dimensionality of the FIQ. Using principle components analysis, examination of the Scree plot indicated that two factors should be retained and rotated (See Figure 3.1). However, using the Kaiser criterion, analysis of the eigenvalues over one suggested retaining three factors. In this latter case, the first factor had an eigenvalue of 4.2 and explained 42.1% of the variance with the two other factors having eigenvalues of 1.2 each and each explaining 12% of the variance, respectively.

In the rotated factor solution shown in Table 3.6, the first factor had strong loadings for the items physical functioning, felt well, unable to work, work difficulty and pain. Variance redistribution for factor one was 24.5%. Factor two had strong loadings for four items: pain, stiffness, anxiety, and depression. The item pain had dual loadings for factor one and factor two. Variance redistribution for the second rotated factor was 17.1%. Factor three had strong loadings for two items: fatigue and felt tired; and redistributed variance explained by the third factor was 24%. In this sample, 66% of the total variance of the FIQ scores was explained by the three factors.

When principal component analysis was performed using a one factor solution as shown in Table 3.7, all the items had strong factor loadings ($> .40$). To further confirm

this unidimensionality, a two-factor solution was also produced, but factor loadings remained strong for only factor one.

A final method used to examine validity was to determine whether the FIQ would converge with the Fatigue VAS, the FACIT-Fatigue, and the Pain VAS. Correlations are displayed in Table 3.8. The total FIQ and the average daily Fatigue VAS scale was significantly correlated. The correlation was $r = .62, p < .001$ indicating that the Fatigue VAS explained 38% of the variance in FIQ scores using the multiple correlation (R^2). Strong correlations were also noted between the FIQ scale and the FACIT-F; and the FIQ score and the average daily Pain VAS. A correlation of $r = -.65 (p < .001)$ was noted between the total score of the FIQ and the FACIT-Fatigue and a correlation of $r = .65 (p < .001)$ was noted between the FIQ and the Pain VAS. Forty-two percent of the variance in the FIQ could be determined using either the FACIT- Fatigue or the Pain VAS.

Correlations between the individual items of the FIQ and the Fatigue VAS ranged from .28 to .50 with all items of the FIQ being significantly correlated with the Fatigue VAS. Correlations between the individual items of the FIQ and the FACIT-Fatigue ranged from -.32 - -.58 with all items of the FIQ being significant except the FIQ item for pain. Comparisons between the individual FIQ items and the Pain VAS ranged .38 - .61. All items of the FIQ were significantly correlated with the Pain VAS except the FIQ item for anxiety. In these results, a combined effect of pain and fatigue appeared to influence the responses on the FIQ.

To further examine this perspective, Pearson's correlations of the FIQ to average daily pain scores combined with average daily fatigue scores were performed and

indicated strong correlations (FIQ: pain x fatigue $r = .69, p < .001$). The fatigue VAS and the Pain VAS administered together could explain 48% of the variance in the FIQ scores.

Discussion

The findings of this study provide further support for the reliability and validity of the FIQ. Considering the prior research that has been conducted with the FIQ, a strong empirical base for its use exists in the literature as reliability assessments published in the peer-reviewed research are similar to the results illustrated here.

Typically, the Fibromyalgia Impact Questionnaire is used as a multidimensional instrument that measures the components of health status believed to be most affected by FM, i.e., physical impairment, feeling good, missing work, doing work, pain, fatigue, restfulness, stiffness, anxiety, and depression, but further analyses tend to suggest that it may be a unidimensional instrument. Initially, in this research, these components were reduced to three factors based on results from the principle component analysis. The first factor interpreted as “physical function”, had strong correlations for the items that make up the subscale physical function and the next 4 items-feel good, work missed, do work, and pain (See Appendix to view the instrument). These items were strongly inter-correlated but were not strongly correlated with the items of the other two factors except for the item pain, which had dual loadings for factor one and two. The second factor interpreted as “mood or affect” had strong loadings and included four items: pain, stiffness, anxiety, and depression. It is reasonable to consider that pain may be an influence on both physical function and influenced by mood. The third factor interpreted

as “sleep quality and fatigue” only contained two correlated items of the FIQ: fatigue and feeling rested.

While it is usually insufficient to define a factor that only contains two items (Streiner & Norman, 2001), these two items of the FIQ are traditionally used in the literature to describe sleep quality in research participants with FM (Agargum, Tekeoglu, & Gomes, 1999; Landis et al., 2003; Millott & Berlin, 1997; Nicassio, Moxham, Schuman, & Gevirtz, 2002; Schaefer, 2003). However, even if this component is interpreted as “sleep quality” for the purposes of this investigation, assessment of sleep quality in FM may require additional measures besides these two items to assess for actual disturbances in sleep. It is more likely that these items are influenced by the participant’s experience of pain and fatigue or even depression on their sleep rather being able to measure an actual alteration in their sleep. This conclusion is further supported by the participant’s ratings on the FIQ for the item-fatigue--the highest mean score obtained on the FIQ was for the item fatigue (8.13), with the next highest being for not feeling rested (7.74). While this finding was not totally unexpected considering that the participants were enrolled in a study seeking women with sleep disturbances in addition to having FM, it does not necessarily indicate that an actual disturbance in sleep is occurring only that the participants did not feel refreshed or well rested.

Another perspective could be that the participants were experiencing depression, which may also enhance body pain and fatigue. As previously noted, 70% of the participants were prescribed anti-depressants, but this study is limited in that confirmation of this diagnosis was not conducted and convergent validity of the FIQ with a measure of depression could not be performed. From these results, it is proposed that

the FIQ measures the combined impact of mood, pain, and fatigue, all of which have a combined effect on sleep quality and impact from FM, and that the FIQ is unidimensional.

Support for this unidimensionality is noted in the second factor analysis performed with only one factor extracted. As noted in table 3.7, all the loadings were stronger than .50 with the strongest item loading noted for depression (.75). This may indicate that the influence of their mood or affect may have contributed to the way the participants completed the instrument which also influenced their pain and fatigue. This unidimensional structure of the FIQ is further supported by the Scree plot. Examination of the Scree plot supports the unidimensional nature of the instrument, in that the elbow of the Scree plot occurs at the second factor, but was not supported by a two factor solution. An explanation for the results of the three factor solution is that the other factors noted may have been produced by fluctuations in measurement error by the combined effects of depression, pain and fatigue. Another way measurement error was demonstrated was by the finding that participants FIQ scores improved from one testing to another without intervention even though they were still strongly correlated between the two administrations.

Internal consistency of the instrument was acceptable and equal to that noted in other research with the FIQ (Gowans, De Hueck, Voss, Silaj, & Abbey, 2004; Redondo et al., 2004). Test-retest reliability of the FIQ was strong indicating stability of the instrument over time even with improvement in scores over a week. Reasons for this change could be due to the placebo effect or possibly that the participants were more aware of their sleep schedule during the study and perhaps experienced improved sleep

hygiene by use of the sleep diary and actigraph. Regardless, these findings were similar to other reports using the FIQ including those with longer durations between administrations of the instrument.

Evidentiary support for construct validity of the FIQ was noted in several ways. With the exception of smoking status, none of the demographic or medical characteristics were related to changes in the FIQ implying that the instrument could be used with different populations. However, like most of the research conducted in persons with FM using the FIQ, the sample in this research was comprised of mostly middle aged, Caucasian women who were likely suffering from depression.

Scores of the FIQ had good convergence with the Fatigue VAS, the FACIT-Fatigue, and the Pain VAS. It was thought that that the FIQ would be extremely sensitive to fatigue ($r > .80$) in this sample because poor sleep quality was an inclusion criterion for participants and high levels of fatigue were expected. These results indicated that fatigue and tiredness were factors impacting the women, but the impact of pain was just as significant. This was evidenced by high mean scores for those items measured by the FIQ (Table 3.6) and high total scores from the Fatigue VAS and the Pain VAS, and low totals for the FACIT-Fatigue (Table 3.2). Comparisons of the FIQ with these other measures indicates that pain and fatigue did contribute to FM impact and in combination with these other measures could explain 48% of the variance in the FIQ scores. However, these results also indicate that other factors, i.e. depression, could also contribute to the impact of FM and result in the perception of poor sleep quality.

Several limitations were noted in this research. The first limitation is the self-report nature of the participant's diagnosis and the use of only self report measures to

determine disease severity. Since no physical examination was performed on the participants to confirm tender points or the presence of them for at least three months, diagnostic confirmation of the criteria established by the American College of Rheumatology was not possible in this research. Another area that this study was limited was that no assessment of mood or affect including depression was conducted. While the item scores for anxiety and depression were moderate on the FIQ, no assessment of construct validity using an instrument that measures depression was addressed in these results. Another area of limitation was the lack of men with sleep disturbances and FM or comparison with a control group of women without FM or without perceived sleep problems. Therefore, the results cannot be generalized to them, to men, or to persons with depression.

These data were obtained from a small homogenous sample of women with FM who considered themselves sleep disturbed. These results demonstrated high item scores for not feeling rested and being fatigued, indicating a perception of poor sleep quality using this instrument. However, sleep quality is affected by many factors and this particular aspect was not thoroughly investigated here using only the FIQ for its contribution to FM impact. It is likely that other co morbid conditions may contribute to FM impact and the perception of poor sleep quality in these women. Using the Charlson Co morbidity Index (CCI), co morbid conditions of the participants were classified based on their seriousness (Charlson, Pompei, Ales, & MacKenzie, 1987). The CCI takes into account the number and the seriousness of co morbid disease and provides a simple method of estimating risk of death. As illustrated in the graph (Figure 3.2), the finding

that ratings of poor sleep quality appears related to the magnitude of existing co-morbid conditions also deserves further investigation in persons with FM.

Conclusion

In conclusion, the FIQ is a valid and reliable instrument for measuring functional disability and health status in sleep disturbed women with FM. Due to the multidimensionality of the impact of fibromyalgia, other measures may be needed in addition to the FIQ for the assessment of other components (mood and sleep quality) that contribute to its impact.

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Table 3.1 Review of Prior Psychometric Evidence: Fibromyalgia Impact Questionnaire Year > 2000

Author, Year	Sample Size	Design	Purpose of Study	Psychometric Evaluation Reported
Gürsoy 2008	107 (B)	Case/Control	Analyze the genotype distributions and allele frequencies for the MAO gene among the patients with fibromyalgia syndrome	Not reported
Huber et al 2008	69 (F)	Single Group	Evaluate effect of psychological distress and well-being in women with chronic musculoskeletal pain	$\alpha = .81$
Jones 2008	165 (B)	RCT	Evaluate effectiveness of pyridostigmine and group exercise on FM symptoms	$\alpha = .88$
Aloush 2007	36 (B)	Single Group	Evaluation of FM symptoms in men and women with ankylosing Spondylitis	Not reported
Ang 2007	19 (F)	Single Group	Determine the effects of motivational interviewing (MI), in patients with FM.	Not reported
Arnold 2007	75 (B)	RCT	Examine efficacy and safety of gabapentin	Not reported

Table 3.1 (continued)

Author, Year	Sample Size	Design	Purpose of Study	Psychometric Evaluation Reported
Bazzichi 2007	120 (B)	Case/Control	Investigate thyroid abnormalities and autoimmunity in fibromyalgia (FM).	Not reported
Birtane 2007	30 (B)	Two Group	Assess the impact of FM on QOL comparing with that of rheumatoid arthritis (RA) patients and control subjects.	Not reported
Brand 2007	90 (F)	Single Group	Assess validity and reliability of Interstitial Cystitis Symptom and Problem Index (ICSPI) in FM	Not reported
Calandre 2007	19 (F)	Single Group	Evaluate open label Pregambalin to improve FM symptoms	Not reported
Calandre 2007	32 (B)	Single Group	Evaluate the effect of Ziprasidone in FM	Not reported
Da Silva 2007	40 (F)	RCT	Verify whether techniques of yoga with and without the addition of <i>Tui Na</i> might improve pain and the negative impact of FM	Not reported

Table 3.1 (continued)

Author, Year	Sample Size	Design	Purpose of Study	Psychometric Evaluation Reported
Duncan 2007	24 (B)	Single Group	Explore the benefits of acupuncture in FM	Not reported
Eksioglu 2007	53 (F)	RCT	Assess the effectiveness of Stanger bath on the treatment of FM	$\alpha = .72$
Hidalgo 2007	35 (B)	Single Group	Assess effectiveness of Quetiapine for FM	Not reported
Jesperon 2007	48 (F)	Case/Control	Evaluate the use of computerized cuff pressure algometry (CPA) in FM (FM) and to correlate deep-tissue sensitivity assessed by CPA with other disease markers of FM	Not reported
Munguia-Izquierdo 2007	60 (F)	RCT	Evaluate the short-term efficacy of exercise therapy in a warm, chest-high pool on pain and cognitive function in women with FM.	Not reported

Table 3.1 (continued)

Author, Year	Sample Size	Design	Purpose of Study	Psychometric Evaluation Reported
McVeigh 2007	24 (F)	Single Group	Aimed to determine the stability of TPC and TMS over time, and to examine how well these measures reflected the patients' perceptions of their condition	Not reported
Naring 2007	28 (B)	Single Group	Examine the frequency of traumatic experiences and somatoform dissociation in patients with FM or rheumatoid arthritis (RA)	Not reported
Paktar 2007	116 (B)	RCT	Investigated the efficacy and tolerability of Paroxetine controlled release in FM	Not reported
Passard 2007	30 (B)	RCT	Assess the effect of unilateral repetitive transcranial magnetic stimulus (rTMS)	Not reported
Ribel-Masden 2007	27 (F)	Case/Control	Assess the metabolism of collagen and the occurrence of collagen metabolism markers to the severity of FM symptoms.	Not reported

Table 3.1(continued)

Author, Year	Sample Size	Design	Purpose of Study	Psychometric Evaluation Reported
Roizenblatt 2007	32 (B)	RCT	Investigate active anodal transcranial direct current stimulation in association with sleep structure changes in FM	Not reported
Rooks 2007	207 (F)	RCT	Compared the effectiveness of 4 common self-management treatments in women with FM	Not reported
Tander 2007	75 (B)	Case/Control	Compare hypothalmpituitary IGF-1 axis ghrelin concentration and relationship with FM and controls	Not reported
Tastekin 2007	36 (B)	Single Group	Aimed to investigate the relation between tender points count and FIQ	Not reported
Tomas-Carus 2007	34 (F)	RCT	Evaluate the effects of a 12-wk period of aquatic training and subsequent detraining on health-related quality of life (HRQOL) and physical fitness in FM.	Not reported

Table 3.1 (continued)

Author, Year	Sample Size	Design	Purpose of Study	Psychometric Evaluation Reported
Wallitt 2007	12 (F)	Single Group	Determine if alterations occur in regional brain metabolism after undergoing a multidisciplinary therapeutic regimen	Not reported
Wiggers 2007	200 (B)	Single Group	Rehabilitation of myofascial pain & FM using multidimensional rehab techniques	Not reported
Ziljisha 2007	224 (B)	RCT	Validation of Dutch translation of FIQ from two trials comparing Spa treatment and Venlafaxine in FM	$\alpha = .91$
Brautbar 2006	217 (B)	Case/Control	To identify patients with Gaucher's disease for whom FM-specific therapy may be therapeutic.	Not reported
Chen 2006	10 (B)	Single Group	Evaluate qigong therapy in FM	Not reported
Fregni 2006	32 (B)	RCT	Transcranial Direct Current Stimulation (tDCS) treatment & pain relief in patients with FM.	Not reported

Table 3.1 (continued)

Author, Year	Sample Size	Design	Purpose of Study	Psychometric Evaluation Reported
Garcia-Campayo 2006	120 (B)	Single Group	Examine some of the psychometric properties of the Spanish version of the Fibro Fatigue Scale	Not reported
Hammond 2006	183 (B)	RCT	Evaluate the effects of a education/exercise program in FM	Not reported
Havermark 2006	240 (B)	Single Group	Evaluate the impact of a physical therapy-based educational program on patients with FM	$\alpha = .81$
Mannerkorpi 2006	69 (F)	Single Group	Investigate the relationship between performance-based tests, ratings of activity limitations, self-efficacy, and pain in FM	Not reported
Rosado 2006	68 (B)	Single Group	Translation of FIQ into Portuguese	$\alpha = .81$
Unlu 2006	46 (F)	Case/Control	Investigate the autonomic dysfunction by recording sympathetic skin response.	Not reported

Table 3.1 (continued)

Author, Year	Sample Size	Design	Purpose of Study	Psychometric Evaluation Reported
Vargas 2006	60 (B)	Case/Control	Define if sphygmomanometry is helpful in the identification of patients with FM.	Not reported
Wennemer 2006	23 (B)	Single Group	Evaluate FM after participation in a functionally oriented, multidisciplinary treatment program	Not reported
Zucker 2006	100 (B)	Single Group	Compare fibromyalgia therapies and to assess the feasibility and outcomes of this approach for practice-based effectiveness research	Not reported
Bennett 2005	315 (B)	RCT	Examine health-related quality of life (HRQOL) from treatment with an analgesic in FM and Controls	Not reported
Burckhardt 2005	23 (F)	Two Group	Compare and contrast characteristics of post-breast cancer surgery women.	Not reported
Da Costa 2005	79 (F)	RCT	Determine the efficacy home-based exercise program in FM	Not reported
Dobkin 2005	39 (F)	Single Group	Identify predictors of maintenance of exercise	Not reported

Table 3.1 (continued)

Author, Year	Sample Size	Design	Purpose of Study	Psychometric Evaluation Reported
Holman 2005	60 (B)	RCT	Assess Pramipexole, a dopamine 3 receptor agonist in FM	Not reported
Marques 2005	178 (B)	Case/Control	Aimed at assessing pain and quality of life of Brazilian females with FM	Not reported
Oliver 2005	187 (F)	Single Group	To identify and compare the effects of cross-section and longitudinal correlates of physical activity.	$\alpha = .79$
Takiz 2005	100 (F)	Single Group	Investigated sexual function in females with FM	Not reported
Bae et al. 2004	62 (F)	Single Group	Translation of FIQ into Korean	$r = .85$
Bellamy 2004	21 (F)	Single Group	To determine diurnal rhythm characteristics of pain, stiffness, and fatigue in self-ratings in FM.	Not reported
Cedraschi 2004	164 (B)	RCT	Evaluate a treatment program in FM based on self management, using pool exercises and education	Not reported
Gowans 2004	37 (B)	Single Group	Follow up measure of mood and physical function after weeks of supervised aerobic exercise in FM	Not reported

Table 3.1 (continued)

Author, Year	Sample Size	Design	Purpose of Study	Psychometric Evaluation Reported
Kendall 2004	60 (B)	RCT	Investigate the effect of Valacyclovir in patients with FM	Not reported
Mannerkorpi 2004	36 (F)	RCT	Evaluate the effects of body awareness therapy combined with qigong for patients with FM	Not reported
Redondo 2004	56 (F)	Two Group	Evaluate the long-term efficacy of 2 interventions	Not reported
Rivera et al. 2004	102 (F)	Single Group	Translation of the FIQ into Spanish	$\alpha = .82$
Altan 2003	50 (F)	RCT	Aim of this study was to compare pool-based exercise and balneotherapy in FM	$\alpha = .86$ for subscale Not reported
Astin 2003	128 (B)	RCT	To test benefits of a mind-body intervention that combined training in mindfulness meditation	Not reported
Bennett et al. 2003	315 (B)	RCT	To evaluate the efficacy and safety of a combination analgesic tablet for the treatment of FM pain	Not reported
Fitzcharles 2003	82 (F)	Single Group	Examine the outcome of FM with standard medical care	Not reported

Table 3.1 (continued)

Author, Year	Sample Size	Design	Purpose of Study	Psychometric Evaluation Reported
Martinez-Lavin. 2003	40 (B)	Two Group	Assessed the responses of patients with FM versus patients with rheumatoid arthritis to the Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale questionnaire	Not reported
Perrot 2003	31 (F)	Single Group	Validation of a French version of the FIQ	$r = .84$
Pfeiffer 2003	100 (B)	Single Group	Determine the effect of a multidisciplinary FM treatment program.	Not reported
Sayar 2003	15 (B)	Single Group	Assess the efficacy of Venlafaxine in FM	Not reported
Sarzi-Puttini 2003	60 (B)	Single Group	Evaluation of Italian FIQ	$\alpha = .90$ $r = .74$
Valim 2003	76 (F)	RCT	Compare 2 exercise modalities, aerobic fitness training and stretching exercises in FM with Qigong movement therapy for FM	$\alpha = .95$ for subscale Not reported
Taggert 2003	39 (B)	Single Group	Investigate the effects of Tai Chi exercise on FM	Not reported
Arnold 2002	326 (F)	RCT	Pooled data to assess Duloxetine in women with FM	Not reported

Table 3.1 (continued)

Author, Year	Sample Size	Design	Purpose of Study	Psychometric Evaluation Reported
Buskila 2002	80 (F)	Two Group	To determine whether the clinical characteristics of FM in men and women.	$\alpha = .93$
Evcik 2002	42 (B)	RCT	Investigate the effects of balneotherapy in FM.	Not reported
Gur et al. 2002	50 (B)	RCT	Examine the effectiveness of low power laser (LPL) and low-dose amitriptyline therapy and to investigate effects of these therapy modalities on clinical symptoms and quality of life (QOL) in patients with FM (FM).	Not reported
Kim 2002	55 (B)	Single Group	Validation of a Korean version of FIQ	$\alpha = .80$ $r = .77$
King 2002	128 (F)	Single Group	Predictors of success of interventions for FM	Not reported
Richards 2002	132 (B)	RCT	Evaluate cardiovascular fitness exercise in people with FM	Not reported
Rooks 2002	15 (F)	Single Group	Determine the consequences of progressive strength training and cardiovascular exercise in FM	Not reported

Table 3.1 (continued)

Author, Year	Sample Size	Design	Purpose of Study	Psychometric Evaluation Reported
Valim 2002	100 (F)	Case/Control	Compare maximum oxygen uptake and anaerobic threshold in patients with FM	Not reported
White 2002	100 (B)	Single Group	Determine if the label of FM has a significant effect on health status, function, and health service utilization	Not reported
Zachrisson 2002	100 (F)	Single Group	Construction of an observer rating scale sensitive to change in FM patients	Not reported
Alfano et al. 2001	119 (B)	RCT	To test effectiveness of static magnetic fields of two different configurations as adjunctive therapies in decreasing patient pain perception and improving functional status in individuals with FM	Not reported
Donaldson 2001	30 (B)	Single Group	Effect of raw vegetarian diet on FM	Not reported

Table 3.1 (continued)

Author, Year	Sample Size	Design	Purpose of Study	Psychometric Evaluation Reported
Jentoft 2001	47 (F)	Two Group	Examine the effects of pool-based and land-based exercise programs on patients with FM.	Not reported
Gowans 2001	57 (B)	RCT	Evaluate the effect of exercise on mood and physical function in individuals with FM	Not reported
Goulding 2001	77 (B)	Single Group	Assess the prevalence of rheumatological disease, fatigue and anxiety	Not reported
Mengshoel 2001	33 (F)	Single Group	To examine symptoms, physical function, and nutritional status in FM after 6 to 8 years	Not reported
Poyhia 2001	82 (F)	Single Group	Examine the natural clinical course of pain in FM	Not reported
Worrel 2001	100 (B)	Single Group	Evaluate the efficacy of a treatment program for FM	Not reported

Table 3.1 (continued)

Author, Year	Sample Size	Design	Purpose of Study	Psychometric Evaluation Reported
Culos-Reed 2000	86 (F)	Single Group	Determine whether individuals with FM differ in various psychosocial characteristics from those who are less active.	$\alpha = .80$
Creamer 2000	28 (B)	Single Group	Aim was to examine nonpharmacologic, behavioral-based treatment in FM	Not reported
Kendall 2000	20 (F)	RCT	Compared the effect of two therapies the Mensendieck system and body awareness therapy in FM	Not reported
Neumann 2000	90 (F)	Single Group	Validate a translated version of the Clinical Health Assessment Questionnaire by Hebrew-speaking populations in FM	$\alpha = .93$
Offenbalcher 2000	55 (B)	Single Group	Translation of FIQ into German	$\alpha = .92$ $r = .62$
Sarmer 2000	51 (F)	Single Group	Translate and adapt the FIQ into Turkish	$\alpha = .72$ $r = .81$

FIQ= Fibromyalgia Impact Questionnaire; B = Both Men and Women; F = Women only; RCT = Randomized Controlled Trial; α = Cronbach's alpha; r = intraclass correlation coefficient; FM = Fibromyalgia

Table 3.2 Characteristics of Women with FM and Sleep Disturbance (n = 50)

Characteristic	<i>n</i>	mean	SD	Minimum	Maximum
Age in years	49	47.6	± 10.7	31	72
BMI	47	30.2	± 7.2	19.3	47.4
Symptom Duration in years	47	7.3	± 7.6	< 1	30
Time to Diagnosis in years	45	4.1	± 5.5	< 1	23
FIQ (0-100)	50				
Prestudy		59.1	± 15.6	28	87
Poststudy		54.0	± 16.2	14	87
FACIT-F (0-52)	46	21.1	± 10	4	49
VAS-Fatigue (0-100)	46	64.2	± 15.7	21	95
Average Caffeine/day*	46	1.7	± 1.2	0	5

*8-ounce caffeinated beverage

Table 3.3 Socioeconomic Characteristics of Women with FM and Sleep Disturbance
(n = 50)

	<i>n</i>	%
<u>Ethnicity</u>		
Caucasian	45	90%
Black	2	4%
Hispanic	1	2%
Arab American	1	2%
Unknown	1	2%
<u>Marital Status</u>		
Married	32	64%
Divorced	10	20%
Single/Widowed	5	10%
Unknown	3	6%
<u>Education</u>		
HS Graduate	12	24%
College/Technical School	20	40%
College Graduate	17	34%
Unknown	1	2%

Table 3.3 (continued)

	<i>n</i>	%
<u>Employment Status</u>		
Full Time	32	64%
Part Time	3	6%
Worker's Comp	1	2%
Retired	6	12%
Disabled	6	12%
Unknown	2	4%

Table 3.4 Lifestyle Characteristics of Women with FM (n = 50)

Characteristic	<i>n</i>	(%)
<u>Caffeinated Beverages</u>		
None	9	18%
One beverage	11	22%
Two beverages	16	32%
Three beverages	6	12%
Four +beverages	4	8%
Unknown	4	8%
<u>Pain Medication Use</u>		
Uses Pain Med	45	90%
Does not use	2	4%
Unknown	3	6%
<u>Sleep Medication Use</u>		
Uses Sleep Med	38	76%
Does not use	9	18%
Unknown	3	6%
<u>Anti-depressant Use</u>		
Uses Medication	35	70%
Does not use	13	26%
Unknown	2	4%

Table 3.4 (contd.)

Characteristic	<i>n</i>	(%)
<u>Non-Narcotic Anti-inflammatories</u>		
Uses medication	42	84%
Does not use	6	12%
Unknown	2	4%
<u>Narcotics</u>		
Uses medication	16	32%
Does not use	31	62%
Unknown	3	6%
<u>Muscle Relaxants</u>		
Uses medication	36	72%
Does not use	12	24%
Unknown	2	4%
<u>Steroids</u>		
Uses medication	6	12%
Does not use	42	84%
Unknown	2	4%
<u>Currently Smokes</u>	10	21%
<u>Exercise Behavior</u>		
Reports Daily Exercise	42	80%
Does not Exercise/		
Unknown	8	20%

Table 3.5 Descriptive Statistics and Internal Consistency Reliabilities for the Total FIQ and Subscales (n = 50)

Scale/Subscale/Item	Number of Items	Mean	SD	Potential Range	Actual Range	Cronbach's alpha
Overall Scale	20	59.12	15.6	0 - 100	28 - 87	.85
Physical Impairment						
Subscale	11	4.19	2.43	0 - 10	0 - 8.8	.52
<u>Items:</u>						
Feel Good	1	6.82	1.91	0 - 10	2.9 - 10	
Work Missed	1	2.98	2.93	0 - 10	0 - 10	
Do Work	1	5.91	2.29	0 - 10	1 - 10	
Pain	1	6.85	1.80	0 - 10	1.5 - 10	
Fatigue	1	8.13	1.40	0 - 10	5 - 10	
Feeling Rested	1	7.74	2.00	0 - 10	0 - 10	
Stiffness	1	7.15	2.34	0 - 10	.5 - 10	
Anxiety	1	4.85	2.91	0 - 10	.5 - 10	
Depression	1	4.77	3.06	0 - 10	.5 - 10	

Table 3.6 Rotated Factor Matrix of Fibromyalgia Impact Questionnaire

Items	Factor ^a		
	1	2	3
Physical			
Impairment	.73	.27	-.07
Feel Good	.64	-.01	.31
Work Missed	.73	.13	.11
Do Work	.72	.30	.20
Pain	.55	.49	.16
Fatigue	.21	.18	.85
Feeling Rested	.11	.20	.86
Stiffness	.19	.79	.12
Anxiety	.10	.83	.12
Depression	.27	.77	.21

^aFactor 1 = Physical Function

Factor 2 = Mood and Affect

Factor 3 = Sleep Quality and Fatigue

Table 3.7 One-dimensional Factor Matrix of Fibromyalgia Impact Questionnaire

Items	Factor
	1
Physical	
Impairment	.62
Feel Good	.53
Work Missed	.64
Do Work	.75
Pain	.73
Fatigue	.60
Feeling Rested	.60
Stiffness	.67
Anxiety	.65
Depression	.74

Factor 1: Combined Effect of Pain, Fatigue, and Mood

Table 3.8 Correlations of FIQ Total and FIQ items to Fatigue VAS, FACIT-F and Pain VAS (n = 50)

FIQ/Items	Fatigue VAS	FACIT-F	Pain VAS
FIQ Total	.62	-.65	.65
Physical Impairment	.38	-.51	.44
Feel Good	.42		.45
Work Missed	.28	-.41	.38
Do Work	.49	-.53	.49
Pain	.33		.59
Fatigue	.39	-.32	.42
Feeling Rested	.50	-.40	.61
Stiffness	.47	-.46	.51
Anxiety	.39	-.42	
Depression	.44	-.58	.39

Note. All correlations shown are significant at the $p < .05$

Figure 3.1 Scree Plot for Fibromyalgia Impact Questionnaire Scores $n = 50$

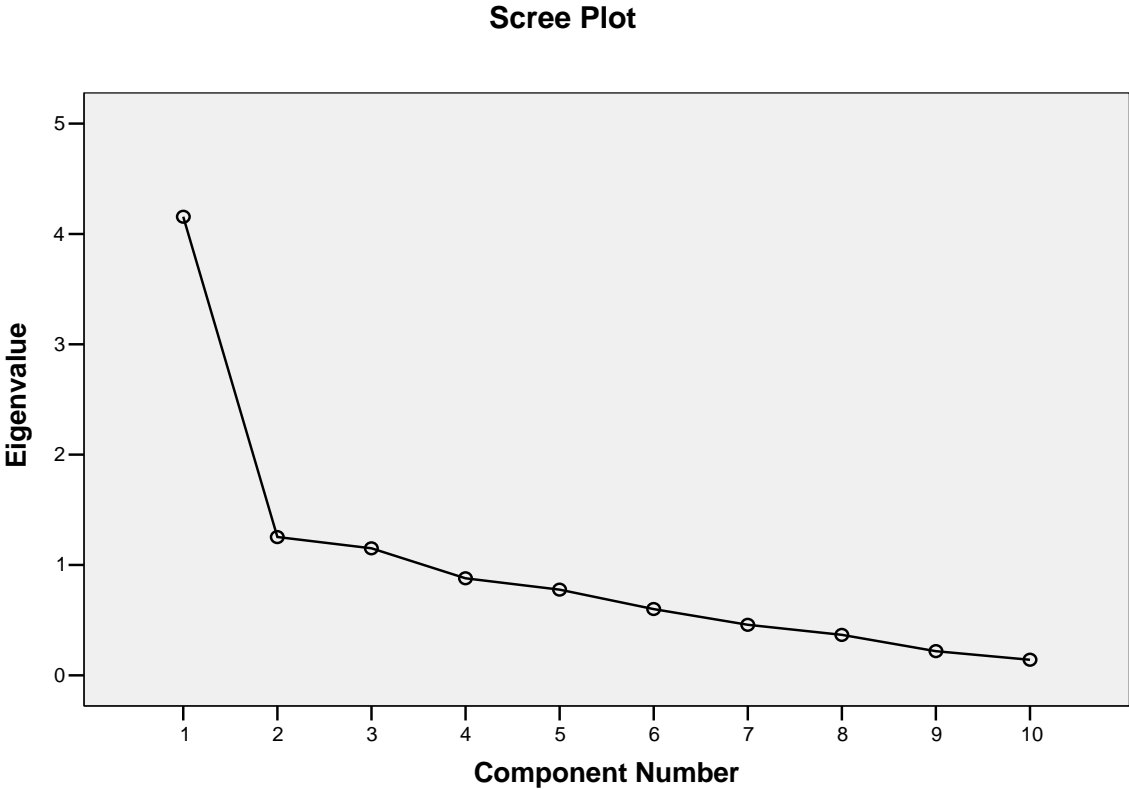
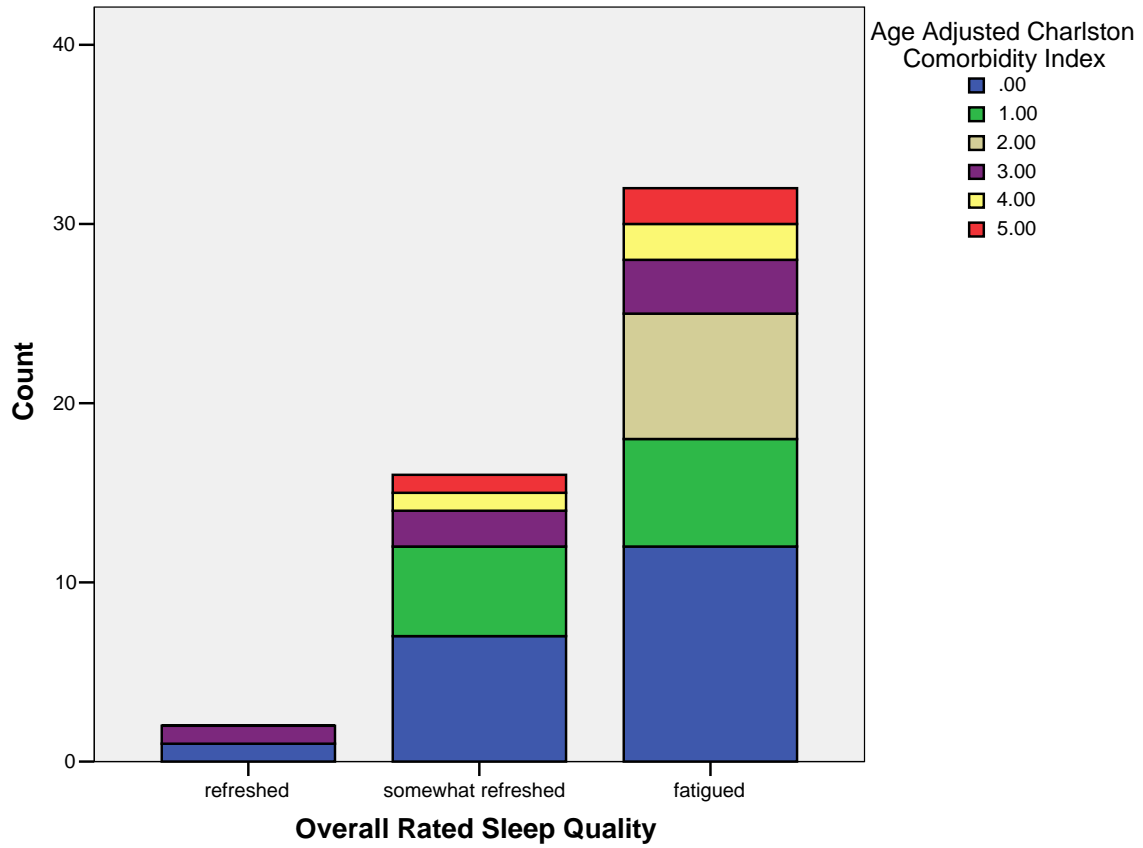


Figure 3.2 Self-Rated Sleep Quality Compared to Charlson Co-morbidity Scale. $n = 50$



CHAPTER FOUR

Psychometric Properties of Activity Based Instruments Compared to Sleep Diaries

The purpose of this investigation was to examine the level of agreement of sleep/wake times obtained through participant created actigraphic time markers to those obtained from entries in the sleep diary performed by women with fibromyalgia. In this study, data obtained using the Actiwatch 16[®] were compared to results from sleep diary entries performed over a week.

Sleep diaries and wrist actigraphy are useful methods for investigation of personal sleep habits and complaints of poor sleep quality (Sadeh, Hauri, Kripke, & Lavie, 1995). Sleep diaries are the most commonly used instrument in sleep research involving insomnia (Vallieres & Morin, 2003). Sleep diaries have been used for collecting information about the sleep wake schedule occurring over multiple cycles or when polysomnography (PSG) is impractical or not indicated (Morgenthaler, Lee-Chiong et al., 2007). Like the sleep diary, actigraphy has also been used to collect data over several days usually in a non laboratory environment. Unlike the sleep diary, the actigraph represents an objective method for estimation of sleep times and patterns.

Actigraphy does not measure sleep as it is defined by PSG nor does it measure the subjective experiences of sleep like diaries or logs (Morgenthaler, Alessi et al., 2007). Polysomnography is a multi-dimensional examination that uses electrocardiography (ECG); electroencephalography (EEG); electrooculography (EOG); electromyography (EMG) including chin movement, limb movements, and respiratory effort (thoracic and abdominal motion); percutaneous oximetry (SPO₂); body position; nasal pressure and airflow; and sound recording of snoring (snorogram) to determine alterations in sleep stages. It usually requires the participant to sleep in a sleep laboratory overnight and the

results require scoring by an expert in sleep medicine to determine the sleep times and alterations in sleep stages (Sewell-Scheuermann & Phillips, 2006).

Sleep diaries collect information about sleep that is recorded by the participant on a daily basis and requires the participant to remember to complete the diary daily and accurately. While sleep diaries are easy to use, the diary may not accurately reflect the actual number of awakenings at night, the time it takes for the participant to fall asleep, or actual time spent asleep.

Actigraphy uses a wrist watch like device worn on the wrist or ankle to measure limb movement (Buysse, 2005; DeSouza et al., 2003). The device contains a miniature motion-based sensor that translates movement into a numerical activity count. Using sophisticated algorithms, actigraphic software converts these raw activity counts to estimates of sleep or wake (Carvalho-Bos, Waterhouse, Edwards, Simon, & Reilly, 2003; Pollak, Tryon, Nagaraja, & Dzwonczyk, 2001; Roehrs, Turner, & Roth, 2000). Sampling of activity counts by the device occurs at frequencies or intervals called epochs, which are stored in the memory of the device for the length of the study. The device may possess a button on the surface that can be used by the participant to mark significant times on the sleep print-outs or actogram, e.g., bedtime and wake time (Currie, Malhotra, & Clark, 2004).

The actigraph was designed as an economical alternative to PSG for collecting objective sleep data. Although PSG and actigraphy both permit an epoch by epoch examination to compare results, one must keep in mind that polysomnography is a multivariate instrument where as actigraphy is univariate (Littner et al., 2003). Research that compares actigraphy to other measures should not imply that one method is better

than the other; instead, it should be viewed as providing evidence about the level of agreement between the methods used to determine sleep (Ancoli-Israel et al., 2003). Discrepancies between methods can only be explained by further research that compares the accuracy of actigraphy to these other measures in other populations and environments.

Review of Literature

Many studies have used actigraphy to estimate sleep times similar to those measured by PSG, the gold standard of sleep research (Morgenthaler, Alessi et al., 2007). These times include bedtime, wake time, sleep onset, sleep offset, TIB, assumed sleep time (AST), total sleep time (TST), SL, sleep efficiency (SE), wake bouts (WB), and wake after sleep onset (WASO). As far back as the 1970's, studies using actigraphy focused on the reliability and validity of actigraphy in measurement of sleep/wake times compared to PSG. In one of the earlier studies, Kripke (1978) noted high level agreement ($> .80$) between actigraphic determined sleep compared to EEG scored sleep ($r = .98, p = .005$), minutes awake within sleep ($r = .85, p = .05$), and TST ($r = .95, p = .01$) in five patients. Elbaz, Roue, and Quera Salva (2002) reported a correlation of $r = .74, p < .0001$ between PSG derived TST and actimetry derived TST, and an absolute TST of 368 ± 81 minutes for PSG versus 373 ± 88 for actigraphy. Shinkoda (1998) reported correlations of $r = .97, p = .001$ for TST and $r = .95, p = .001$ for SL between actigraphy and PSG in six healthy participants. Other reports found similar agreement between actigraphy and PSG for TST in 15 normal subjects (90% agreement) (Matsumot et al., 1998), 228 patients with sleep related breathing disorders (84% agreement)

(Hedner et al., 2004), and 26 infants (84% agreement) (Sazonov, Sazonava, Schuckers, & Neuman, 2004).

Sadeh (1994) reported agreement between actigraphic devices worn on both wrists (91% to 93%) and PSG for sleep/wake identification. In this last study, sleep wake algorithms used with the data explained 62% of the variance according to the multiple correlation reported ($r^2 = .62, p < .0001$). These studies suggest that actigraphy reliably estimates sleep duration similar to PSG (DeSouza et al., 2003).

In contrast to these results, other research has not been as supportive. Actigraphic results from a study of 14 healthy adults suggested that the average probability that a sleep prediction was correct using actigraphy in a 24-hour period was 62.2% (Pollak et al., 2001). Investigators explained this discrepancy as due to the transition between wake and sleep not being fully demonstrated by the actigraph, in other words, that the actigraph may record quiet wakefulness as sleep and nocturnal movements while asleep as being awake. Likewise, Hauri, P., and Wisbey (1992) reported that actigraphy overestimated sleep duration (TST) compared to PSG in 13 people suffering from insomnia (341 minutes versus 313 minutes) and in other participants with a sleep-state misconception, the actigraphy estimations for TST were either inaccurate or underestimated compared to PSG (337 minutes versus 373 minutes). A sleep state misconception is when a person experiences sleepiness and insomnia symptoms without objective findings of a sleep disturbance (Edinger & Fins, 1995). Another important notation noted in these studies was that the night by night variability of sleep estimates was greater in actigraphic measures collected in the participant's home than those measured with actigraphy in the laboratory. This discrepancy in inter-night

stability has been noted in healthy persons and persons with insomnia (Lichstein et al., 2006; Wilson, Watson, & Currie, 1998) and might be explained by the more controlled environment of the laboratory compared to the participants home setting.

Sleep diaries and actigraphy have been used in the assessment of insomnia, jet lag, shift work, sleep apnea, and in many other conditions and populations (Cole, Kripke, Gruen, Mullaney, & Gillin, 1992; Eriksen & Akerstedt, 2006; Hinds et al., 2007). Vallieres and Morin (2003) compared sleep diaries and actigraphy to PSG in 16 participants with insomnia. Pair-wise comparisons revealed that sleep-diary data differed significantly from actigraphy and PSG data and that both the diary and actigraphy overestimated total WASO relative to PSG. Objective sleep estimates (OSE) indicated that actigraphy and the sleep diary underestimate TST and SE; and that actigraphy underestimates SL while the sleep diary overestimates it compared to PSG determined times.

Unlike the above results, Wilson (1998) found the sleep diary and actigraphy were consistent in the estimation of TST (318 ± 105.4 minutes versus 349 minutes ± 125.5) and SE (70.5 ± 21.2 versus 76.4 ± 21.6) in 40 patients with chronic musculoskeletal pain; however across night variability was high resulting in low to moderate reliability coefficients for these measures (TST $r = .34 - .40$ & SE $r = .14 - .24$) and low estimates of shared variance (r^2) between the sleep diary and actigraphy (1-19%). In Westermeyer et al. (2007), results suggest that sleep logs did not reproduce actigraphic readings in patients with post traumatic stress syndrome (PTSD) even though the sleep logs were reliably quantified ($n = 21$). Currie (2004) noted correlations of $r = .46$, $p = .001$ for TST determined by sleep diaries compared to actigraphy in recovering

alcoholics. Evaluation of 49 blind individuals noted statistically significant differences in all sleep parameters compared to subjective assessments (Lockley, Skene, & Arendt, 1999). In Lockley's study, actigraphy showed shorter SL, earlier sleep onset, delayed sleep offset, and longer sleep duration compared to sleep diary. The discrepancy was largest when measuring sleep duration and smallest when comparing sleep timing (sleep onset & offset). All together, these research conclude that actigraphy underestimates SL and over estimates TST and SE and that sleep diaries over estimate SL and underestimate TST and SE compared to PSG (Tryon, 2004).

Research conducted with actigraphy in persons with fibromyalgia has been sparse. Results from a review of the literature of studies conducted in persons with fibromyalgia and using actigraphy are noted in Table 4. 1. Even though the scope of these studies was not to compare diaries to actigraphy, these reports are evident of the usefulness of actigraphy. All three studies compared groups using sleep diaries and actigraphy and noted significant differences in variables measured by actigraphy between the groups. This finding reinforces the usefulness of actigraphy to detect differences between intervention groups and to identify differences in sample characteristics regardless of its concordance to sleep diary and PSG.

The specific aims of this study were to: determine the degree of concordance of sleep times over seven days (bedtime, sleep onset, sleep offset, wake time, and time in bed [TIB]) of the actigraph and the sleep diary; evaluate the internal consistency and stability of the sleep diary and the actigraph in the measurement of the total sleep time (TST) and sleep latency (SL); and determine the level of agreement for TST and SL between the two methods in women with FM and sleep disturbance. It was hypothesized

that the internal consistency of the sleep diary and actigraph over 7 days will be strong due to the use of actigraphic sleep markers and an easy-to-complete sleep diary to establish bedtime and awake time in conjunction with reliable software that determines sleep onset and offset; however, inter-night stability will be weak ($< .60$) due to factors that affect the regularity of the sleep schedule over time in sleep disturbed women. $.85$ is considered benchmark for both internal consistency and stability (Currie et al., 2004).

Methods

Sample and Design

Fifty-seven women with a prior diagnosis of FM (self-report) and perceived poor sleep quality consented to participate in a week long sleep study using actigraphy and a sleep diary. The longitudinal data for this psychometric assessment were collected from a volunteer, community based sample of women aged 18 or older recruited using an institutional review board approved flyer. The recruitment flyers were placed in physician's offices or posted on FM related websites on the internet. Fifty women enrolled, who fulfilled the inclusion and exclusion criteria, and completed the study procedures.

To enroll, the participants had to have FM and perceive their sleep quality as poor. Women who worked night shift, did not have a diagnosis of FM, or were diagnosed/treated for sleep apnea were excluded from participation. The criteria were verified with each participant in person, by phone, or by email before enrollment. The diagnosis of FM and the type of physician that diagnosed them was reported by the participants, however, a physical exam was not performed nor were medical records used to verify the diagnostic criteria of FM. According to the American College of

Rheumatology, 11 of 18 tender points for three or more months is diagnostic for FM (Wolfe et al., 1990). To estimate the number of tender points, the women were asked to note painful areas on a body map included in the study materials. The percentage of body pain and number of tender points were estimated using procedures previously published (Margolis, Tait, & Krause, 1986).

Actigraphic Measures

Objective estimates of sleep obtained using the Actiwatch are noted in Table 4.2 (Mini Mitter Company, 2004). Most of the women wore the wrist watch device constantly for at least seven days. The device was configured to sample activity every minute during the time that the device was on the participant, thus the sampling interval was 1 minute epochs. The device was placed on the non-dominant wrist (Littner et al., 2003). The sensitivity threshold was set at 40 or medium sensitivity (Edinger, Wohlgemuth, Krystal, & Rice, 2005). The software used with the device to determine sleep times was Actiware Sleep 3.4 (Mini Mitter Company, 1998-2003). Reliability of this device to PSG has been published elsewhere (Gironda, Lloyd, Clark, & Walker, 2007; Kushida, 2001). Initial configuration of the device was performed immediately before being placed on the participant; however, in this data set the device might have also been mailed to the subject and started when received by them. The time record of the Actiwatch was verified using the world clock located online. The actigraphic study start time was noted by the participant depressing the button on the watch when applying it for the first time, thereby placing a marking at that time in the data of the device (Korszun et al., 2002). Participants were instructed to wear the device constantly, depress the same button at bed time and awake time, as well as when taking a nap during the day or when getting up out of bed at night. These markings can be seen on print-outs

or actograms (See Figure 4.1). Each device's data was downloaded and examined manually using the software.

Sleep Diary

The participant also completed a sleep diary once a day, which asked them to indicate various sleep times (bedtime, wake time, time to fall asleep, number of times awake after sleep onset, and number of times out of bed), any special medication use, and other questions regarding caffeine, naps, and exercise. If the participant recalled waking up or got up out of bed or took a nap or exercised, these events were also recorded in the sleep diary. An example of the sleep diary is noted in the appendix.

In addition to the sleep diary and the actigraph, a detailed demographic and medical history questionnaire was completed by the participants. This questionnaire also included several standardized instruments: the Fibromyalgia Impact Questionnaire (FIQ), the Epworth Sleepiness Scale (ESS), the Functional Outcomes of Sleep Questionnaire, a pain visual analogue scale (Pain VAS), and a fatigue visual analogue scale (Fatigue VAS) (Burckhardt, Clark, Bennet, 1991; Chervin, 2003; Weaver et al., 2007).

Using these two methods, two sets of data on sleep times were created. First, using the bedtime and wake time from entries in the sleep diary, the actigraph software determined sleep onset, offset, TIB, TST, and SL. Then using actigraphic markers created by the participant for bedtime and wake time, the software again determined the same variables for these markers. If markers were not present, the software automatically set times for bedtime or wake time and these were used here.

Procedure

The study was approved by the Medical Institutional Review Board at the University of Kentucky. Informed consent was obtained in writing from each participant in person or through the mail by mailing the consent to her home. The actigraph and study materials were mailed to participants. Data from the actigraph and sleep diary were collected over one week. These two sets of data (bedtime, sleep onset, TIB, sleep offset, & wake time) were compared using paired sample *t* tests and Pearson's correlation. The TST and SL were scored for each night of the week and Cronbach's alpha was calculated to examine internal consistency for this 7-day period. To examine the stability of the sleep diary and actigraph, the data from nights one and two were averaged and compared with the averaged data from nights 5 and 6 using Pearson's *r*. To examine the agreement between the sleep diary and the actigraphy on TST and SL, these results were averaged and compared using Pearson's correlation. This procedure was used previously with actigraphy and sleep logs (Currie et al., 2004). The averaged absolute disagreement between the sleep diary and actigraphy was determined for the sleep estimates. The objective sleep estimate (OSE) was calculated as reported in Currie (2004). An OSE = $SD/ACT \times 100\%$, where SD is the sleep diary parameter (TST, SL) and ACT is the actigraphy parameter (TST, SL). An OSE of 100% means perfect agreement. A finding $> 100\%$ means the sleep diary was greater.

Results

Participants completed their sleep diaries 100% of the time compared to applying time markers only 87% of the time. The demographics for the sample are summarized in Table 4.3. The sample was female, mostly Caucasian (90%) with a mean age of $47.9 \pm$

10.4 years, and diagnosed with FM for at least 3.9 ± 5.3 years. The duration of disease was 7.2 ± 7.6 years; 21% currently smoked cigarettes; their mean BMI was 29.9 ± 7.2 ; and 72% of these women were employed in some capacity (see Table 4.4). The entire sample had at least a high school education and 34% of the sample were college graduates. Sleep characteristics for the cohort using sleep diary times averaged over seven days indicated decreased total sleep time (TST) ($M = 06:19 \pm 1:17$) and mean SL of at least 00:30 minutes to fall asleep (see Table 4.5). Table 4.6 reveals the mean times recorded for bedtime, wake-time, sleep onset, sleep offset, and total time in bed calculated for the seven days of actigraphy and sleep diary entries.

Eighty six percent indicated that they did not have refreshing sleep and 88% of the sample self-reported that they had trouble falling asleep or staying asleep. Fifty-seven percent of the sample indicated that they wake up in the early hours unable to fall back asleep. According to the sleep diary, the participants rated their sleep latency or the time it takes them to fall asleep as a mean of 46 minutes (SD 41 minutes) or more and indicated that their actual sleep time was 6.87 hours (2.33). Almost half of the participants indicated that they used an alarm clock to awaken themselves. When asked to rate their overall sleep quality (0 = refreshed, 1 = somewhat refreshed, and 2 = fatigued), 31% indicated their sleep was somewhat refreshed and 65% indicated that they were fatigued. Only 3.5% indicated that they felt they had refreshing sleep.

Using paired sample t tests, significant differences were noted in sleep onset time between the sleep diary and actigraphy on day 4 [$t(49) = 2.18; p = .03$]; otherwise, no other differences were noted between times reported in sleep diaries and times noted by actigraphic time markers (See Table 4.7). Intraclass coefficients (ICC) revealed

significant correlations for all times for all days. ICC's were good for bedtimes with all correlations $> .60$ (see Table 4.8). The other comparisons had a mixture of weak to strong correlations ranging from $.31 - .89$. Overlapping variance of the two measures was calculated using the multiple correlation or by squaring the ICCs (r^2). The percentage of variance explained ranged from 9-79% across 7 days.

Assessment of the consistency of the two methods over seven days using Cronbach's alpha revealed strong coefficients $> .85$ for both the sleep diary and actigraphy for sleep onset and sleep offset, but the consistency of remaining variables was stronger for the sleep diary than for the actigraphic time markers (see Table 4.9). Coefficients for TIB, SL, and TST ranged $.78 - .83$ for the 7-day sleep diary, whereas alpha coefficients for actigraphy ranged $.54-.62$ for TIB, SL and TST. The average internal consistency coefficients for the sleep log and the actigraphy measures across multi-night assessment are $.85$ and $.70$, respectively. Table 4.10 provides summary statistics comparing estimates for averaged parameters derived from the sleep diary to their actigraph counterparts. The averaged nightly correlation between the diary and the actigraph ranged $.71$ for SL and $.73$ for TST. Over one week, the averaged absolute disagreement between the methods ranged 28 minutes for SL to 43 minutes for TST. The OSE for SL indicates the sleep diary/actigraphy estimate were 100% for SL and 96.7% for TST, or the sleep diary and actigraphy was in perfect agreement for the SL and sleep diary slightly longer for TST than the actigraph.

Discussion

These results confirm poor sleep quality in this sample of women with FM. Decreased sleep duration and increased sleep latency are reflected in both the sleep diary

and actigraphic data. Discrepancies between the results of the two methods parallel the findings of other studies (Wilson et al., 1998). Poor sleepers spend more time trying to fall asleep and more time awake after sleep onset so more random error is associated with their assessment (Currie et al., 2004).

Remarkably, this sample of women completed the sleep diaries 100% of the time, with the actigraphic markers being noted an average of 87% of the days. Sleep times recorded and calculated using both methods were similar and their means were not statistically different. Since the participants had no way to retrospectively mark the actogram by pushing the button, this indicated that the entries in the sleep diaries--even if some were applied retrospectively --were comparable to the bedtime and wake time of the actigraphic time markers or software applied times.

The intercorrelation coefficients (ICC's) between the two methods were strong for bedtime and moderate the first few days for the other sleep variables. The ICC's for wake time, sleep onset, sleep offset, and TIB did increase in strength overtime. This could be due to less spread between the estimates or this could also be statistical artifact due to the range of sleep duration widening even if the measures are constant (Gale, Signal, & Gander, 2004). From these bi-variate correlations, we calculated the correlation coefficient squared (r^2) also called the coefficient of determination or multiple correlation (*Nieswiadomy, 2008*). The square of a correlation coefficient is a direct indication of the percentage of variability in one variable that can be explained by variability in the second variable. In this example, it is the shared proportion of variance that can be explained by actigraphy and the sleep diary. Or put another way, to explain 50% of the variance in the results, a correlation of .708 would be necessary between the

two. R^2 calculated from these results ranged from .10-.79 meaning that certain days the sleep diary and actigraph together could be used to explain 10 -79% of the variance of the results. Shared variance using both instruments had a wide range, but was good to moderate and explained more variance in the sleep times than in previous research (Wilson et al., 1998). Moderate correlations mean decreased explanation of variance. Unfortunately, the unexplained variance in the estimates also had a wide range over the 7 days.

Sleep estimates for TST ($r = .73, p < .01$) and SL ($r = .71, p < .01$) were comparable between the methods when averaged over the seven days, but stability was poor for SL using the sleep diary ($r = .27, p = \text{NS}$) compared to the actigraph ($r = .61, p < .01$). The opposite occurred with TST, with the sleep diary having better stability coefficients ($r = .58, p = .01$) compared to the actigraph ($r = .18, p = \text{NS}$). These results parallel other studies reporting extensive night to night variability typical of persons suffering from insomnia (Vallieres, Ivers, Bastien, Beaulieu-Bonneau, & Morin, 2005) .

A proposed explanation for these results is that the participant was consistent about writing in the sleep diary and pushing the actigraph event marker resulting in highly consistent sleep onsets and sleep offsets. However, the results of these methods are subject to other influences in determining the actual time to fall asleep (SL) and the actual time spent asleep (TST). These influences may be tendencies to lay quietly in bed while awake where movement is too sparse for detection by the actigraph resulting in the software interpreting it as sleep or significant movement at night while still asleep that is interpreted as being awake. Or episodes noted as wakefulness on the actigraph may not be remembered by the participant so a discrepancy exists between the actigraph and the

sleep diary. This discrepancy between the actigraph and the sleep diary to determine sleep onset after bedtime or to identify actual arousal after sleep onset may create reliability issues for some investigators considering these instruments for the estimation of sleep times. This is the case with nocturnal actigraphic wake bouts.

Throughout the week, the participants in this research were noted to have a mean count of 23 wake bouts throughout each night lasting approximately two-minutes on average. It is unknown whether these events are actually associated with wakefulness or the sensitivity of the device to motion. This is particularly important if arousals result in fragmented sleep rather than just shortened sleep (Tryon, 2004). However, if they are bouts of wakefulness, the frequency and duration of them could significantly impact overall sleep duration or TST.

In this research, further analyses of the study variables were performed using the mean wake bout frequency for these women with FM as a mid-point: wake bouts of 23 or less were compared to participants with more than 23 using independent sample *t* tests (see Table 4.11). Significant differences in TIB, assumed sleep time, TST, circadian period, and sleepiness were noted. Interestingly, lower levels of nocturnal wake bouts (< 23) were associated with lower TIB, lower TST, prolonged circadian period, and increased ESS scores or self reported hypersomnolence in these patients. It may be that these arousals, although transient, may not result in behavioral awakening, but do contribute to overall impact on sleep time, sleep quality and circadian rhythm. Further, the sleep diary may not be efficient in determining short bouts of wakefulness that appear as wakefulness on the actigraph despite the indication that the instruments estimate similar sleep times.

The frequencies of actigraphic wake bouts have been reported in the literature. In healthy children 12 – 60 months old, four or more wake bouts per night lasting three or more minutes were noted on actigraphy (Acebo & LeBourgeois, 2006). In this case, actigraph-based wake minutes and wake bouts were higher than maternal diary reports for all age groups. In a study of hospitalized children with cancer, the number of nocturnal awakenings per night ranged from 0–40, although some of these may have been due to the frequency of hospital staff entering the child’s room for care purposes. They were found to be related to higher fatigue levels by patient report. Children who experienced 20 or more awakenings had significantly higher fatigue scores than those with fewer awakenings (Hinds et al., 2007). Lockley (1999) reported significantly different frequencies of nocturnal awakenings on actigraphy compared to sleep diaries (7 versus 2, $p < .05$) in 49 registered blind individuals. Despite this, there was good agreement between the methods for measuring changes in sleep patterns over time. Actigraphic studies conducted with adolescents compared to adolescents with chronic musculoskeletal pain reported similar frequencies of wake bouts using actigraphy in both groups (1.6 versus 3.8, $p = .18$) (Palermo, Toliver-Sokol, Fonareva, & Koh, 2007).

Studies with frequencies greater than those reported in this research occurred in a study comparing participants with heart failure to normal controls (Redeker & Stein, 2006). Participants with heart failure had 56 bouts of actigraphic wakefulness compared to 41 bouts in the comparison group ($p = .002$). Children aged 6 – 12 years with attention deficit hypersensitivity disorder (ADHD) and sleep onset insomnia (SOI) had similar frequencies of wake bouts compared to ADHD children without SOI (38.8 versus 38.2, $p = NS$) (Van der Heijden, Smits, Van-Someren, & Gunning, 2005). The

significance of these actigraphic wake bouts to the level of sleep fragmentation remains unknown.

The frequency of these wake bouts was much lower than that demonstrated in sleep disordered conditions frequently associated with sleep disordered breathing, e.g. obstructive sleep apnea, upper airway resistance syndrome. This finding may be explained several ways. One perspective is that the usual criteria applied to patients with sleep disordered breathing may not be applicable in sleep disturbed persons with FM. Typically, respiratory effort related arousals (RERA) noted on polysomnography are associated with increasing respiratory effort and progressively more negative esophageal pressure terminating in an arousal that lasts longer than 10 seconds which actigraphy may not be sensitive enough to determine (ASDA/SRS, 1992; Kushida et al., 2005).

In the absence of sleep disordered breathing (SDB), sleep disruption and sleep fragmentation have been shown to produce daytime sleepiness. Daytime sleepiness in persons with FM has been linked to greater severity of symptoms from FM (Sarzi-Puttini, Rizzi, & Andreoli, 2002). This research showed that persons with hypersomnolence and FM had significantly greater PSG determined nocturnal arousals per hour (10 versus 6, $p = .01$), more tender points (15 versus 12, $p = .01$), higher pain scores (72 versus 52, $p = .05$), and greater fatigue (80 versus 62, $p = .05$) compared to the FM group without hypersomnolence. Arousals noted on PSG are characterized by changes in the EEG and other PSG determined measures using specific criteria to properly and reliably score sleep stages, but the transient nature of those determined by actigraphy has not been investigated thoroughly.

Within this research, the variance of the average SL and TST explained by sleep diary and actigraphy (50 – 53%) appears satisfactory compared to the evidence on variance explained by other important medical tests like the measurement of arterial oxygen saturation using finger pulse oximetry ($r^2 = .71$); or detection of rheumatoid arthritis by Immunoglobulin-G ($r^2 = .65$), or identification of deep vein thrombosis by ultrasound ($r^2 = .36$) (Meyer, Finn, & Eyde, 2001). A lower level of agreement may be acceptable and appropriate depending on the context of the study or clinical situation, but it should not infer that one method is better or more accurate than the other is or that it is without error.

In fact, the minimum agreement between actigraphy and sleep diaries has not been determined (Tryon, 2004) and we agree there is no reason to hold actigraphy to a higher standard than the common medical tests used in everyday practice; instead we must investigate the systematic differences between the instruments and the random error that fluctuates with their use between participants and within them. Complete concordance between instruments cannot be expected when the instruments purportedly measure the same thing in different ways.

More important to any investigation is the ability of all instruments combined to explain more of the differences or variability within the intended application. The strength of actigraphy lies in evaluating patterns of sleeping and its intra-individual stability over time including trends like weekday to weekend day study or examination of daily circadian rhythms (Hauri & Wisbey, 1992).

Actigraphy can provide opportunities for estimations of sleep/wake rhythm information that sleep diaries or PSG are limited or cannot determine, e.g., naps, daytime

activity, mobility within the study, caloric expenditure, etc. However, since measurement of sleep quality remains a complex process that is influenced by individual lifestyle, multiple measures are necessary to capture its components especially in women with FM.

A final implication of our study is that women in our study consider themselves suffering from insomnia. Estimates of sleep from their sleep diaries and actigraphy confirm this. These absolute estimates and averages of them provide sufficient reliable information about the group effects suffering sleep disturbance and therefore have the potential to be sensitive to individuals suffering with insomnia. The differences noted between and within the methods may be biological and not necessarily technical (Pollak et al., 2001). The clinical significance of a 28-minute disagreement on SL between the diary and actigraphy may be insignificant if both methods show that the individual is having trouble falling asleep, is awakening frequently, and the person perceives it this way. For individual clinicians using actigraphy with their clients that have similar findings, further evaluation of their sleep is necessary in a formal sleep laboratory to rule out other pathological conditions. For investigations using actigraphy to discover differences from treatment effects, these findings should be very encouraging.

Several limitations are noted with this research. Because the women did not undergo PSG, concordance between these measures and the significance of these wake bouts with the gold standard could not be reported. PSG would have also been helpful to rule out other undiagnosed conditions that contribute to nocturnal activity or arousal during sleep. These include restless leg syndrome (RLS), paroxysmal leg movement (PLM), and sleep disordered breathing (SDB) (Sforza, Johannes, & Claudio, 2005). Only a few of these women had undergone a PSG and those that did, did not demonstrate

conclusive findings of these conditions. Unfortunately, from this research, no evidence was provided that actigraphy can reliably identify the time or duration of nocturnal awakenings that may occur as a result of pain, anxiety, or any one or more of these other conditions (Pollak et al., 2001). The advantage of actigraphy over PSG is that its use does not require a laboratory and because of this fact it may not actually have differences in estimations of sleep latency or duration as it has been demonstrated to do in the lab in these other studies, however, it may not be sensitive enough to diagnose a sleep related breathing disorder or differentiate between insomnia and restless legs that may contribute to the inter night variability of activity (Lauderdale et al., 2006). Further research is necessary to identify the significance of wake bouts noted on actigraphy compared to arousals on PSG in people without RLS, PLM, and SDB or FM. Another limitation is the absence of a control group to examine the concordance and stability in a group of women without FM or in men with FM. However, none of these limitations detracts from this evidence the usefulness of actigraphy in the evaluation of women with FM.

Areas for future research might focus on the potential artifacts that arise in the combined use of sleep diaries and actigraphy. These might include the reliability of one's memory in completing the sleep diary or pushing the event marker. Or might include a more intensive investigation using PSG to determine nocturnal movements resulting in arousal and concordance of the actigraph to correctly predict wakefulness compared to PSG scored arousals.

Conclusion

These results further support the use of actigraphy as a reliable measure in determination of sleep patterns and individual estimation of sleep times. Actigraphy has

been previously compared to other instruments to measure sleep quality with the assumption that these methods may be more or less reliable than actigraphy for determining sleep wake. Instead, the conclusion of any comparisons should be that these methods measure sleep differently from each other and through their combined use allow researchers to explain higher percentages of the variance in their results and improve generalizability of their results.

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Table 4.1 Actigraphic Studies Conducted in Persons with Fibromyalgia

<u>Author</u>	<u>Sample</u>	<u>Study Purpose</u>	<u>Measures Used</u>
Edinger 2005	47 Persons with FM & chronic insomnia complaints Randomized Controlled Trial	Compared CBT, sleep hygiene instructions, and usual care	Polysomnography Sleep logs Actigraphy Questionnaires
Korzun 2002	16 Persons with FM 6 with FM/Depression 9 with Depression 28 Healthy Controls	Compared levels of activity and sleep in FM patients with & without depression to depressed persons & healthy controls	Actigraphy using Event Markers
Landis 2003	23 Women with FM 22 Women Controls (without FM)	Compare self- reported sleep quality, fatigue, between women with and without FM	Sleep diary Actigraphy Questionnaires

FM = Fibromyalgia CBT = cognitive behavioral therapy

Table 4.2 Terms and Definitions of Sleep Times obtained by the Actigraph

- **Bedtime**-this parameter is set by the entries in the sleep diary or the actigraphic time marker applied by the participant. It represents the time that the subject went to bed or turned off the lights. It is expressed in hours and minutes.
- **Wake time**-this parameter is set by the entries in the sleep diary or the actigraphic time markers. It represents the time that the subject left the bed or turned on the lights. It is expressed in hours and minutes.
- **Sleep onset**-this parameter is automatically calculated by Actiware Sleep 3.4. It was determined by the software searching for the first 10 minute period in which no more than one epoch is scored as mobile. It is expressed in hours and minutes.
- **Sleep offset**-this parameter is automatically calculated by Actiware Sleep 3.4. It was determined by the software searching for the last 10 minute period in which no more than one epoch is scored as mobile. It is expressed in hours and minutes.
- **Total time in bed (TIB)**-this parameter is the difference between bedtime and wake time. It is determined in hours and minutes.
- **Assumed sleep time (AST)**-this parameter is the difference between bedtime and wake time minus the time to fall asleep or sleep latency. It is determined in hours and minutes.
- **Total Sleep Time (TST)**-this parameter is the difference between bedtime and wake time minus the sleep latency and minus the total time after sleep onset recorded as a wake (wake bout). It is expressed in hours and minutes.
- **Sleep Latency (SL)**-this parameter is the time required for sleep onset after going to bed. Latency is the period between bedtime and sleep onset.

Table 4.2 (continued)

- **Sleep Efficiency (SE)**-this parameter is a ratio of AST to TIB. Determined by dividing AST by TIB x 100.
 - **Wake Bout**- this parameter represents the number of continuous blocks of wake calculated by the software between the times of sleep onset and sleep offset.
 - **Mean wake bout time**-this parameter is the average length of bouts of continuous wake determined by the software.
-

Table 4.3 Characteristics of Women with FM and Sleep Disturbance (N = 57)

Characteristic	<i>n</i>	Mean	SD	Minimum	Maximum
Age in years	53	47.9	10.4	31	72
BMI	51	29.9	7.2	19.3	47.4
Disease Duration (yr)	51	7.2	7.6	0	30
Time to Diagnosis (yr)	49	3.9	5.3	0	23
FIQ (range 0-100)	53				
Pre-study		59.0	15.6	28	87
Post-study		54.2	15.8	14	87

BMI = Body Mass Index

FIQ = Fibromyalgia Impact Questionnaire

Table 4.4 Socioeconomic Characteristics of Women with FM and Sleep Disturbance

(N = 57)

Characteristic	<i>n</i>	%
<u>Ethnicity</u>		
Caucasian	48	90%
Black	2	4%
Hispanic	1	2%
Native American	1	2%
Arab American	1	2%
<u>Marital Status</u>		
Married	33	64%
Divorced/Widowed	19	36%
<u>Education</u>		
HS Graduate	13	22%
Some College/		
Technical School	20	41%
College Graduate	18	35%
Unknown	1	2%
<u>Employment Status</u>		
Full Time	32	64%
Part Time	3	6%
Worker's	1	2%
Compensation		
Retired	6	12%
Disabled	6	12%
Unknown	2	4%

Table 4.5 Sleep Characteristics of Sleep Disturbed Women with FM: Averages over 7 days (n = 50)

Maximum Characteristic	# (SD)	Min/Max	Mean (SD) hh:mm	Minimum hh:mm	hh:mm
Total Time in Bed			8:21 (1:13)	04:04	11:22
Assumed Sleep Time			07:20 (01:32)	04:21	09:56
Total Sleep Time (TST)			6:19 (1:17)	03:05	08:41
Average Sleep Latency (SL)			00:31 (0:35)	00:01	02:52
Length of Wake bout			00:02 (0:01)	00:01	00:06
Average Wake bouts					
After sleep onset	23 (7)	9/50			

Total Time in Bed = (Bedtime –Wake time from Sleep Diary)

Assumed Sleep Time = (Bedtime –Wake time from Sleep Diary) – (Sleep Latency)

Total Sleep Time = (Bedtime –Wake time from Sleep Diary) – (Sleep Latency)-(Total Wake Bout time x #Wake bouts)

Sleep Efficiency = Actual Sleep Time/Total Time in Bed

Table 4.6 Sleep Times from Sleep Diary and Actigraphic Time Markers ($n = 50$)

Day	Bedtime (hh:mm) (SD)	Wake time (hh:mm) (SD)	Sleep Onset (hh:mm) (SD)	Sleep Offset (hh:mm)(SD)	Total in Bed (hh:mm)(SD)
Day 1					
Sleep Diary	23:23 (1:55)	7:36 (2:30)	00:00 (1:53)	7:25 (2:27)	8:13 (2:25)
Actigraphic Time Markers	23:03 (2:04)	8:10 (2:59)	23:49 (2:05)	7:10 (2:16)	8:45 (2:03)
Day 2					
Sleep Diary	23:36 (1:54)	8:03 (2:07)	00:00 (1:53)	7:25 (2:27)	8:27 (2:32)
Actigraphic Time Markers	23:18 (1:58)	7:51 (2:25)	23:51 (1:58)	7:53 (3:10)	8:36 (2:26)
Day 3					
Sleep Diary	23:38 (1:51)	7:49 (1:39)	00:11 (2:05)	7:11 (1:52)	8:11 (1:46)
Actigraphic Time Markers	23:34 (1:50)	7:53 (2:02)	00:07 (2:06)	7:48 (2:54)	8:05 (1:59)
Day 4					
Sleep Diary	23:19 (1:31)	7:44 (1:57)	00:01 (1:33)	7:08 (2:04)	8:24 (1:47)
Actigraphic Time Markers	23:15 (1:59)	7:58 (2:18)	23:45 (1:48)	7:39 (2:20)	8:38 (2:01)
Day 5					
Sleep Diary	23:25 (1:43)	7:48 (1:43)	23:52 (1:45)	7:21(1:46)	8:24 (1:45)
Actigraphic Time Markers	23:33(2:01)	7:55 (2:18)	23:59 (2:05)	7:36 (2:19)	8:24 (1:51)
Day 6					
Sleep Diary	23:31 (1:40)	7:43 (1:25)	00:01 (1:46)	7:22 (1:31)	8:12 (1:16)
Actigraphic Time Markers	23:17 (1:53)	7:44 (1:43)	23:40 (1:47)	7:29 (1:41)	8:28 (1:48)
Day 7					
Sleep Diary	23:25 (1:42)	7:43(1:49)	23:57 (1:44)	7:21 (1:59)	8:19 (1:15)
Actigraphic Time Markers	23:17 (1:53)	7:38 (2:03)	23:45 (1:56)	7:19 (2:06)	8:15 (1:24)

Table 4.7 Paired Sample T Tests of Sleep Times Recorded by Sleep Diary Entries versus Actigraphic Time Markers

Day	BEDTIME <i>T</i> (DF); <i>P</i> value	WAKETIME <i>T</i> (DF); <i>P</i> value	ONSET <i>T</i> (DF); <i>P</i> value	OFFSET <i>T</i> (DF); <i>P</i> value	TOTAL IN BED <i>T</i> (DF); <i>P</i> value
Day 1					
Sleep Diary	1.72 (49); <i>p</i> =.09	-1.22 (49); <i>p</i> =.22	.65 (49); <i>p</i> =.52	.80 (49); <i>p</i> =.43	-1.45 (49); <i>p</i> =.15
Actigraphic Time Markers					
Day 2					
Sleep Diary	1.2 (49); <i>p</i> =.23	.65 (49); <i>p</i> =.52	.67 (49); <i>p</i> =.51	-1.12 (49); <i>p</i> =.27	-.39 (49); <i>p</i> =.69
Actigraphic Time Markers					
Day 3					
Sleep Diary	.28 (49); <i>p</i> =.78	-.28 (49); <i>p</i> =.79	.30 (49); <i>p</i> =.77	-1.88 (49); <i>p</i> =.07	.28 (49); <i>p</i> =.78
Actigraphic Time Markers					
Day 4					
Sleep Diary	.32 (49); <i>p</i> =.74	-.82 (49); <i>p</i> =.42	2.18(49); <i>p</i>=.03*	-2.02 (49); <i>p</i> =.05	-.84 (49); <i>p</i> =.41
Actigraphic Time Markers					
Day 5					
Sleep Diary	-.58 (48); <i>p</i> =.56	-.58 (48); <i>p</i> =.57	-.59(48); <i>p</i> =.56	-1.59 (48); <i>p</i> =.12	-.02 (48); <i>p</i> =.99
Actigraphic Time Markers					
Day 6					
Sleep Diary	.99 (47); <i>p</i> =.32	-.06 (47); <i>p</i> =.95	1.9 (47); <i>p</i> =.05	-0.70 (47); <i>p</i> =.49	-1.05 (47); <i>p</i> =.31
Actigraphic Time Markers					
Day 7					
Sleep Diary	.65 (46); <i>p</i> =.51	.38 (46); <i>p</i> =.38	1.22 (46); <i>p</i> =.23	.24 (46); <i>p</i> =.81	.46 (46); <i>p</i> =.65
Actigraphic Time Markers					

*Significant at alpha level <.05

Table 4.8 Intraclass Coefficients and Variance of Sleep Diary Times and Actigraphic Time Markers

BEDTIME ACTOGRAM	SLEEP DIARY							<i>p</i> value	<i>r</i> ²
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7		
Day 1	.78							.00	.61
Day 2		.60						.00	.36
Day 3			.62					.00	.38
Day 4				.69				.00	.48
Day 5					.67			.00	.45
Day 6						.60		.00	.36
Day 7							.74	.00	.55
WAKE TIME ACTOGRAM	SLEEP DIARY							<i>p</i> value	<i>r</i> ²
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7		
Day 1	.31							.03	.10
Day 2		.52						.00	.27
Day 3			.54					.00	.29
Day 4				.54				.00	.29
Day 5					.75			.00	.56
Day 6						.60		.00	.36
Day 7							.78	.00	.61
SLEEP ONSET ACTOGRAM	SLEEP DIARY							<i>p</i> value	<i>r</i> ²
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7		
Day 1	.53							.00	.28
Day 2		.66						.00	.44
Day 3			.77					.00	.59
Day 4				.87				.00	.76
Day 5					.76			.00	.58
Day 6						.76		.00	.58
Day 7							.80	.00	.64

Table 4.8 (continued)

SLEEP OFFSET ACTOGRAM	SLEEP DIARY							<i>p</i> value	<i>r</i> ²
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7		
Day 1	.51							.00	.26
Day 2		.50						.00	.25
Day 3			.60					.00	.36
Day 4				.68				.00	.46
Day 5					.88			.00	.77
Day 6						.74		.00	.55
Day 7							.89	.00	.79

TOTAL TIME IN BED ACTOGRAM	SLEEP DIARY							<i>p</i> value	<i>r</i> ²
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7		
Day 1	.35							.01	.12
Day 2		.44						.00	.19
Day 3			.30					.03	.09
Day 4				.46				.00	.21
Day 5					.53			.00	.28
Day 6						.35		.01	.12
Day 7							.77	.00	.59

Table 4.9 Reliability and Internal Consistency of Subjective and Objective Sleep Measures in Women with FM (*n* = 50)

Variables	Sleep Log ^b Stability		Actigraph ^b Stability	
	Internal Consistency ^a	Nights 1 – 2 to 5-6	Internal Consistency ^a	Nights 1 -2 to 5 -6
Bedtime	.95	.52^c	.92	.83^c
Awake time	.88	.45^c	.88	.57^c
Sleep Onset	.93	.86^c	.92	.86^c
Sleep Offset	.89	.54^c	.85	.64^c
Total Time In Bed	.80	.45^c	.62	.49^c
Sleep Latency	.78	.27	.54	.61^c
Total Sleep Time	.83	.58^c	.58	.18

^aCronbach's alpha

^bPearson's r

^cp significant at < .01

Table 4.10 Comparison of Objective and Subjective Measures of Sleep (n = 50)

Variables	Sleep Log ^a (hh:mm)	Actigraph ^a (hh:mm)	Correlation ^b	Average Absolute Disagreement	OSE
Sleep					
Latency	00:32 (00:51)	00:31 (00:44)	.71^c	00:28 (00:44)	103%
Total					
Sleep Time	07:20 (01:32)	07:35 (00:58)	.73^c	00:43 (00:44)	96.7%

OSE = Objective Sleep Estimate (SD/ACT X 100%)

SD = Sleep Diary Derived

ACT = Actigraphy Derived

^aAveraged over 7 days

^bPearson's r

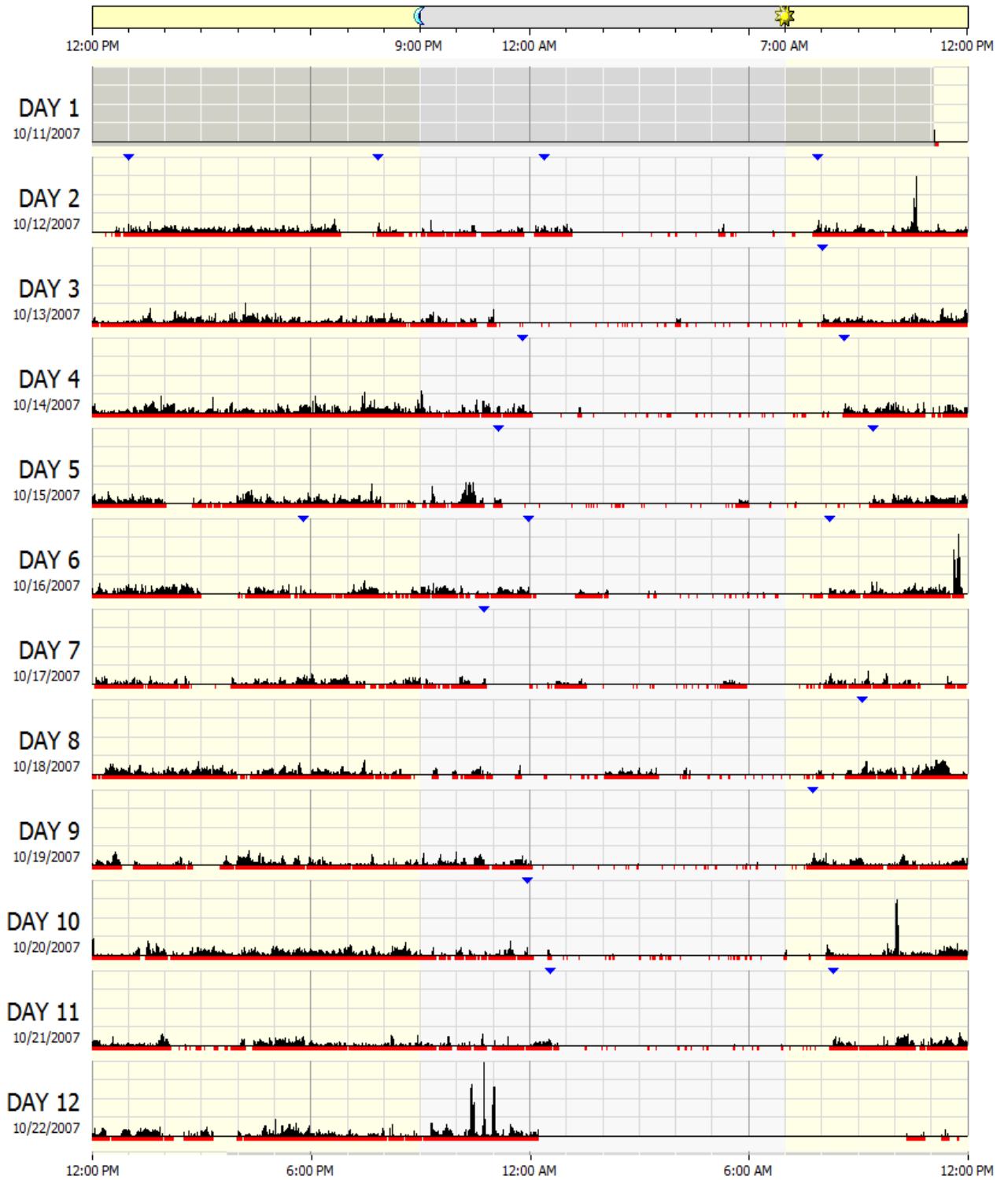
^cp significant at < .01

Table 4.11 Independent Sample *t* Tests by Number of Wake Bouts

Variable	Wake Bouts		t (df)	p value
	≤ 23	> 23		
Total Time in Bed (min)	475.7 (80)	527.9 (56)	-2.7 (48)	.01
Assumed Sleep Time (min)	425.1 (85)	485.0 (45)	-3.1 (48)	.00
Total Sleep Time (min)	355.0 (91)	404.5 (52)	-2.7 (48)	.02
Sleep Latency (min)	25.5 (34)	37.3 (34)	-1.2 (48)	.23
Sleep Efficiency (%)	74.6 (14)	77.3 (8)	-.86 (48)	.23
Circadian Period (hours)	26.4 (1.8)	24.9 (2.4)	2.4 (48)	.02
Epworth Sleepiness				
Scale	12.9 (6)	9.3 (6)	2.2 (45)	.03
FIQ	58.0 (17)	59.8 (16)	-.38 (48)	.71
Body Map %	32.6 (21)	40.2 (27)	-1.1 (45)	.29
Tender Points (#)	10.4 (5)	9.7 (4)	.59 (45)	.56
FOSQ	11.3 (3)	12.2 (3)	-.99 (48)	.33
Avg. Daily Pain	63.1 (16)	59.5 (21)	.70 (48)	.49
Avg. Daily Fatigue	63.6 (16)	63.7 (14)	-.01 (47)	.98
Avg. Daily Caffeine				
Intake (8 ounces)	1.6 (1)	1.9 (1)	-.66 (48)	.51
Age	47.2 (10)	48.9 (11)	-.55 (48)	.58

FIQ = Fibromyalgia Impact Questionnaire; FOSQ = Functional Outcomes of Sleep Questionnaire

Figure 4.1 Example of Actogram with Participant Initiated Time Markers



Note: Actigraphic Markers are blue arrows

CHAPTER FIVE

Strategies for Analysis of Circadian Rhythm Using an Actigraphy Data Set: A Comparison of Four Techniques

The purpose of this study was to examine four statistical methods for determination of circadian period from actigraphic-derived activity data obtained from 48 women with fibromyalgia and sleep disturbance. The circadian period is the time in hours and minutes that it takes to complete a full cycle of activity/rest, usually 24 ± 4 hours. Circadian rhythms are 24-hour cycles of rest and wakefulness regulated by the biological clock or circadian pacemaker in the suprachiasmatic nucleus (SCN) of the hypothalamus (Martin et al., 2006). Circadian rhythms occur even in the absence of environmental cues like day or night. However, when these rhythms are disrupted human function can be affected, functional performance may be impaired, and a weakened or enfeebled state of health may occur until realignment is achieved (Sack et al., 2007a, 2007b).

Actigraphy is a useful tool for objective examination of circadian activity rhythms (CR) and sleep phase shifts (Klerman, Goldenberg, Brown, Maliszewski, & Adler, 2001; Morgenthaler, Alessi et al., 2007; Morgenthaler, Lee-Chiong et al., 2007). Actigraphy uses a wrist watch like device worn on the wrist or ankle of the study participant that measures limb movement (Buysse, 2005; DeSouza et al., 2003). Individual patterns of activity/rest behavior that people exhibit can be demonstrated in a non-laboratory setting using activity based actigraphy (Brown, Smolensky, D'Alonzo, & Redman, 1990; Sack et al., 2007a, 2007b), however, multiple methods for quantifying circadian periodicity exist.

Data analysis in circadian rhythm physiology involves a variety of both graphical and numerical procedures that characterize the mean or mesor, amplitude (peak oscillation), acrophase (timing of peak), and period of the waveform of activity created over time (Refinetti, 1993). An illustration of these parameters and definitions are noted in figure 5.1 (Cugni, 1993). The waveform obtained by limb actigraphy appears as a series of peaks and troughs of activity counts measured over time. Each component of the wave (mean, amplitude, acrophase, and period) can be measured.

More activity or movement is reflected by higher activity counts recorded by the actigraph. A right assumption is that more activity will be present in the waveform during the waking hours and less activity will be present while sleeping or resting. By examining these waveforms, patterns of activity can be analyzed from these non-stationary cyclic phenomenon using plots of the limb activity called actograms. Analysis of the actogram allows determination of trends or patterns in the activity (Cugni, 1993). The waves of the actogram can reflect changes in personal daytime/nighttime activity and cyclic patterns of wake/rest. In addition to quantitatively determining the circadian period and robustness of the rhythm, the extent of clustering of activity and examination of patterns in activity over time can be examined graphically. The most basic approach is to plot the time series and look at individual increases or decreases in activity, changes in the patterns of activity, absence of activity or other trends. Then, emphasis may be placed on the statistical calculation of the circadian period.

Several strategies for calculation of the circadian period exist; each with its own methodological issues that must be acknowledged for the results to be accurate and reliable (Celec, 2004; Diambra & Menna-Barreto, 2004). Determination of the period in

the literature is most commonly achieved using Cosinor analysis. Other methods besides Cosinor analysis are available from the software that accompanies the actigraphic device. It provides three different methods for determining the circadian period: Fast Fourier Analysis (frequency analysis), Enright's periodogram (periodogram), and Linear Regression of Onsets (Mini Mitter Company, 1998-2003, 2004; Refinetti, 1993).

This paper compares circadian periods calculated using the four methods and investigates the methodological issues associated with actigraphy data that may contribute to measurement error in the calculation of circadian period. A comparison of the four statistical methods and their assumptions for determining the period will be examined using a data set obtained from 48 women with fibromyalgia and sleep disturbance.

Background

The circadian rhythm of activity is a series of peak activity and trough activity that occur in cycles over time. When plotted, it appears as a wave. The circadian period is measured either from peak to peak or trough to trough. The period is a measurement of the duration from the start of one cycle to the beginning of another cycle using either the peak or trough of the oscillation (Cugni, 1993). With the actogram, the trough is usually zero activity so the peak is used here to determine the period. The timing of this peak oscillation in the waveform is known as the acrophase and is referred to as circadian if the duration is 24 ± 4 hours. Periodic events or activity/rest cycles lasting less than 20 hours or greater than 28 hours are referred to as ultradian or infradian periods, respectively (Zhang, Lin, & Sowers, 2000).

The wave has several properties besides the peak and trough that can be measured including the amplitude, the acrophase, the mesor or mean, and the consistency of the rhythm or percent rhythm. Properties of the wave are influenced by change in the amplitude of the activity or change in the mesor or mean activity of the rhythm. Over time, this is illustrated as a crescendo or decrescendo effect to the waveform. In other words, the wave of activity/rest is affected by seasonality and trends and these effects influence the overall circadian rhythm and its periodicity (Hayes & Mitchell, 1998). Trends are factors that change over time and do not repeat or at least not during the time being studied. Seasonal factors repeat in systematic intervals of time. Trends and seasonality can coexist and will influence time series data overall (Statsoft, 2007) .

Since biological rhythms of activity/rest evolve over time, this evolution modifies the periodic properties of the waveform (Cugni, 1993). The study of biological rhythms illustrates how the period of activity/rest changes over time in a graphical manner, but does not identify the causal factors of that change (Youngstedt, Kripke, Elliott, & Klauber, 2001). Control of the biological activity/rest rhythm involves an interaction between endogenous and exogenous time-keeping mechanisms including the generation of internal rhythm by the neurons of the suprachiasmatic nucleus (SCN) of the hypothalamus and entrainment/exposure to environmental signals including solar light and darkness, meal timing, social routines, work shifts, or changes in physical activity (Dunlap, Loros, & DeCoursey, 2004; Sack et al., 2007a). The endogenous rhythm is not a free running cycle, but instead is obliged to adjust in accordance with exogenous cycles (Tresguerres et al., 2001). The strongest influence on the circadian rhythm is typically light exposure, but individual systematic events having a cyclical pattern can also

modulate the internally determined rhythm (Cugni, 1993; Wulff, Joyce, Middleton, Dijk, & Foster, 2006).

Desynchronization of the internal and external influences on the period may be demonstrated in the person's behavior including an increased desire to fall asleep, falling asleep quicker, and the increased duration in bed that sometimes occurs following extended wakefulness (Painnain & Cauter, 2007) or even changes in mental and physical readiness when sleep is deprived or when changing time zones (Tresguerres et al., 2001). This later shift is due to a phenomenon called "jet lag". These instances shift the circadian period of activity abruptly but not necessarily the internal rhythm (Dinges et al., 1997; Haimov & Lavie, 1997; Painnain & Cauter, 2007).

For example, a person who stays up later than their usual bedtime for a special event or shortens their overall duration of sleep, usually falls asleep quicker when they do retire and then possibly sleeps later the next morning or maybe naps. This response to prolonged wakefulness shifts both the trough and the peak of their activity levels later and may increase the period transiently. This is reflected in the waveform as a longer period of time from peak oscillation to peak oscillation. Returning back to their normal schedule occurs when the exogenous influences realign to the internal circadian rhythm and thus may include a transient shortening of the circadian period. The period of circadian rhythm can differ from day to day and be less or greater than 24 hours (Ancoli-Israel et al., 2003). This misalignment due to social schedules has been referred in the literature as "social jet lag" (Wittman, Dinich, Mellow, & Roenneberg, 2006).

These modulatory effects on circadian rhythm occur in normal healthy adults and those with chronic conditions (Pati, Parganiha, Soni, Roy, & Choudhary, 2007) and they

contribute to the variability of the circadian period by increasing the random error or noise in the data. This is also known as masking. Daily inconsistent change in environmental cues noted as changes in the timing of the peaks are associated with poor sleep schedule adherence, sleep deprivation, and daytime recovery sleep (naps) (ASDA, 1995). In addition to changes in the duration of the period, if these circumstances of frequent napping, poor sleep schedule etc. are chronic, they influence the stability or robustness of the rhythm over time (Martin et al., 2006). This would affect a change in the parameter known as the percent rhythm (Dowling et al., 2005).

Internal circadian rhythmicity is masked by these environmental factors that consequently influence the period. Inferential statistics provide several methods for examination of it. Knowing the circadian period contributes important information necessary to future inferences about the impact of having a poor sleep schedule, sleep deprivation, or frequent napping. Although these phenomena may be constantly changing the duration of the activity/rest period, circadian rhythmicity is always present and measurable using descriptive, inferential time series analysis.

Cosinor Analysis and Actigraphy

Cosinor analysis is the most common descriptive method used to evaluate time series data like actigraphy. In this procedure, a least square approximation of time using a cosine function of a known period is performed using the mesor or midline estimating statistic, the amplitude, and the acrophase (Hamilton, 1994). Cosinor analysis is a non-linear model that has a linear representation upon transformation (Refinetti, 1996-2008). It quantifies the best fitting sinusoidal wave and other parameters like percent rhythm and provides a rhythm detection probability level.

In a brief review of the literature, six studies using Cosinor and Actigraphy were available. Twenty-three healthy adults without history of sleep abnormality were monitored for 5 days by wrist actigraphy (Brown et al., 1990). Circadian rhythms of high amplitude were detected using Cosinor analysis. Dowling et al. (2005) used Cosinor analysis to determine that disturbances in circadian rhythm are prominent in persons with Alzheimer's disease (AD) ($n = 46$, mean age 84 years) (Dowling et al., 2005). In another study, the difference in timing of lights out-lights on and the number of naps was significantly different in older adults compared to younger adults, but no age related difference was detected in the circadian acrophase period using Cosinor analysis (Kripke et al., 2005). Cosinor analysis was used to quantify the rhythm amplitude and mesor in nine adolescents and 15 healthy adults (Reimberg, Bicakova-Rocher, Mechkouri, & Ashkenari, 2002). A 24-hour sleep-wake rhythm was detected in almost all cases ($24:0 \pm 0:30$ h).

Cosinor analysis was used with melatonin levels, cortisol levels, and actigraphy to examine shifts in circadian period in pilots traveling across multiple time zones (Tresguerres et al., 2001). Activity rhythms, as measured by wrist actigraphy, resynchronized rapidly to the new time zones traveled by the pilots; however, desynchronization with internal rhythm inferred by melatonin and cortisol testing appeared unchanged as noted by the levels of these secretions remaining in the pre-travel patterns or similar to that of initial-time-zone controls. Further, this out of sync pattern was associated with low mental alertness and physical performance of the pilots during the flight (Eriksen & Akerstedt, 2006).

The results reported by Pati et al. (2007) validated a significant circadian rhythm in rest-activity with a prominent period of 24-hours for most cancer patients and control subjects. However, results of some individual cancer patients revealed that they did experience a drastic alteration in the circadian rest-activity rhythm parameters (Pati et al., 2007). For example, they spent significantly longer time in bed (TIB), had greater number of wake bouts after sleep onset, and increased frequency of naps compared to controls. This was characterized by dampening of the amplitude, lowering of mean or mesor, and phase advancement.

Fast Fourier Analysis and Actigraphy

Fast Fourier Transformation (FFT) is another well known method for the study of rhythmicity (Korte, Wulff, Oppe, & Siegmund, 2001). FFT is an inferential analytic method based on an unknown period that is represented by a waveform described by a combination of pure cosine and sine waves (Refinetti, 1993). Fast Fourier Transformation procedures transform data in the time domain to the frequency domain for the purpose of finding the period that represents the wave. FFT allows identification of seasonal fluctuations that may present as lesser peaks (ultradian) in addition to the circadian component as seen in the example (see figure 5.2). FFT can be used in actigraphy data by taking the sum of squares of the coefficients of the sine and cosine terms for that known period. If there is an oscillation, this will show up as a peak in the periodogram (Refinetti, 1993). FFT is useful for circadian pattern recognition but not as much for precise quantitative reporting of the period (Calandre, Hildalgo, & Rico-Villademoros, 2007).

In Korte et al. (2001), FFT demonstrated that the majority of preterm neonates ($n = 10$) had a multitude of ultradian frequencies (smaller peaks) compared to circadian frequencies in full term neonates ($n = 10$). Another study compared FFT with chi square periodogram in 30 children 9 months to 11 years of age in their home environment with actigraphy. The results showed that motor activity becomes less robust and more fragmented as the child developed while retaining an underlying circadian rhythm. In this case, an overall 24-hour rhythm was noted with activity becoming less robust and with other frequent irregular peaks noted using the graphical display (Hayes & Mitchell, 1998).

Enright's Periodogram and Actigraphy

Enright's periodogram involves the calculation of a ratio of variances (Enright, 1965; Refinetti, 1993) (see figure 5.3). Like the FFT, the periodogram describes how the variance of a time series is distributed with frequency. This method is based on the assumption, that a set of data collected over time and when broken into sections or periods, will be similar to each other if they share the same period; or not, if they do not share the same period. Each period is associated with a quotient or Q_p value. The period with the highest Q_p value is considered the true circadian period (Refinetti, 1993). One study using periodogram analysis with actigraphy observed intra-individual variation over 10 days in seven neonates and their mothers (Jenni, Deboer, & Achermann, 2006). Intra-individual variation is an indication of poor stability of the rhythm and changing daily parameters including the period when they are compared to each other.

Linear Regression of Onsets and Actigraphy

Only one study used the method of Linear Regression of Onsets to determine circadian period (Refinetti, 1993) (see figure 5.4). In this study, Refinetti (1993) compared six different methods for the determination of the period of circadian rhythms using actigraphy in three sets of laboratory data with known periodicity and composed pure cosine, pure square, and mixed waves. The six methods were: Cosinor, Fourier Analysis, autocorrelation, Enright's periodogram, Linear Regression of Onsets, interonset averaging, and acrophase counting. All methods successfully detected the period in the pure cosine/sine and pure square waveforms, but Fourier Analysis and Periodogram were superior to the other methods in the analysis of more complex waveforms (mixed) which may resemble more closely actual circadian rhythms. In this research, it was concluded that Enright's periodogram was the best choice as a general method for determining the period. As in this latest research, calculation of circadian period is the parameter of interest and the easiest, most quantitative way to determine it in women with fibromyalgia is the specific aim.

Methods

Design and Sample

Fifty-three women consented to participate in a week long sleep study using an actigraph or actometer-a wrist-watch like device that measures activity based motion. Forty eight women wore the device for at least 7 days. The longitudinal data for this study were collected from a volunteer, community based sample of women with a previous diagnosis of FM and sleep disturbance. Women over the age of 18 years old recruited using flyers placed in physicians' offices or from information posted on the

internet could enroll in the week long study. Informed consent was obtained in writing from each participant in person or through the mail by mailing the consent to her home. Women who worked night shift or were diagnosed/treated for sleep apnea were excluded from participation.

Participants were asked if they have restorative sleep, 86% indicated that they did not and 88% indicated that they had trouble falling asleep or staying asleep. Fifty-seven percent of the sample indicated that they wake up in the early hours unable to fall back asleep. Overall, participants indicated the time to fall asleep was 46 minutes (SD 41 minutes) or more and total sleep time was 6.87 hours (2.33). When asked to rate their overall sleep quality (0 = refreshed, 1 = somewhat refreshed, and 2 = fatigued), 3.5% indicated that they had refreshing sleep, 31% indicated their sleep was somewhat refreshed and 65% indicated that they were fatigued.

Actigraphic Measures

The data were obtained using wrist actigraphy. An actigraph or actometer is a wrist watch like device worn on the wrist or ankle of the study participant that measures limb movement (Buysse, 2005; DeSouza et al., 2003). The device contains a miniature motion based sensor that translates movement into a numerical activity count (Carvalho-Bos, Waterhouse, Edwards, Simon, & Reilly, 2003; Pollak, Tryon, Nagaraja, & Dzwonczyk, 2001; Roehrs, Turner, & Roth, 2000). Limb activity can be viewed as an actogram (see example in Figure 5.4) or as time stamped raw activity counts that may be viewed in most spread sheets or statistical programs. The actogram and the time stamped raw activity counts are used to obtain the periods, depending on the method, and each are described in the procedures section.

Procedures

The study was approved by the University of Kentucky Medical Institutional Review Board. Informed consent was obtained in writing from each participant in person or through the mail by mailing the consent to her home. The study watch was applied once criteria for enrollment were met. The participants were provided with detailed instructions about wearing the watch as much as possible.

Prior to application, the device was configured to sample activity every minute during the time that the device was on the participant. The internal clock of the device was configured based on the participant's time zone and the current time was set according to the manufacturer specifications to confirm accuracy. When they applied the device to their wrist, the participant was asked to depress the marker button on the watch, thereby placing a marking at that time in the data of the device (Currie, Malhotra, & Clark, 2004).

Participants started the study on different days and at different times to provide convenience in scheduling for those in the study. The device was worn on the non-dominant wrist (Littner et al., 2003). A data set of time stamped raw activity counts for seven days was collected. The participants completed an extensive survey regarding their health prior to the study.

Data Analysis

Cosinor analysis was performed on the raw activity counts using a free software package available online (Refinetti, 1996). The first 00:00 after the initiating marker of the study was used as the reference point and periods were obtained for each participant. In the study of circadian periodicity, the reference time is usually midnight, mid-sleep or

the time of the acrophase of another physiologic variable such as body core temperature (Chronobiometry, 2004). All available data points for each participant were used in the calculation--up to a total of 10080 data points (7 days) and were analyzed in 1 minute bins with a known period range analyzed from 20:00 to 28:00 for rhythmicity. This average period formed the score for this result.

FFT or frequency analysis was performed by the Actiware 3.01 software using the same start day (first 00:00 after the initiating factor) and time stamped raw activity counts. The analysis included 8192 bins or 5.85 days averaged using a one hour resolution. The average period obtained using FFT from each individual for the 8192 data points formed the score for this result.

The periodogram also was performed by the Actiware 3.01 software using the same start day and raw activity counts. The analysis was performed with a resolution of 1 minute. 8640 data points were examined using a period of 20:00 – 28:00. The period obtained using this periodogram from each individual for the 8640 data points formed the score for this result.

Linear Regression of Onsets, used when the actogram is visually inspected, identifies the onset of activity in each cycle as a marker of a new cycle (Refinetti, 1993). A straight line is drawn through the onsets of activity (τ) and the drift in time over several days is measured and used to calculate the mean deviation from 24 hours across several days. The Linear Regression of Onsets was started on the same first day as noted above, and the regression line drawn over 6 days. This mean deviation formed the score for the Linear Regression of Onsets result.

Analysis of the periods was conducted using descriptive statistics, Pearson's correlation and analysis of variance (ANOVA). Results of each method were graphed to examine normality. Pooled periods categorized according to method (1 = Cosinor, 2 = FFT, 3 = Periodogram, 4 = Linear Regression of Onsets) that were significant ($p < .05$) were evaluated post hoc using Bonferroni and Tukey procedures. Tests for homogeneity were performed using Levene's test.

Results

The data were obtained from a sample of women recruited from four time zones (EST, CST, PST, MST), mostly Caucasian (90%) with a mean age of $47.9 \pm SD 10.4$ years, and diagnosed with FM for at least $3.9 \pm SD 5.3$ years. The duration of disease was $7.2 \pm SD 7.6$ years; and 72% of these women were employed in some capacity. Twelve percent of the women were disabled. The women had at least a high school education and 34% of the sample were college graduates. Characteristics of sleep estimated by the actigraph over seven days and averaged indicated decreased total sleep time (TST) ($M = 06:19 \pm 1:17$ SD) and mean sleep latency (SL) of at least 00:30 minutes to fall asleep.

The periods for each individual calculated by the four methods are shown in Table 5.1 ($n = 48$). In five of the cases, the participants did not apply the device until well after the recording time was over or did not wear the device for at least 7 days, so no actigraphic data was obtained on these subjects who had materials mailed to them. In the determination of period, all means for each 7 day series were 24 hours $\pm SD 1$ hour. Correlations performed on the means of the periods for each analysis are noted in Table 5.2.

Periods obtained by Cosinor analysis and periodogram procedures were moderately correlated ($r = .51, p = .01$), followed by Cosinor and regression of linear onset ($r = .34, p = .05$). Correlations between periodogram and regression of linear onsets were also significant ($r = .49, p = .01$); however, remaining correlations between FFT and Cosinor analysis ($r = .311, p = .05$) were low or insignificant when compared to the periodogram or regression methods.

ANOVA performed on the pooled series indicated statistically significant differences between the mean periods [$F(3, 188) = 5.21, p = .002$]. Post hoc comparisons noted significant differences between periods obtained by Cosinor and FFT (24.00 versus 23.77) and FFT and Periodogram (23.77 versus 24.08). Graphs of the data were examined for normality and skewness (Figure 5.5). Normal distribution in a bell-shaped like curve appeared in the Cosinor, Periodogram and Linear Regression of Onsets, but Cosinor analysis had the most normal looking histogram. A non-normative plot was noted in FFT. FFT determines the period by frequencies using time-specified categories and the results are not normally distributed. The Levene's test was significant indicating heterogeneity of random error or unequal error terms.

Discussion

In the study of circadian period, natural phenomenon like circadian period are measureable using systematic and objective methods like actigraphy. Time is not a random variable for it can be numerically predicted if the relationship between activity and time itself remain unchanged (Qin & Guo, 2006). This results in a linear relationship; however, if the relationship changes due to exogenous factors, then a non-linear phenomenon exists. This property is known as being non-stationary (Refinetti, 1996-

2008). Circadian rhythms of activity/rest evolve over time and are not stationary, which tends to modify the periodic properties. The very nature of the type of measurements used here to determine circadian period precludes the existence of a conventional gold standard for determining the true circadian period.

Comparison of the methods used to determine period revealed statistical differences in the methods. From these results, circadian period would be the same or similar if obtained by Cosinor Analysis, Periodogram, and Linear Regression of Onset, but different if obtained by FFT, although this may also be due to variable random error and violations to the assumption of normality. Recommendations on which method should be used would depend on the phenomenon under study and the resolution of the data. The benefit of Cosinor analysis is that it is not sensitive to noise and it does not require data to be equally distributed in time to detect the rhythmic period, but its use is recommended with activity/rest waveforms that are sinusoidal (Cugni, 1993). This procedure also permits structuring of models for lower (ultradian <24h) and higher periods (infradian >24h) (Arendt, Minors, & Waterhouse, 1989).

Fast Fourier Transformation is recommended for data sets of at least seven days. FFT is not recommended when a precise circadian period is needed rather it is better suited for when alterations in rhythmicity or patterns (clustering) are being examined. For data sets shorter than seven days or when a precise period calculation is required, the periodogram procedure is recommended (Mini Mitter Company, 1998-2003). Enright's Periodogram were correlated with the other methods and would result in similar periods.

Linear regression of onsets is recommended for shorter data sets or when examining individual sleep shifts associated with behavioral artifact that may mask the

true rhythm. It is also useful prior to performing Cosinor, FFT, or periodogram on larger data sets (Mini Mitter Company, 2004).

In this data set, several issues were noted that could contribute to measurement error and increase noise in circadian rhythm measurements using actigraphy. Actigraphy measurements are discrete, non stationary time series data. It is assumed that time series data consist of a systematic pattern and random noise (error) which usually makes the pattern difficult to identify (Cugni, 1993). Most techniques involve filtering the noise to make the patterns more visible. These methods to determine circadian period do estimate the random error or noise that accompanies the systematic pattern of activity/rest; however, it is unable to filter or discern all of it especially when it is changing intra-individual and inter-day as was demonstrated in these data. Visual examination of the actigraphy data in many of these participants noted changing bed times, changing wake times, naps, and varying durations of time in bed. These daily changes in individual sleep schedule are lost when averaging data over several days and pooling the effects of the group. This observation has been noted in other research (Eriksen & Akerstedt, 2006; Padhye & Hanneman, 2007).

Analysis of multiple day time series data suffers from problems different from that of short series data. In this research, the procedure using Cosinor analysis resulted in different periods (more normalized) when more days were analyzed and averaged together as opposed to analysis of one day at a time. When the first and last day artifact was removed and the period was calculated individually for each day, significantly different results were obtained as noted in Table 5.3. It is likely that this discrepancy in the calculation of the period was related to the tendency to make up for sleep on the

weekend that was lost throughout the week due to work or other responsibilities. The participants had altered circadian periods from day to day that essentially normalized over a week. When less than seven days were used to calculate the period, the periods were significantly different. This is an example of a circaseptan rhythm, a rhythm that repeats itself over one week and which has been previously noted in pilots after a transmeridian flight over 7 or more days (Cornelissen, et al., 2005; Halberg, et al., 2003; Simpson, Pauson, & Halberg, 1990).

Other research has pointed out that errors in time series data are correlated and instead recommends the use of autoregressive procedures that capture the evolution and interdependencies between multiple days of time (Greenhouse, Kass, & Tsay, 1987). Use of the least squares Cosinor method, assumes that errors are uncorrelated and normally distributed. Heterogeneity of error variance is likely associated with intra-individual changes in circadian activity (irregular sleep patterns) occurring from day to day in the non-laboratory environment. So while this finding might make one cautious of the results, it is a manifestation of the daily changing activity/rest patterns that accompanies the lifestyle of these individual participants that affects their circadian period over time.

Another issue is the sampling interval for activity based measurements used here. In this data set, a sampling interval of one minute was used. Research with actigraphy had noted this sampling interval previously (Landis et al., 2003). Sampling at this frequency only allowed study for 11 days using this particular device. This limitation guided the selection of a 1-week sleep study, but would less frequent sampling intervals and longer study perhaps as much as 30 days be a better examination considering all the

lifestyle factors that affect sleep and circadian rhythm e.g. job schedule, travel, and family.

For example, in order to make inferences about a circaseptan rhythm or the “work day” effect of full time employment on circadian rhythm, it would require study of participants for longer than seven days. Unfortunately, by conducting the study over fewer than 10 days, information is limited on short term variations like these, which may influence or possibly impact the determination of the true circadian period. Using a less frequent sampling interval and a longer study may provide a better examination of sleep patterns and these trends that exist when studied over more days rather than more minutes.

When considering the use of actigraphy for the study of CR period, consideration must be given to how the results will be generalized or used in clinical practice; as they reflect the characteristics of the participants in the sample which are influenced by their own individual behaviors (e.g., smoking, exercise, caffeine use, and medications) and co-morbid conditions (e.g., pain, fatigue, and other diseases). Use of actigraphy to examine the impact of sleep behaviors or these other conditions on circadian period is possible in individuals being initially evaluated for poor sleep quality. Clinical use to identify gross disturbances in sleep times related to poor sleep patterns can be reliably determined using actigraphy. Actigraphy is very useful for determining shifts in activity/rest within individuals that may indicate a desynchronization between the internal clock and the participant’s lifestyle.

On the contrary, pooled effects like these that may be used in large randomized trials to evaluate the effects of drugs or treatments in samples of people may need to be

used with caution with the discovery of variable random error noted in these statistical procedures; especially if the research environment is one that the participant has ultimate control over. The heterogeneity of the random error may lead to rejection of their hypothesis when in fact no differences really exist between the groups.

In time series analysis, an assumption that the error term has a constant variance is true if the observations of the error term are assumed drawn from identical distributions. However, if the error term varies or increases with each observation, it is a violation of this assumption (Hamilton, 1994). Heterogeneity of variance may be the result of genuine and unexplained random differences, but statistically it can create significant findings when there are none. For clinical research with actigraphy, these important assumptions might be addressed better within studies using larger samples over longer durations with more exclusive entry criteria so that the effect size can be considered in addition to the significant results associated with the statistics. These are important considerations when examining any variable for its precision and statistical significance.

Conclusions

This paper compared four common methods for determining circadian period of actigraphy data. All four methods performed on sets of data from 48 individuals revealed similar means for each series or within an hour of each other; however, between group tests revealed statistically significant differences in the results. Each particular method has specific procedures and assumptions, which may make them more or less difficult to use or interpret. Considering these results, the procedure recommended for determining the period of circadian activity for large data sets would be either Cosinor

Analysis or Enright's periodogram. For smaller sets, the Linear Regression of Onsets would be useful. FFT might be better used for examining patterns of sleep associated with circadian rhythm disturbance, but not quantitative calculation of the circadian period. Replication of these results is recommended in larger data sets.

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Table 5.1 Periods calculated by Cosinor, Fourier's Frequency, Periodogram, and regression of linear onsets ($n = 48$)

Subject	Cosinor	FFT	Periodogram	Linear onset
1	24.5	0:10	0:08	24
2	24.2	0:04	0:08	24.38
3	24.3	0:04	0:02	24.08
4	24.3	23:45	0:03	24.03
*6	24.6	0:36	0:17	23.99
7	23.5	23:32	0:10	23.93
8	24.5	0:23	23:56	23.89
9	23.8	0:23	23:51	23.81
10	23.9	23:32	23:53	23.36
11	23.8	23:32	0:02	24.24
12	24.1	0:23	0:01	23.99
13	23.6	23:32	23:35	23.48
14	24.2	23:32	0:17	24
15	24	23:32	23:59	24
16	23.3	23:32	0:00	24.01
17	23.5	23:32	0:14	24.22
18	23.9	0:23	0:46	24.18
19	23.9	23:32	23:58	23.75
20	24.3	0:23	23:23	23.69
21	23.8	23:32	23:43	23.7

Table 5.1 (continued)

22	23.6	23:32	23:01	24.32
23	24	23:32	0:29	23.7
24	24.3	0:23	0:05	24.51
25	23.8	23:32	23:29	23.49
26	23.8	23:32	23:40	23.65
27	23.3	23:32	0:06	24
28	24.3	23:32	0:05	24.02
*30	24.4	23:32	0:25	24.31
31	24.1	0:23	0:05	24.06
32	23.5	23:32	0:05	24.01
33	24	23:32	0:07	24.12
34	23.6	23:32	23:39	23.6
35	23.8	23:32	0:58	23.97
36	24.3	23:32	0:03	23.93
37	22.9	23:32	23:27	##
38	23.8	0:23	0:03	24.04
*40	23.8	23:32	23:52	23.98
41	23.9	23:32	23:53	23.61
42	24.7	0:23	1:33	24.25
43	25.7	23:32	1:17	24.32
44	23.9	23:32	23:38	23.97
*46	24.4	23:32	0:06	23.74

Table 5.1 (continued)

*48	24.1	23:32	23:59	24.07
49	24.4	23:32	0:05	24.07
50	24	23:32	23:57	23.93
51	24.5	23:32	1:32	24.55
52	24	0:23	23:52	23.9
*53	23.3	23:32	0:12	23.69

*Cases missing due to having less than 7 days of actigraphy recording

unable to perform measure due to variable onsets of activity

Table 5.2 Means and Correlations Among the Four Methods of Period Evaluation

Method	Mean (SD)	FFT	Period	RLO
Cosine	24.00 (.46)	.31*	.51**	.34*
FFT	23.77 (.37)		.10	.19
Periodogram	24.09 (.48)			.49**
Regression of Linear Onset	23.96 (.26)			

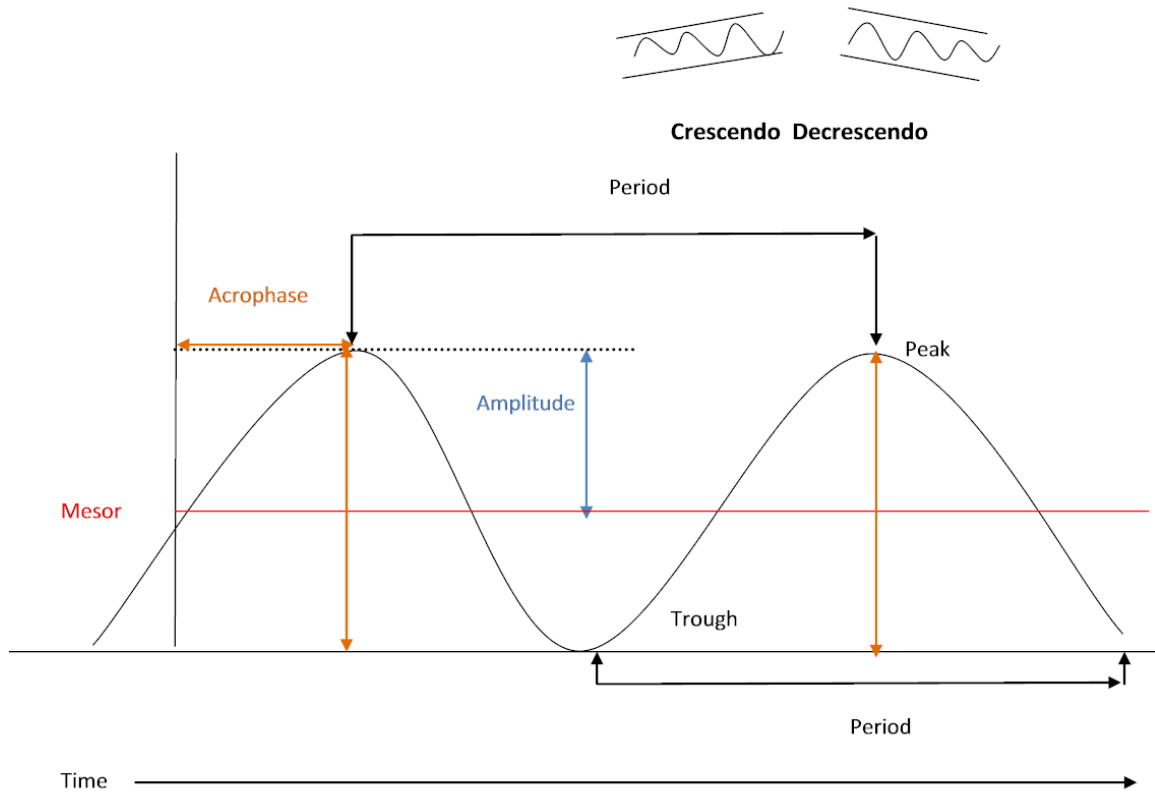
* $p = .05$

** $p = .01$

Table 5.3 Comparison of periods calculated by Cosinor Analysis to periods with first and last day artifact removed.

	Mean (SD)	t	(df)	<i>p</i> value
7 day Period (hr) (total 10080 bins)	24.00 (.46)	-4.72	(46)	.00
Daily Period (hr) (total 8640 bins)	25.59 (2.29)			

Figure 5.1 Illustration of Time Series Waveform and Definitions of Rhythm Parameters

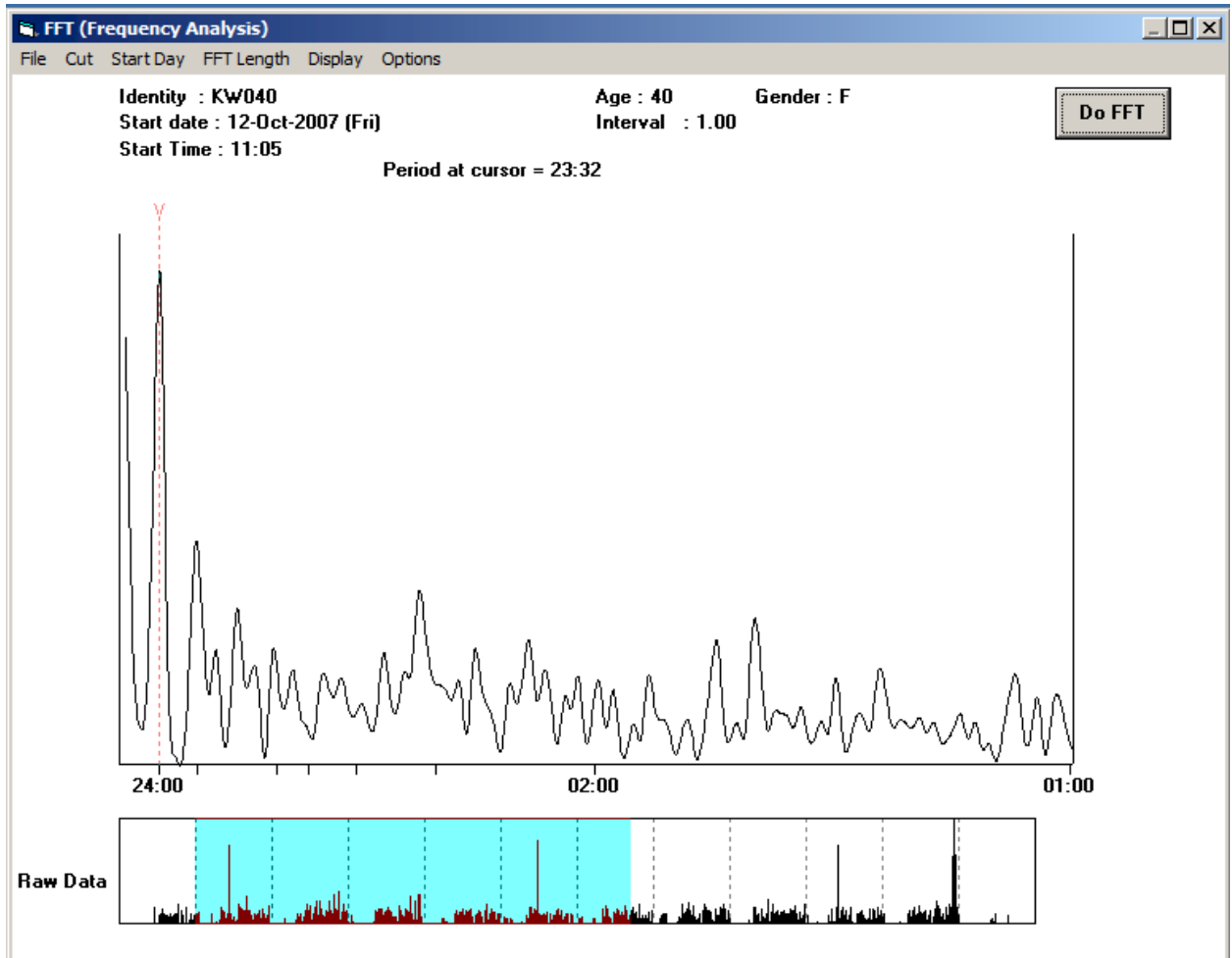


Definitions:

- Acrophase is the timing of the oscillatory crest or peak of the waveform.
- Amplitude is the extent of oscillation from the mesor.
- Period is the episodic duration of the whole revolution of the waveform in relation to the timing of its peaks or troughs. The period is also known as tau.
- Mesor is the mean level of the periodic function (midline estimating statistic of rhythm).
- Peak is the highest point on a wave
- Trough is the lowest point on a wave
- Crescendo is the amplitude gradually increasing
- Decrescendo is the amplitude gradually decreasing

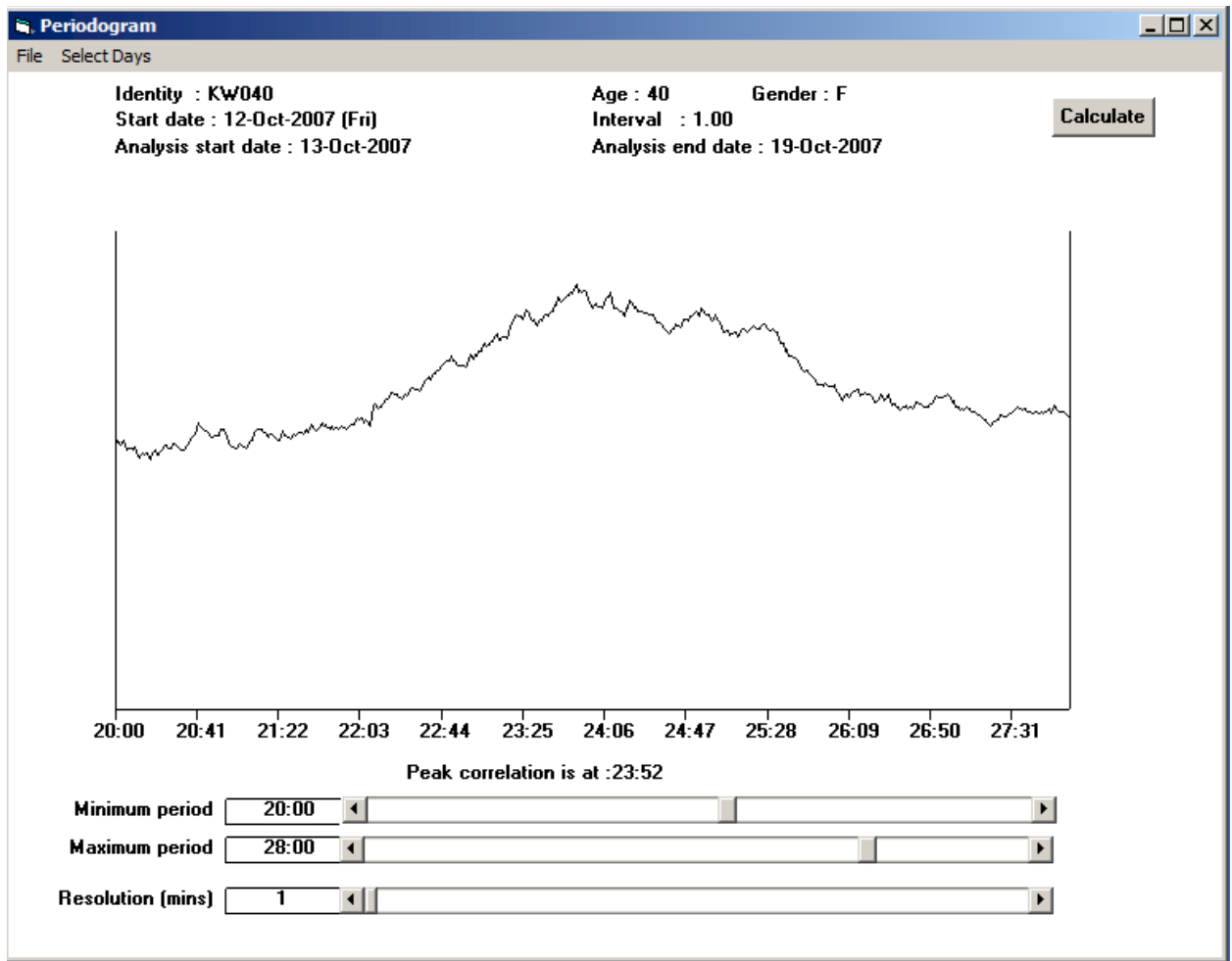
Reference: (Cugni, 1993)

Figure 5.2 Example of Fast Frequency Transformation



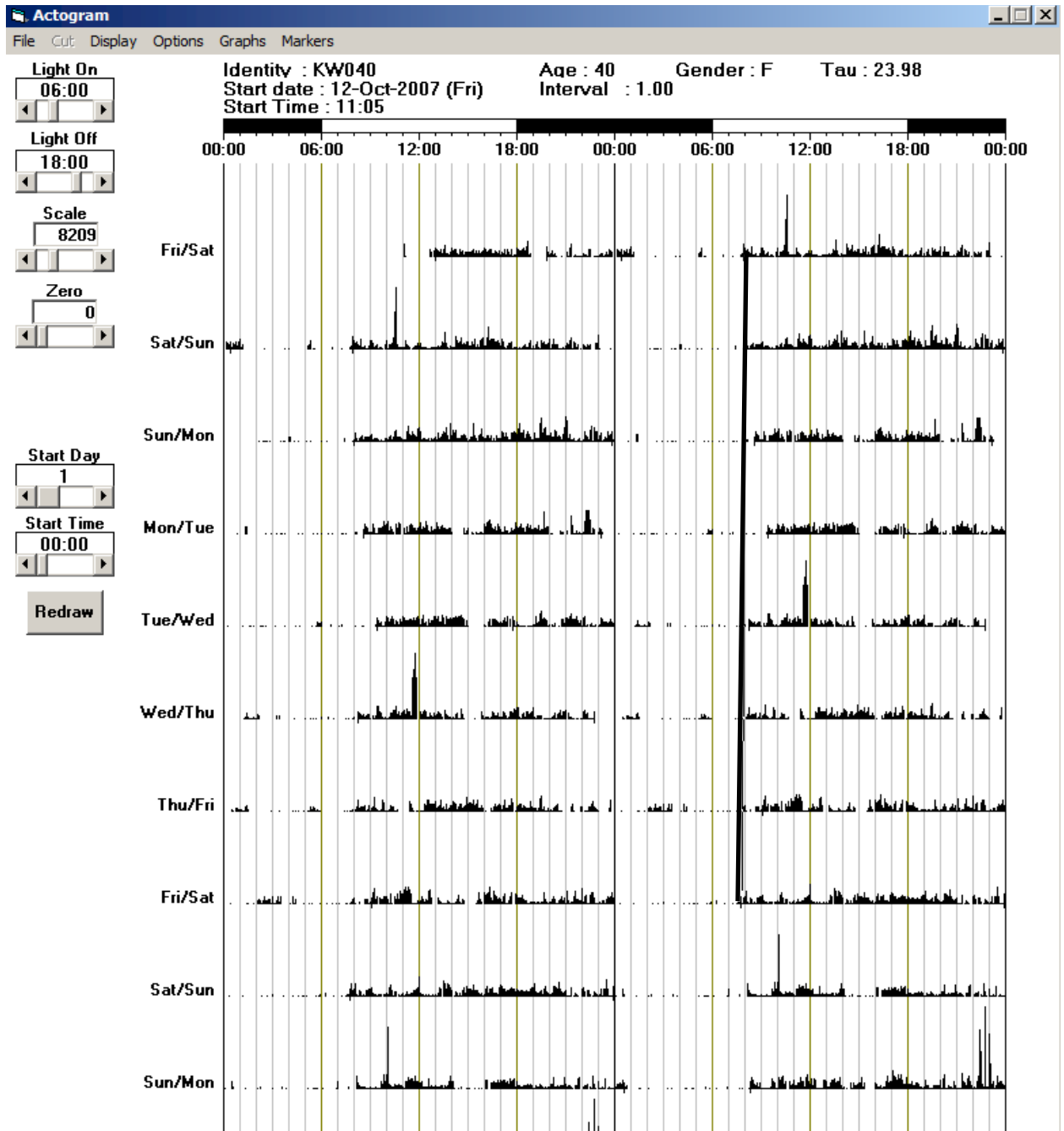
Peak Circadian Activity over 7 days noted by cursor at 23:32

Figure 5.3 Example of Periodogram



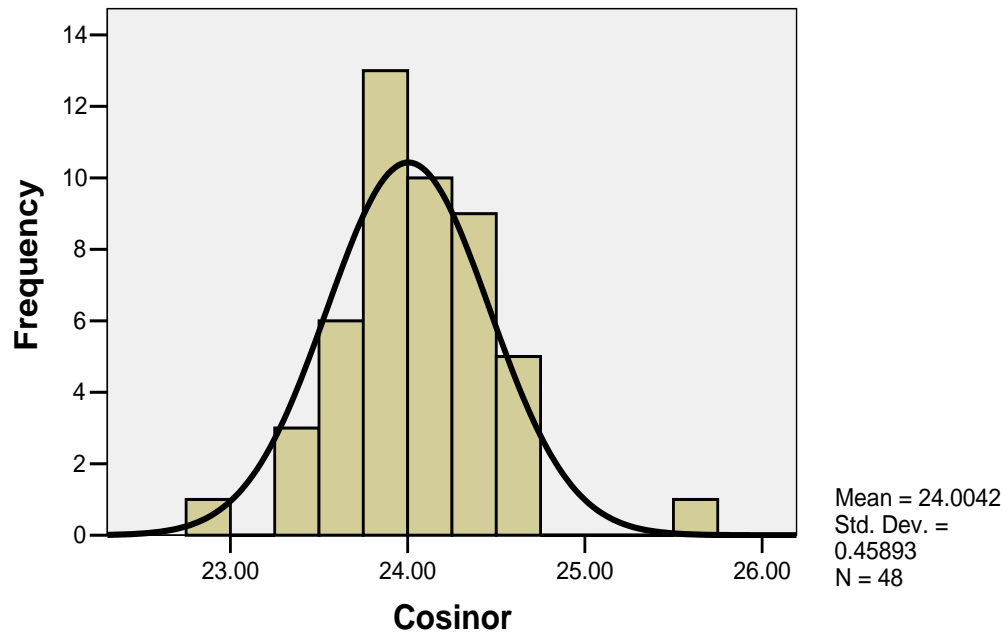
Peak Correlation of Circadian Activity over 7 days noted by cursor at 23:52

Figure 5.4 Example of Linear Regression of Onset Performed on Actogram

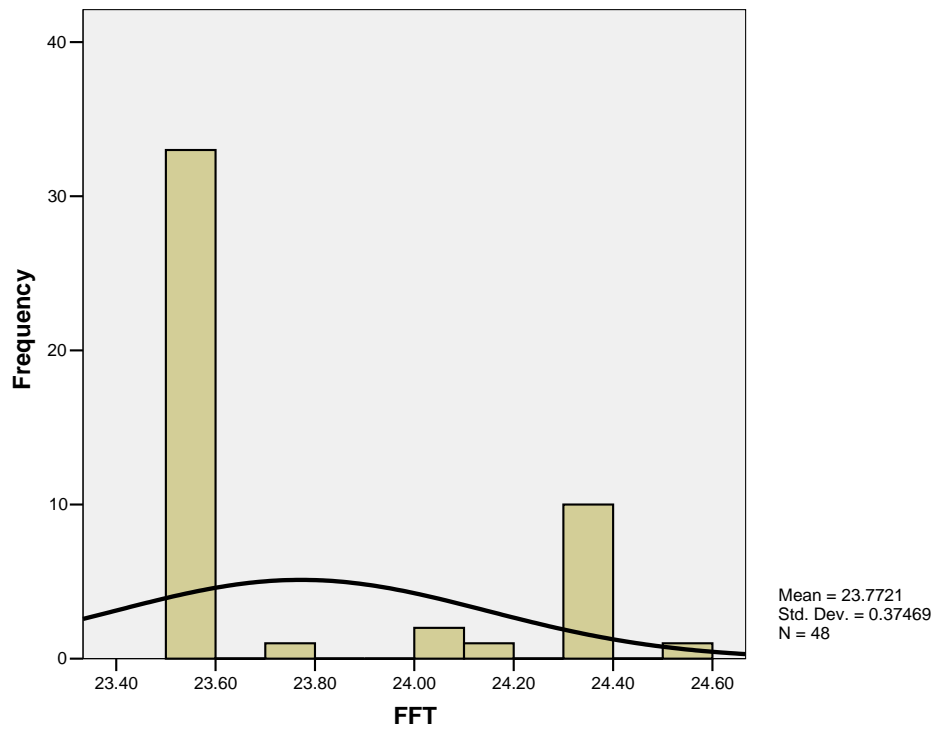


Cursor drawn from one period to another period and Tau (circadian period) noted in upper right corner as 23.98

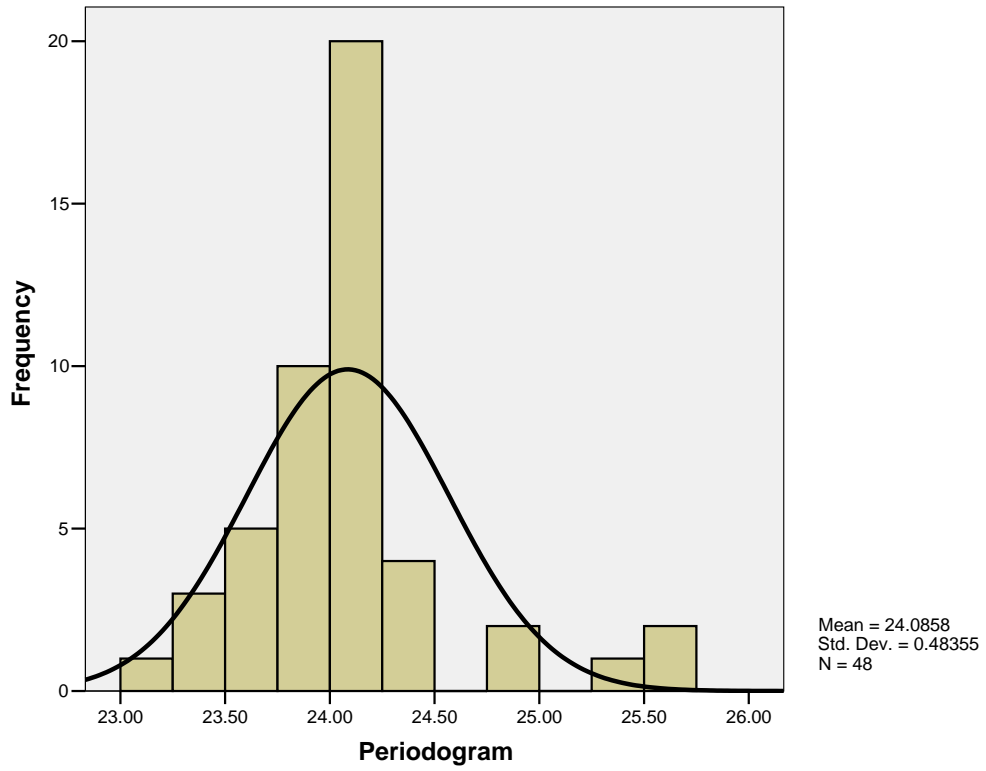
Figure 5.5 Histogram of Circadian Period by Method



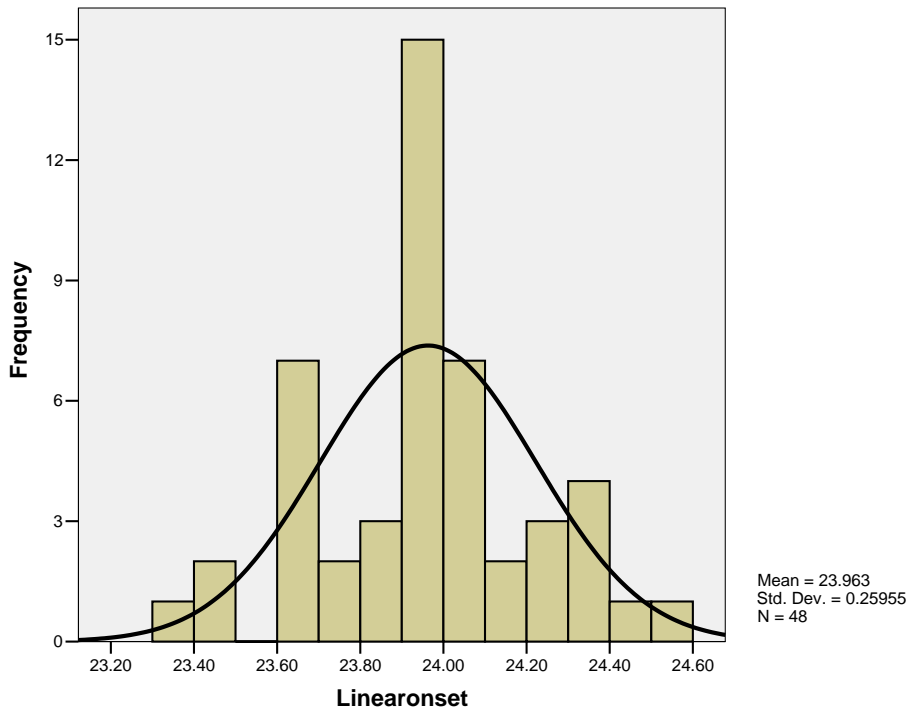
a. Cosinor Analysis



b. Fast Fourier Analysis



c. Enright's periodogram



d. Linear Regression of Onsets

CHAPTER SIX

Predictors of Fibromyalgia Impact

The purpose of this study was to identify factors that contribute to fibromyalgia (FM) impact. For more than a decade, clinical researchers have struggled to explain and treat the symptoms of those suffering from fibromyalgia (FM) (Hawley, Wolfe, & Cathey, 1988; Mease, 2005; Peterson, 2007). Fibromyalgia is characterized by widespread non-articular pain for three months or more (Wolfe, Ross, Anderson, Russell, & Herbert, 1995; Wolfe et al., 1990). Persons with FM also manifest with fatigue, headache, precordial pain, asthma, gastro-esophageal reflux, bloating and diarrhea, depression, cognitive dysfunction, anxiety, depression, and sleep disturbances including insomnia (Peterson, 2007; Silver & Wallace, 2002; Wigers & Finset, 2007).

FM is neither a degenerative nor a progressive disease, although high rates of disability and low rates of employment are associated with its diagnosis (Akerstedt et al., 2002; DeWalt, Reed, & Pincus, 2004; Friedman, 1997). Adverse effects on activities of daily living (ADL) in persons with FM are comparable to that of persons with rheumatoid arthritis (Birtane, Uzunca, Tastekin, & Tuna, 2007; Goldenberg, Mossey, & Schmid, 1995). It affects more women than men (Buskila, Neumann, Alhoashle, & Abu-Shakra, 2000) and occurs in persons with poor physical fitness and decreased physical activity; although this may be due to chronic pain and unrelenting fatigue that interfere with exercising and being active (Havermark & Langius-Eklöf, 2006; Rutledge, Jones, & Jones, 2007). While FM patients have similar clinical presentations, there is no such thing as a textbook case of FM; no group of aberrancies can classify all people with FM (Rutledge et al., 2007). Almost all persons with FM report significant fatigue and poor

sleep quality in addition to chronic pain (Hamilton, Catley, & Karlson, 2007; Moldofsky, 2008).

Much of the research in FM points to complex relationships among neurobiologic/hormonal, psychosocial, and behavioral factors occurring alone or in combination that may somehow “trigger” the onset of FM symptoms or increase its impact (Clauw & Crofford, 2003; Wasseem, Beckham, & Dudley, 2001; Waxman, 2005). Adequate restorative sleep is critical to those that must manage day to day with chronic pain and stress, but a sensitive marker for assessment of sleep disturbance in these persons is still needed.

Factors like poor pain management, unrelenting fatigue from un-refreshed sleep, morning stiffness, decreased physical activity, irregular sleep schedule, occupational demands, or other behaviors like smoking or excessive caffeine use may contribute to increased FM impact and should be examined further (Dobkin, Abrahamowicz, Fitzcharles, Dritsa, & Costa, 2005; Huber, Suman, Biasi, & Carli, 2008; Yunus, Arslan, & Aldag, 2002). Identification of modifiable factors that increase the severity and impact of FM may help maximize therapeutic management of this condition (Goldenberg et al., 1995). Therefore, the purpose of this study was to identify factors that contribute to FM impact.

Background

Despite presenting with a similar collection of somatic symptoms and chronic pain, the etiology of FM remains unknown. Chronic pain is the most common reason that people with FM seek medical care (Hawley et al., 1988; Menefee et al., 2000) and also may be the most significant factor associated with poor sleep quality (Affleck,

Urrows, Tennen, Higgins, & Abeles, 1996). Pain may contribute to symptoms of insomnia, cognitive impairment, depression, fatigue, sleepiness, and insufficient sleep (<6h) (Foley, Ancoli-Israel, Britz, & Walsh, 2004). FM and co morbid depression may contribute to fatigue and sleep disturbance, which in turn may cause persons with FM to have more severe impairment of their health status (Bergman, 2005; Niccassio, Moxham, Schuman, & Gevirtz, 2002). Depression itself may be the cause of FM symptoms like fatigue, pain, and poor sleep as patients with depressive symptoms and body pain experience significantly more complaints of pain than those with pain alone (Greenberg, Leong, Birnbaum, & Robinson, 2003). One study showed that FM is experienced by 22 – 45% of current depression sufferers (Epstein, et al, 1999).

Although sleep disturbances are prevalent in our society, its causes are varied (Akerstedt, Fredlund, Gillberg, & Jansson, 2002). According to Schneider-Helmert et al. (2001), sleep disturbances are classified into two types: trouble falling asleep (prolonged sleep latency) and trouble staying asleep (wakeful arousals after sleep onset); both resulting in a reduction of estimated sleeping time. Epidemiological studies show that sleep disturbances are more common among older adults and women (Dement, 2000; Martin et al., 2006). Unfortunately, pain and poor sleep are not the only complaints of persons with FM. Unrelenting fatigue and other somatic symptoms are commonly associated with chronic pain and poor sleep quality in FM (Rutledge et al., 2007; Soderberg, Lundman, & Norberg, 2002). What still remains unclear is whether trouble falling asleep and trouble staying asleep are the only classifications of sleep disturbance in persons with FM.

Poor sleep behaviors including irregular sleep schedule, frequent daytime naps, or increased occupational demands resulting in poor sleep schedule may contribute to FM impact (Akerstedt et al., 2002). Poor quality sleep can result in muscle aches, fatigue, trouble with concentration and other somatic complaints, similar to those found in people with circadian rhythm disturbances (CRSD) like jet lag or night shift work (Klerman, Gershengorn, & Kronauer, 2002; Klerman et al., 2001; Schaefer, 2003). Large differences in the preferred timing of sleep and activity exist in humans and are regulated by the circadian clock (Wittman, Dinich, Mellow, & Roenneberg, 2006). Social schedules may interfere considerably with these sleep preferences due to the timing of work days and free days. This discrepancy between biological time and social time has been referred to in some sources as “social jet lag”. In research on social jet lag, the most striking correlation existed in smokers who were characterized as “night owls” or who went to bed later than early risers ($r = .40, p < .001$). This interaction between biological timing and social timing may lead to a chronic disturbance in circadian rhythm similar to that experienced in shift workers and those with jet lag. Behaviors like smoking or lack of physical exercise have been associated with musculoskeletal pain, but should be examined further (Ludovic, Van Amelvoort, Jansen, & Kant, 2005; McBeth & Jones, 2007; Yunus et al., 2002). Of lifestyle factors associated with chronic pain, smoking was more frequent among women reporting fibromyalgia (Ostensen & Schei, 1997); however earlier studies did not report this association (Makela & Heliovaara, 1991). The nature of the relationship between smoking, circadian rhythm, and FM remains unclear. Knowledge about factors that contribute to FM impact would be beneficial, especially if these factors are modifiable (Foley et al., 2004).

According to a consensus of experts that care for persons with FM, domains that should be investigated in clinical trials include pain, fatigue, sleep disturbance, multi-dimensional function, quality of life, mood disorders and cognitive function (Mease, et al., 2007). However, persons suffering with FM identified three key features: pain, fatigue, and disturbed sleep. Therefore, the purpose of this investigation is to identify factors that predict the impact of fibromyalgia.

Methods

Design and Sample

The design of the study is illustrated in Figure 6.1. This hybrid design combined cross-sectional surveys and longitudinal assessment of sleep using wrist actigraphy and sleep diaries completed over a week. Data for this study were collected from a volunteer, community based sample of women with a self-reported diagnosis of FM, who lived throughout the United States. The participants were not examined physically nor were the American College of Rheumatology diagnostic criteria for the number of tender points verified. Women with FM and perceived sleep disturbances were recruited in person, by phone, and by mail. Women over the age of 18 years old were recruited using flyers placed in community centers, physician's offices, or from information posted on the FM related websites. Exclusion criteria included not having a diagnosis of FM, a previous diagnosis or treatment of sleep apnea, or working a night shift occupation. These criteria were verified with each participant in person, by phone or by email before enrollment. When asked if they get restorative sleep, 86% indicated that they did not. Fifty-seven women with FM consented to participate in the week-long study. Fifty-two

women enrolled and completed study procedures. Only women wearing the actigraphy device for at least seven days were included.

Measures

Data were collected on the impact of FM, age, body mass index (BMI), ethnicity, occupational status, functional outcomes of sleep (FOSQ), exercise status, total sleep time, circadian period, wake bouts, peak activity, daily pain medication use, daily sleep medication use, daily pain, daily fatigue, caffeine use, daily naps, and co morbidity.

These variables and their level of measurement are shown in Table 6.1.

Sleep Characteristics/Quality

Objective measures of sleep were obtained using the Actiwatch (Mini Mitter Company, 2004). The Actiwatch is a wrist watch-like device worn on the wrist or ankle to measure limb movement (Buysse, 2005; DeSouza et al., 2003; DeSouza, Nogueira Pires, Poyares, Tufik, & Calil, 2001). The device contains a miniature motion-based sensor that translates movement into a numerical activity count. Sampling of activity counts by the device occurs at frequencies or intervals called epochs. Using sophisticated algorithms, actigraphic software converts these raw activity counts to epochs of sleep or wake. The device was configured to sample activity every minute during the time that the device was on the participant; thus, the sampling interval was one minute epochs. The device was placed on the non-dominant wrist (Littner et al., 2003). The sensitivity threshold was set at 40 or medium sensitivity (Edinger, Wohlgemuth, Krystal, & Rice, 2005). These data were used to calculate total sleep time, actigraphic wake bouts, and peak activity.

Actigraphy may also be used to calculate the period or length of the circadian biorhythm using the methods provided by the software of the device or by using Cosinor analysis (Carvalho-Bos, Waterhouse, Edwards, Simon, & Reilly, 2003; Pollak, Tryon, Nagaraja, & Dzwonczyk, 2001; Roehrs, Turner, & Roth, 2000). The software used with the device to estimate sleep times was Actiware Sleep 3.4 (Mini Mitter Company, 1998-2003). Factors measured by the Actiwatch include total sleep time (TST), daily circadian period, frequency of actigraphic wake bouts, and peak daily activity counts over 24 hours. Actigraphic wake bouts were frequencies of per night bouts of wakefulness determined by the actigraphy software defined as 40 or more activity counts per minute noted after sleep onset of at least 10 minutes. Cosinor analysis was used to calculate the circadian period and peak activity for each day and then averaged. The first and last day was not used in the calculations to decrease artifact associated with different study start and stop times resulting in less than 24 hours of data.

Cosinor analysis is commonly used to quantify circadian period from time series data like actigraphy. A least square approximation of time using a cosine function of a known period is performed using the mesor or midline estimating statistic, the amplitude, the known period, and the acrophase (Hamilton, 1994). Cosinor analysis is a non-linear model that has a linear representation upon transformation (Refinetti, 1996-2008).

Impact of Fibromyalgia

Fibromyalgia impact was measured using the Fibromyalgia Impact Questionnaire. The FIQ is a self-administered questionnaire that takes approximately five minutes to complete and is composed of 20 items. The FIQ, developed by Burckhardt et al. (1991), was created for evaluation of FM patients within the research setting. Higher scores on

the scale indicate increased limitations (Fallon, Bujak, Guardino, & Weinstein, 1999; Gowans, DeHeuck, Voss, Abbey, & Reynolds, 2001; Gowans, DeHeuck, Voss, & Richardson, 1999). The only subscale contains 11 items related to physical functioning rated on a 4 point Likert-type scale. The next two items ask the person to mark the number of days they felt well (0-7), the number of days that they were unable to work due to their symptoms (0-7). The remaining items are horizontal linear scales marked in 10 increments on which the patient rates work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety and depression. The range of single item scores is 0 - 10, with 0 indicating no impairment and 10 indicating maximum impairment. The overall score ranges from 0-100 such that the higher the score the higher the impact. Data supporting the reliability and validity of the instrument have been reported (Burckhardt et al., 1991; Buskila & Neuman, 1996; Dunkl, 2000).

Daily Sleep Indices

The participants also completed a daily sleep diary, which asked them to indicate various sleep times (bedtime, wake time, time to fall asleep, number of times awake after sleep onset, and number of times out of bed), any special medication use, exercise performance, caffeine use, and other questions regarding their sleep. In addition, participants were asked to rate their daily pain and fatigue level using 100-mm anchored horizontal linear or visual analogue scales (VAS). A comprehensive survey regarding demographic, socioeconomic, and health status were completed by each participant. The variables included age, body mass index (BMI), occupational status, ethnicity, smoking status, daily use of medication for sleep, daily use of medication for pain, average daily pain level, exercise obtained, number of caffeinated beverages, sleepiness, functional

outcomes of sleep, and average daily fatigue level. The survey also included the Epworth Sleepiness Scale (ESS) to measure daytime sleepiness (Johns, 1991) and the Functional Outcomes of Sleep Questionnaire (FOSQ) to measure functional status (Weaver et al., 2007). Both instruments are frequently used to measure outcomes in persons with sleep disordered breathing.

The ESS is an easy to complete, 8-item instrument used in persons with sleep disorders like obstructive sleep apnea/hypopnea. The items are answered using a Likert scale (0 = no chance of dozing to 3 = high chance of dozing). Scores range from 0 – 24 with scores > 15 associated with severe sleepiness. The FOSQ is a 30-item instrument also used in persons with sleep disorders. A Likert-type scale (1 = extreme difficulty to 4 = no difficulty) is used for responses with lower scores representing greater impact on functional status. Scores range from 5 – 20.

Procedure

The study and procedures were approved by the University of Kentucky Institutional Review Board (IRB). Each participant was informed of the study requirements and written consent was obtained. Frequencies and measures of central tendency were performed on the data. Bivariate analysis using two-sample t-tests and Pearson's product moment correlation were conducted to identify individual factors associated with FM; the alpha level for significance was set at .05 throughout. All variables associated with FM Impact were entered as predictors of impact in a multiple regression model; a backward stepwise procedure was used to sequentially eliminate the regressors not significant in the model. This method was used to develop a parsimonious model in light of the limited sample size, and the adjusted R^2 was used to summarize the

model as a conservative estimate of the percent of variability in FM Impact predicted by the model (Stevens, 2002).

Results

Two women did not place the device on their wrist in time to record seven days of data and three women did not wear the Actigraphy device or complete the questionnaires despite consenting to participate, so the effective sample size was 52 participants. Health status and socio-demographic characteristics of the sample are shown in Tables 6.2, 6.3, and 6.4. The sample was female, mostly Caucasian (90%) with a mean age of 47.6 (SD = 10.5), and diagnosed with FM for at least 4.1 ± 5.5 years (SD). On average, the duration of disease was 7.3 ± 7.6 years; 25% currently smoked cigarettes; their mean BMI was 29.6 ± 7.2 ; and 64% of these women were employed in some capacity. The entire sample had at least a high school education and 36% of the sample was college graduates. Sleep characteristics for the cohort using sleep diary times averaged over seven days indicated mean actual sleep time (AST) of 06:19 hours $\pm 1:17$ and mean sleep latency (SL) of at least 00:30 minutes to fall asleep. Seventy-nine percent indicated difficulty falling asleep (DFA) or staying asleep. Fifty percent indicated difficulty maintaining sleep (DMA) and 75% complained of un-refreshed sleep, which are all characteristic of insomnia (Buysse, 2005; Phillips, 2005). Scores on the ESS showed that the women were moderately sleepy ($M = 11.3 \pm 5.8$) with moderate impact on functional status (FOSQ) from their sleep ($M = 11.8 \pm 3.2$). The mean FIQ score for the participants was 59.5 (SD 15.6). Using the body pain map, the average number of tender points rated by the participants was estimated at 10 (± 4) (slightly less than diagnostic criteria) and the average total percentage of body pain was 37.5% ($\pm 25\%$).

Almost 60% of the participants indicated that they had more than four or more co-morbidities. Co morbidities self-reported by the participants included: migraines (62%), arthritis (46%), sciatica (34%), fractures (30%), carpal tunnel (28%), endometriosis (24%), thyroid disease (22%), asthma (22%), hypertension (22%), psychiatric problems (18%), skin problems (18%), spastic colon (18%), osteoporosis (16%), post traumatic stress syndrome (PTSS) (14%), cancer (12%), heart disease (10%), gastric ulcers (10%), lung disease (8%), diabetes mellitus (4%), hepatitis (4%), lupus (4%), stroke (2%), sjogren's (2%), and venereal disease (2%). Using the Charlson Co morbidity Index (CCI), co morbid conditions of the participants were classified based on their seriousness (Charlson, Pompei, Ales, & MacKenzie, 1987). The CCI takes into account the number and the seriousness of co morbid disease and provides a simple method of estimating risk of death. The mean CCI for this sample was 1.4 (\pm 1.6 SD) indicating low levels of mortality related co morbidities.

Seventy four percent indicated that they used a medication to induce sleep. Medications reportedly used for sleep included: antihistamines, benzodiazepines/tranquilizers, sedative/hypnotics (non-benzodiazepines), opiates, and alcohol. Ninety four percent of the participants indicated that they used a medication for pain. Medications reportedly used for pain included: non-steroidal anti-inflammatories, antidepressants, steroids, acetaminophen, Tramadol, and narcotics.

Pearson's correlations of the FIQ with daily pain, daily fatigue, age, circadian period and the FOSQ are shown in Table 6.5. Fatigue was strongly correlated with pain ($r = .80, p < .001$) and pain levels had a slightly stronger correlation with FIQ scores than fatigue scores. Significant correlates with FIQ included pain, fatigue, FOSQ, circadian

period and age, but these were not strongly correlated with each other or with pain and fatigue. No significant correlations were noted with total actigraphic wake bouts, ESS scores, sleep duration, total caffeine consumed, peak activity, or BMI.

As shown in Table 6.6, independent sample *t* tests revealed significant differences in FIQ scores between smokers and non-smokers [$t(50) = -3.59, p < .001$]. No other significant differences were found in FIQ scores by exercise status, naps, pain medication use daily, sleep medication use daily, or occupational status. As noted in Table 6.7, smokers were also significantly younger than non-smokers (43 years versus 50 years), rated their pain significantly higher (70.9 mm versus 59.4mm), and consumed more caffeine (2.4 8-oz cups versus 1.4 8-oz cups) than non-smokers.

Six factors associated with FM impact in bivariate analyses were included in the full model: average daily pain, average daily fatigue, average daily circadian period, age, smoking status, and the FOSQ. As shown in Table 6.8, the backward stepwise solution resulted in four predictors being retained in the regression equation: average daily pain; average daily fatigue, average circadian period; and age. Significant beta coefficients and standardized beta coefficients are noted in the table. This model was significant [$F(4, 47) = 18.72, p < .0001$]. Smoking status and the scores of FOSQ were eliminated as non-significant predictors of FM impact even though there were significant differences in FIQ scores. The equation derived from the sample was: $FIQ = 103.75 + .252 \text{ average pain levels} - 2.60 \text{ circadian period} - .294 \text{ age} + .321 \text{ average fatigue}$. All predictors were significant at $p < .05$. Using R^2 , 61% of the variance was predicted in the FIQ scores. An adjusted R^2 (Wherry) estimated how much variance on the dependent variable would be accounted for if the equation was derived from the population from which the sample is

drawn. Very little shrinkage was noted with the Wherry adjusted R squared ($R^2 = .58$). Assumptions of normality were not violated as a mostly bell shaped distribution of residuals was evident (Figure 6.2). Plots of the standardized residuals revealed no systematic patterns in the spread that would indicate serious violations of normality, homoscedasticity, or linearity (Figure 6.3). The variance inflation factor (VIF) was noted to be < 3 for all predictors.

Examination for outliers was performed by examining the standardized residuals, the centered leverage values (CLV), and Cook's distance. No cases were noted whose standardized residuals exceeded 2.0. Using a calculated threshold [$(3(k + 1)/n)$, where k = number of predictors and n = sample size], a centered leveraged value $> .29$ would identify cases that may be an outlier. The maximum CLV was .39 and only one case met the above criteria. Cook's distance > 1.0 would be associated with a case (s) that affects the regression coefficient, no cases were noted that exceeded a Cook's distance of 1.0 (Stevens, 2002). Four predictors were selected: average fatigue, average pain, average circadian period, and age.

As noted in Table 6.9, the derived scores compared to the observed scores were strongly correlated ($r = .79, p < .0001$). Paired sample t - tests revealed no significant differences in the means of the predicted FIQ scores compared to the observed scores [$t(51) = -126, p = .90$]. Plots of the predictors revealed normally distributed histograms for all except circadian period, which was skewed to the right ($-.66 \pm 33$) (see Figure 6.4). In this case, the mode of the circadian period was higher than the mean (28 hours versus 25.5 hours) indicating that more participants in the study had longer circadian periods than that measured by the mean.

Discussion

People with FM often experience symptoms for years before they are diagnosed (Goldenberg et al., 1995). By the time that they are diagnosed, they have physically and psychosocially adapted to their disease severity. This adaptation to their condition may take the form of poor physical fitness, decreased activity, poor sleep schedule, obesity, decreased sexual contact, and use of a variety of therapies for pain or sleep (Table 6.10).

To examine the factors that might contribute to disease severity, data were collected from 52 women recruited from the community. No limitations were placed on their activities of daily living. They were not given information that might have changed their lifestyles during the week-long study. The participants were similar to research participants with FM in other studies (Altan, Bingol, Aykac, Koc, & Yurtkuran, 2003; Bae & Lee, 2004; Bennet et al., 2005; Chen, Hassett, Hou, Staller, & Lichtbroun, 2006; Da Silva, Lorenzi-Filho, & Lage, 2007). Our sample was female with a duration of symptoms of seven years or more and an average age of 47.6 years (Table 6.1). The women had high levels of pain as noted by averaged daily pain VAS levels of 61.9 (maximum score = 100) and decreased functional status as evidenced by mean FIQ scores of 59.1 (maximum score = 100) (Burckhardt 2002; Burckhardt et al., 1991; Burckhardt & Jones, 2005). Twenty-five percent of the sample smoked. Unlike prior research, two-thirds of the women were employed full time and only 12% of the sample was disabled.

Using the FIQ as a global measure of FM impact, these results point out the complex, multidimensional relationships that contribute to overall impact of FM. Demographic factors like older age were associated with reduced FM impact, but this

might be due to these women being less likely to work fulltime when compared to their younger counterparts. Unmanaged chronic pain and fatigue were primary contributors to FM impact as were alterations in daily circadian period. Increases in FM impact were noted in women who smoked, but the extent of this interaction with FM impact and its influence on the other variables remains unsolved.

Pain, fatigue, circadian period, and age when entered into a regression model predicted 61% of the variance in the FIQ scores using multiple correlation. The Wherry adjusted R^2 of .58 did not represent much shrinkage from the multiple correlation. Evidence that supports this regression equation as reliable include predictors with low intercorrelations; moderate to strong correlations between the predictors and the dependent variable FM impact; no systematic clustering of standardized residuals; and no influential data points that affected the prediction equation. FM impact can be predicted using average pain, average fatigue levels, daily circadian period, and age.

Previous longitudinal research conducted in persons with FM has noted pain levels and fatigue as significant correlates of disease severity, but no prior research has linked activity based circadian period alterations with FM impact. Research using multiple regression modeling to predict disability and disease severity in FM has been conducted, although no models have contained the same set of factors and no research has examined circadian period as a predictor of FM impact. Investigation of the impact of circadian periodicity in these women deserves more investigation.

Within this research, adjustment of daily circadian rhythm was noted in the actograms of these participants and may be an adaptation to FM by these women. (See Figure 6.5) This was evident by the finding that calculations of circadian periodicity

(Chapter 4) in this sample using an average over one week resulted in what appeared to be a normal circadian period (23.98 hours \pm .48 hours). However, calculation of *daily* circadian periods with the first and last day artifact removed used in this regression revealed different results than that averaged over one week (25.54 hours \pm 2.22) in these women. The differences in these calculated periods (average daily versus average weekly) may relate to the effect of a work schedule trend, also known as “social jet lag” that will require study over longer than 7 days. Further, when the averaged seven day values for circadian period were used in place of the daily calculations, the backward solution only retained the predictors of pain and smoking ($p < .01$) essentially controlling for the work week effect and removing social schedule from the equation. Assessment of circadian periodicity in persons with FM may require longer study, and possibly autoregressive averaging procedures to further investigate these findings.

This research confirms the association of several known factors that impact FM severity. A closer look into these contributors in an even larger study is needed to validate this model. Healthcare professionals who care for persons with FM may find these results useful in helping to establish therapeutic strategies that may improve the outcome of individual patients with FM. Strategies that maximize pain management might include non-pharmacologic therapies like water therapy, massage, and acupuncture in addition to prescribed therapeutics for treatment of pain. In fact, these therapies were frequently indicated by participants as helpful for reducing pain in this study but were not necessarily treatments prescribed by their health care provider.

Other pertinent strategies might include sleep counseling on mechanisms for assuring regular sleep scheduling and behaviors that improve sleep. In some cases,

disturbances in sleep like insomnia, may require sleep restriction if it is found that symptoms are occurring in persons having adequate time in bed. Using actigraphy, individuals with poor sleep quality that are found to have more than adequate time in bed may need to be assessed for depression, as insomnia may be an early sign of this condition (O'Malley, et al., 2000).

Strategies for good sleep might be reinforced using actigraphy to assess and determine ongoing alterations in sleep schedule associated with non adherence, occupational schedule demands, or lifestyle behaviors. In fact, many of the individuals in this study reported that they slept better during the study than they had been previously. This may have been due to better awareness of their bed times and sleep schedule while wearing the actigraph.

On the other hand, if other signs and symptoms like hypertension or severe sleepiness are also present without gross abnormalities found using actigraphy and sleep diary, evaluation in a sleep laboratory for assessment of sleep disordered breathing conditions like sleep apnea may need to be performed (Phillips & Mannino 2007; Sewell-Scheuermann & Phillips 2006). In this sample of women, more than 50% met the criteria for sleep disordered breathing according questions similar to that of the Berlin questionnaire, but less than 10% had been evaluated in a sleep laboratory despite history of sleepiness, hypertension, obesity, and snoring (Netzer, Stoohs, Netzer, Clark, & Strohl, 1999). Obstructive sleep apnea may be an undiagnosed condition in some of these individuals (Heistand, Britz, Goldman, & Phillips, 2006).

Other important strategies to decrease FM impact should include encouragement to stop smoking as increases in FIQ scores were noted in smokers compared to non-

smokers, although this effect may be associated with smokers having shorter circadian periods combined with increased amounts of caffeine consumed compared to non smokers. In this research, analyses showed a significant difference in FM impact associated with smoking, decreased circadian period, increased caffeine intake, and younger age, but smoking and caffeine did not represent significant predictors in the regression model. A potential reason for this may be due to a mathematical discrepancy discovered when calculating the circadian period from these data. Circadian periods obtained from Cosinor analysis of seven days of averaged data showed a different result than those obtained from daily calculations of circadian period that had the first and last day artifact removed and then averaged. This unexpected discrepancy may be the result of impact from a work week effect even though no differences in FIQ scores were noted between fulltime employed and not employed women. Interestingly, when the results from circadian periods calculated from all data points were used in the regression model instead of the averaged daily periods with first and last day removed, smoking was retained as a significant predictor. Thorough investigation of these mathematical differences in periodicity was a limitation of this study due to the length of the study. Regardless, this interaction with smoking on FM impact and its association with circadian rhythm needs further examination.

In summary, pain, fatigue, circadian period, and younger age were associated with increased FM impact in a small community based sample of women with FM. These significant factors demonstrate that modifiable behaviors like irregular sleep schedules, unresolved pain, and fatigue can influence the overall disease activity of FM and that

adaptation to these factors may occur as one ages. Further study of these factors including the unknown impact of smoking of FM is needed to validate these results.

Conclusion

Healthcare professionals can assist their clients with alternative pain management strategies and reinforce better sleep habits by using wrist actigraphy. Actigraphy may be used to assess sleep/wake patterns that are counterproductive to sleep, to determine circadian period, and to assist their clients to achieve better sleep by using actigraphy to reinforce proper sleep hygiene with their clients. Strategies to decrease pain, improve poor sleep habits, and assistance to stop smoking will help these persons start to feel better and reduce the impact of their FM.

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Table 6.1 Operational Definitions of Variables

Variable	Measure	Level of Measurement
Age	Age in years	Ratio
Body Mass Index	weight (kg) / [height (m)] ²	Ratio
Occupational Status	1 = Full Time, 0 = Not Working	Nominal
Daily Exercise	1 = Yes, 0 = No	Nominal
Total Sleep Time	Average Minutes of time asleep	Ratio
Circadian period	Average Hours and Minutes	Interval
Wake Bouts	Average Number of bouts/night	Ratio
Peak Activity	Average Activity Counts/24 hours	Ratio
Daily pain medication use	1 = Yes, 0 = No	Nominal
Daily sleep medication use	1 = Yes, 0 = No	Nominal
FOSQ	Functional status Score (5 – 20)	Ratio
ESS	Sleepiness Score (1 -24)	Ratio
Average Daily Pain	Average measure in millimeters	Ratio
Average Daily Fatigue	Average measure in millimeters	Ratio
Caffeine use daily	0 = Zero, 1 = ≤ 2, 2 = >3	Nominal
Daily Naps	1 = Yes, 0 = No	Nominal
Ethnicity	1 = Caucasian 2 = Native American 3 = African American 4 = Asian/Pacific Islander 5 = Hispanic 6 = Arab American	Nominal

ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcomes of Sleep

Table 6.2 Characteristics of Women with FM and Sleep Disturbance (n = 52)

	mean	SD	Minimum	Maximum
Age (yr)	47.6	10.7	31	72
Body Mass Index	30.2	7.2	19.3	47.4
Disease Duration (yr)	7.3	7.6	< 1	30
Time to Diagnosis (yr)	4.1	5.5	< 1	23
FIQ (0-100)	59.5	12.3	28	87
VAS - Pain (0-100)	61.9	18.1	6	95
VAS-Fatigue (0-100)	64.1	15.7	21	95
Mean Circadian Period (hours)	25.6	2.2	20	28
Average Caffeine Intake/day	1.7	1.2	0	5
Functional Outcomes of Sleep	11.8	3.2	7	19
Epworth Sleepiness Scale	11.3	5.8	1	21

BMI – Body Mass Index

FIQ-Fibromyalgia Impact Questionnaire

VAS-Visual Analogue Scale

SD-Standard Deviation

Table 6.3 Socioeconomic Characteristics of Women with FM and Sleep Disturbance

(n = 52)

Characteristic	<i>n</i>	(%)
<u>Marital Status</u>		
Married	32	(61.5%)
Divorced	12	(23.1%)
Single/Widowed	5	(9.6%)
Unknown	3	(6%)
<u>Education</u>		
HS Graduate	12	(23%)
Some College/ Technical School	20	(40%)
College Graduate	19	(36%)
Unknown	1	(2%)
<u>Full Time Employment Status</u>		
Yes	33	(64%)
No	11	(20%)
Unknown	2	(4%)
Disabled	6	(12%)
<u>Ethnicity</u>		
Caucasian	47	(90%)
Black	2	(4%)
Hispanic	1	(2%)
Arab American	1	(2%)

Table 6.3 (continued)

Residing Time Zones:

Eastern Standard Time	44	(83.6%)
Central Standard Time	2	(3.6%)
Mountain Standard Time	1	(1.8%)
Pacific Standard Time	5	(10.9%)

Table 6.4 Health Characteristics of Women with FM and Sleep Disturbance (n = 52)

Characteristic	<i>n</i>	(%)
Number of Health Conditions besides Fibromyalgia		
○ None	4	(7.5%)
○ 1 – 3	19	(35.8%)
○ > 4	30	(56.6%)
Frequency of Caffeinated Beverages (8-oz)		
○ None	9	(18%)
○ ≤ 2	31	(59.6%)
○ > 3	8	(16%)
○ Unknown	4	(7%)
Currently Smokes	13	(25%)
Reports Daily Exercise	42	(81%)
Uses Sleep Med	44	(74%)
Uses Pain Med	49	(94%)
Takes Naps	18	(34%)

Table 6.5 Pearson's Correlations for FM impact and Predictor Variables with Women diagnosed with FM (n = 52)

Variable	FIQ Score	Average Daily Fatigue	Average Circadian Period	FOSQ	Age
Average Daily Pain	.65*	.80*	.34**	-.35**	-.15
Average Daily Fatigue	.62*		-.18	-.45**	.28**
Average Circadian Period	-.51*			-.34**	-.00
Functional Outcomes Of Sleep Questionnaire	-.37				.08
Age	.32**				

*p <.01
 **p < .05

Table 6.6 Independent *t* tests of Demographic Variables on FIQ (*n* = 51)

Variable	<i>n</i>	FIQ Scores		t Statistic	<i>p</i> -value
		Mean (SD)			
<u>Exercises</u>					
No	9	62.9 (16.1)		.82 (49)	.42
Yes	42	58.1 (15.9)			
<u>Takes Naps</u>					
No	15	59.4 (15.1)		.24 (47)	.81
Yes	34	58.2 (16.7)			
<u>Pain Med</u>					
No	2	65.5 (21.9)		.59 (49)	.56
Yes	49	58.7 (15.8)			
<u>Sleep Med</u>					
No	9	60.3 (14.8)		.28 (49)	.78
Yes	42	58.7 (16.2)			
<u>Employed FT</u>					
No	15	61.6 (16.6)		.77 (50)	.44
Yes	37	57.9 (15.4)			
<u>Smokes</u>					
No	37	54.7 (15.6)		-3.5 (49)	.001
Yes	14	70.4 (11.6)			

FT = Full Time

Table 6.7 Differences in Means of Major Study Variables by Smoking Status (n = 51)

Variable	Smoking Status		t Statistic	p-value
	Yes Mean (SD)	No Mean (SD)		
FIQ scores	70.43 (11.6)	54.74 (15.6)	-3.59	.001
Caffeine Drinks	2.44 (1.2)	1.37 (1)	-3.30	.002
Age	43 (7.3)	50.03 (11.2)	2.67	.01
Circadian Period	24.51 (2.3)	26.05 (2.0)	2.80	.01
Pain levels	70.9 (19.4)	59.37 (17)	-2.50	.02
Peak Activity	2123.85 (672.7)	2114.31 (549.9)	-.09	.93
Body Mass Index	28.21 (6.9)	30.42 (7.6)	.97	.33
Fatigue	69.75 (11.2)	61.54 (15.8)	-1.87	.07

Table 6.8 Backward Stepwise Elimination to Identify Best Predictive Model for FM

Impact (n = 52)

Model/ Variables	B Coefficient	Beta Coefficient	<i>p</i>	<i>R</i>	<i>R</i> ²	Wherry <i>R</i> ²
<u>Model 1</u>						
Pain	.27	.30	..03	.79	.63	.58
Period	-2.23	-.31	.00			
Age	-.23	-.15	.13			
Fatigue	.26	.25	.09			
Smoking	4.83	.14	.20			
FOSQ	-.20	-.04	.70			
<u>Model 2</u>						
Pain	.27	.30	.03	.79	.63	.59
Period	-2.25	-.31	.00			
Age	-.23	-.15	.16			
Fatigue	.28	.26	.06			
Smoking	5.06	.14	.17			
<u>Model 3</u>						
Pain	.25	.29	.04	.78	.61	.58
Period	-2.60	-.36	.00			
Age	-.29	-.19	.04			
Fatigue	.32	.30	.03			

FOSQ – Functional Outcomes of Sleep Questionnaire

$$\text{Wherry Adjusted } R^2 = 1 - \frac{[(n \times 2) - 1]}{[(n \times 2) - 2]} \times (1 - R^2)$$

Table 6.9 Derived Scores compared to Observed Scores (n = 52)

Model	Mean (SD)	R^a	t test (df)	p
Derivative Scores ¹				
Pain, Fatigue, Period, Age	59.67 (16.0)	.79*	-.126 (51)	.90
Observed Scores ¹				
Pain, Fatigue, Period, Age	59.50 (12.33)			

¹Predictors: Average Daily Pain, Circadian Period, Age

^aPearson's Correlation significant at * $p < .05$

Table 6.9 Pharmacologic and Non-Pharmacologic Therapies Used for Treatment of Fibromyalgia (n= 51)

<u>Pharmacologic Therapies</u>	<u>Percent</u>
Non-Steroid Anti-inflammatories	78%
Narcotics	33%
Oral Steroids	33%
Steroid Injections	30%
Antidepressants (all)	74%
Muscle relaxants	23%
Herbal preparations	32%
Chinese herb preparations	11%
<u>Non Pharmacologic Therapies</u>	<u>Percent</u>
Exercise	63%
Physical Therapy	59%
Transcutaneous electrical nerve stimulation (TENS)	29%
Massage	58%
Acupuncture	23%
Biofeedback	9%
Diet Modification	30%
Surgery	5%
Psychotherapy/counseling	23%
Chiropractor services	37%

Figure 6.1 Description of Study Design

Day

Screening Visit Items	1	2	3	4	5	6	7	End of Study Visit (Day 7+2)
Informed Consent obtained	X							
Demographic Survey	X						X	
Fibromyalgia Impact Questionnaire completed	X						X	
Application & Wearing of the Actiwatch	X	X	X	X	X	X	X	Removal of Actiwatch
Start Study Diary	X	X	X	X	X	X	X	Collection of Study Diary

Figure 6.2 Histogram of Standardized Residuals of FIQ Scores

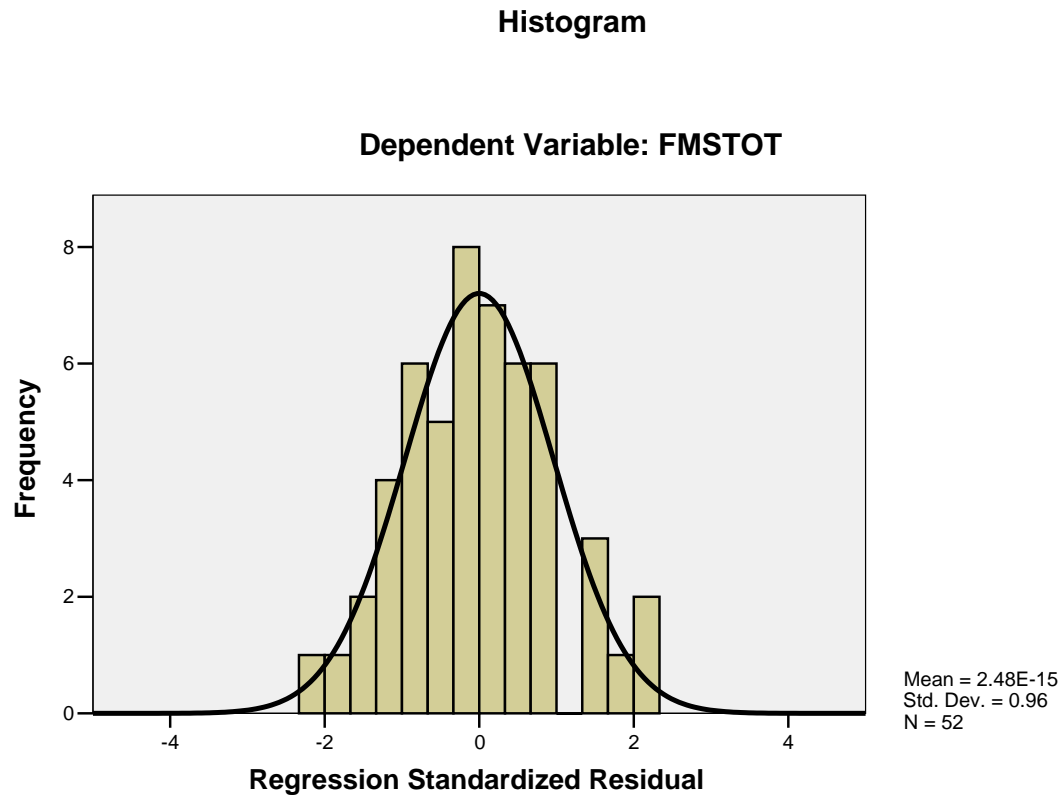


Figure 6.3 Scatter Plot of Standardized Residuals of Fibromyalgia Impact Questionnaire

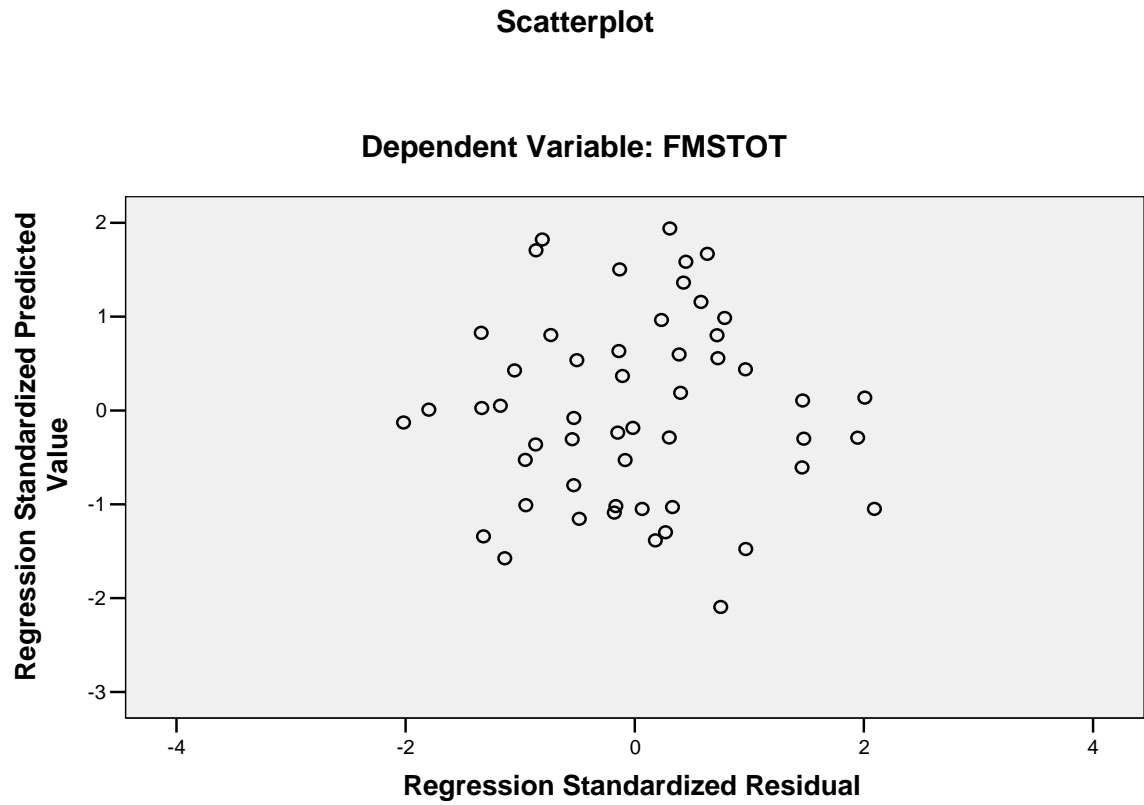
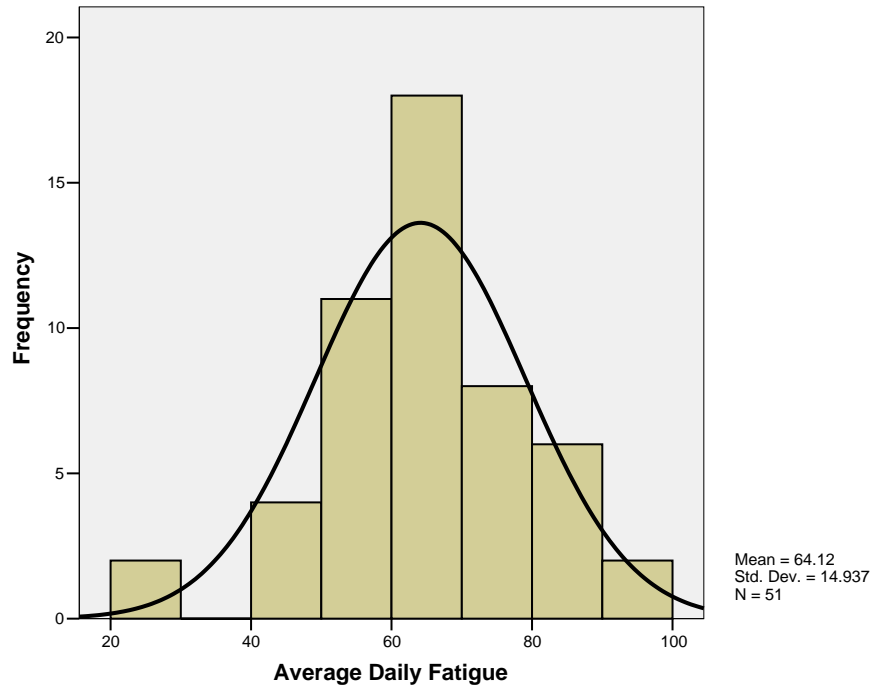
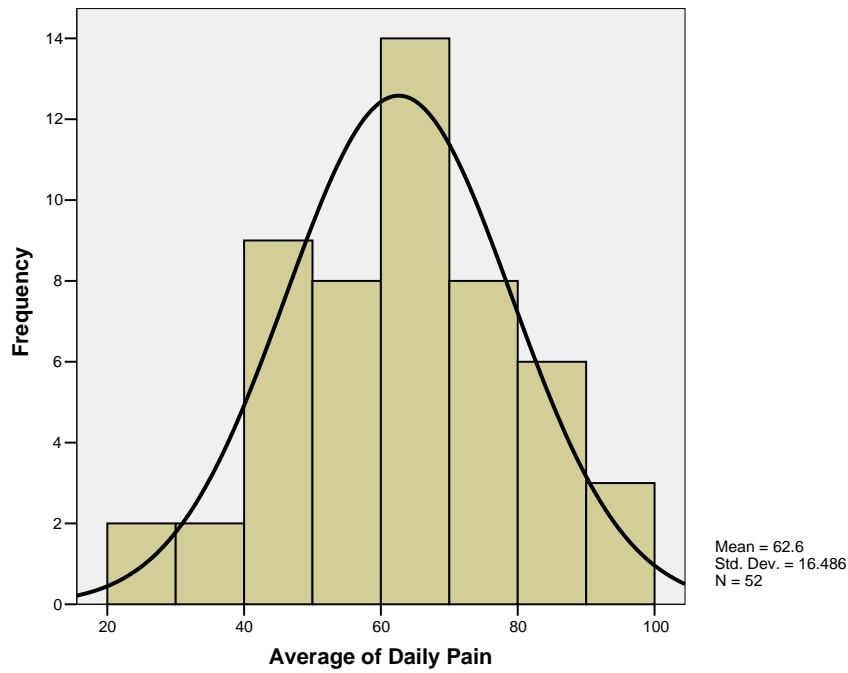


Figure 6.4 Histograms of Predictors

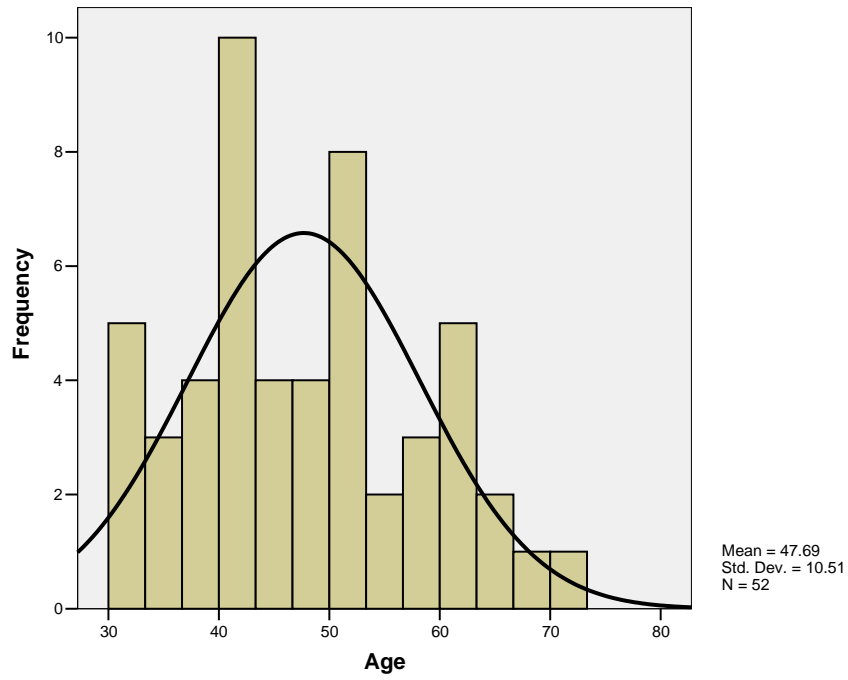
a. Average Fatigue



b. Average Pain



c. Age



d. Circadian Period

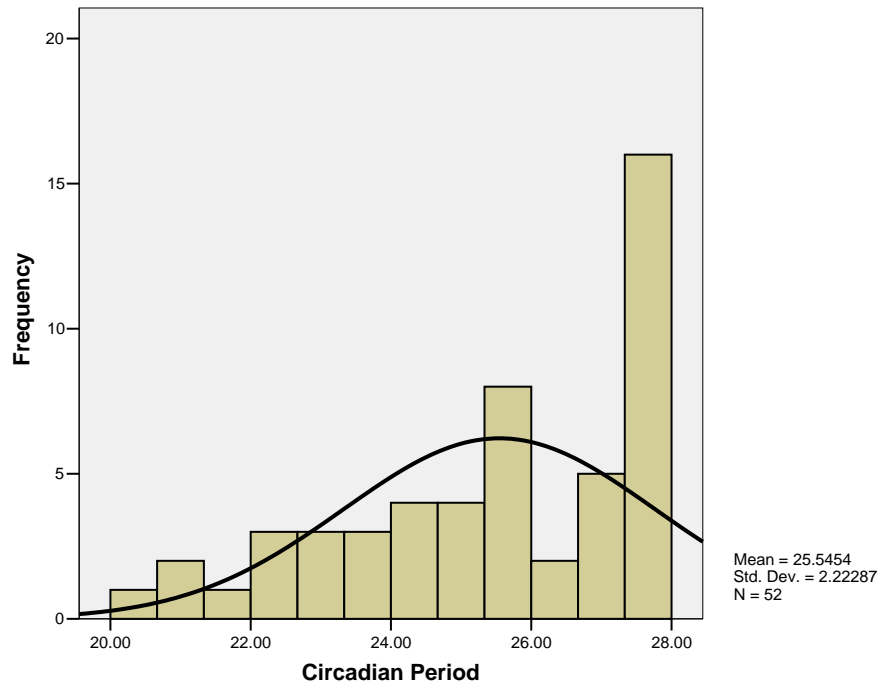
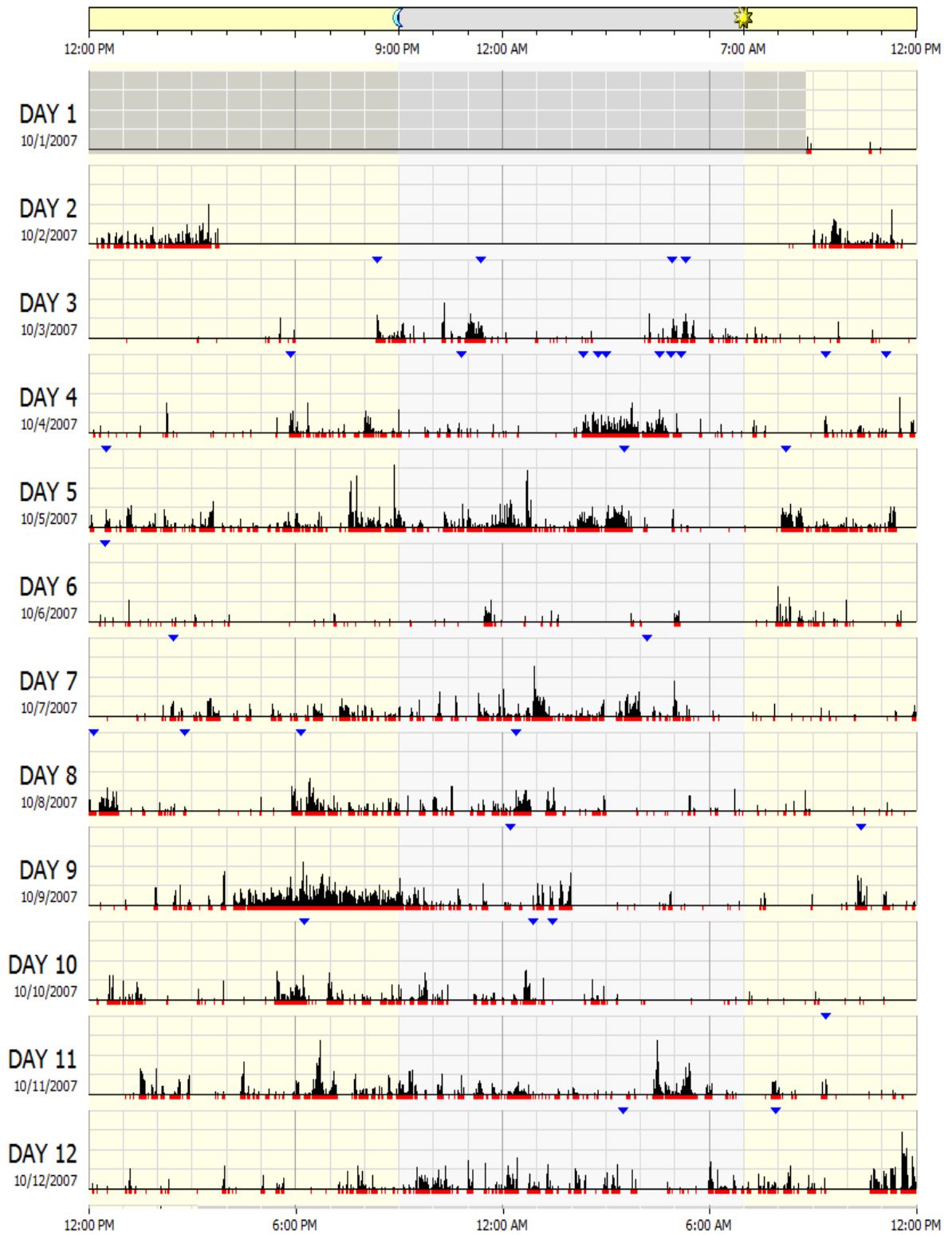


Figure 6.5 Actogram of Individual Participant's Varying Circadian Rhythm



CHAPTER SEVEN

The purpose of this dissertation was to explore the complaint of poor sleep quality in women suffering with fibromyalgia. Using limb actigraphy and sleep diaries, an examination of sleep quality, fibromyalgia impact, and circadian rhythm was performed with 50 women volunteers over at least one week. While the sleep times of these women were not grossly disturbed, their complaints of poor sleep quality, difficulty falling asleep, and difficulty staying asleep are indicative of insomnia. Results suggest that women with fibromyalgia may be altering their circadian rhythm to adapt to their disease.

The first aim of the dissertation was to examine the literature on the use of actigraphy in persons with FM. Research involving actigraphy was vast in the literature, prompting a recommendation by the AASM to recommend actigraphy as a guideline for assessment of CRSD (Brown, Smolensky, D'Alonzo, & Redman, 1990; Sack et al., 2007a, 2007b; Sadeh, Hauri, Kripke, & Lavie, 1995). However, use of actigraphy in persons with FM was limited to three publications that used actigraphy to assess sleep quality related to sleep times (Edinger, Wohlgemuth, Krystal, & Rice, 2005; Korszun et al., 2002; Landis et al., 2003). In these three publications, differences between groups or treatments used actigraphy to estimate sleep times as an independent variable. No studies were found in which actigraphy was used to determine circadian period or disturbances in circadian rhythm in persons with FM.

The second aim of the dissertation was to examine the reliability and validity of the FIQ for measurement of FM impact. At first glance, the factor analysis revealed that the FIQ consisted of three dimensions. The first factor was labeled physical function

and had strong loadings on the first 4 items of the scale: physical function, felt good, missed work, and pain. (See Appendix to view the instrument). The second factor was labeled as “mood” and had strong loadings for the next four items: pain, stiffness, anxiety, and depression. Pain had dual loadings for this factor and physical function. However, the third factor only contained two items with strong factor loadings fatigue and feeling rested. As discussed in chapter three, retaining a factor that only contains two items is usually considered insufficient to define a factor (Streiner & Norman, 2001). However, these two items of the FIQ are traditionally used to describe sleep quality in the published research on participants with FM (Agargum, Tekeoglu, & Gomes, 1999; Landis et al., 2003; Millott & Berlin, 1997; Nicassio, Moxham, Schuman, & Gevirtz, 2002; Schaefer, 2003). While this factor analysis emphasized the usefulness of the FIQ for measuring impact from FM, it also emphasized the need for additional measures that might provide more information on the sleep of persons with FM.

Typically, the Fibromyalgia Impact Questionnaire is considered a multidimensional instrument that measures the components of health status believed to be most affected by FM, i.e., physical impairment, feeling good, missing work, doing work, pain, fatigue, restfulness, stiffness, anxiety, and depression, but further analyses conducted here tend to suggest that it may be better used as a unidimensional instrument. A multidimensional instrument is one that measures separate components, but in persons with FM, so many of the constructs are related. From these results, it is proposed that the FIQ measures the combined impact of mood, pain, and fatigue, all of which have a combined effect on sleep quality. Although this instrument is a primary instrument used to measure FM impact and was developed to assess more than one domain, it is more

realistic to consider the FIQ as a unidimensional scale that captures a summary or combination of the dimensions it proposes to measure.

The FIQ is a reliable tool. Test-retest reliability of the FIQ showed that the instrument had a high degree of stability ($r = .74, p < .01$) when administered to the same participants one week apart even though the results from the two administrations differed significantly from week to week without intervention. Differences between the scores over the week were not unexpected as mood, fatigue, and pain levels change daily as does sleep quality. The finding that FM scores in these participants decreased over time was consistent with many of the women indicating that they slept better through the week. Most likely, this improvement in sleep quality and FIQ scores was related to a greater awareness of sleep times related to completing the sleep diary.

Convergence of the FIQ with two fatigue scales and a pain scale, the FACIT ($r = -.65, p < .01$), Fatigue VAS ($r = .62, p < .01$), and the Pain VAS ($r = .65, p < .001$) was strong. A combined effect of pain and fatigue appeared to influence the responses on the FIQ. To further examine this perspective, Pearson's correlations of the FIQ to average daily pain scores combined with average daily fatigue scores were performed and indicated strong correlations (FIQ: pain x fatigue $r = .69, p < .001$). The fatigue VAS and the Pain VAS administered together could explain 48% of the variance in the FIQ scores using the multiple correlation. Internal consistency of the instrument reported using Cronbach's alpha was similar to those found in other research reports ($\alpha = .85$) using the FIQ (Eksioglu, Yazar, Bal, Demir, & Cakci, 2007; Huber, Suman, Biasi, & Carli, 2008; Jones et al., 2008). This further supports the FIQ as a unidimensional measure of the combined effects of these constructs.

The third aim of the dissertation was to determine the reliability of the sleep diary and actigraphy to measure estimates of sleep. This research demonstrated that sleep diaries combined with actigraphy were reliable methods for estimation of sleep times (bedtime, wake time, sleep onset, sleep offset and total time in bed). With the exception of one time point (Day 4), no differences were noted in times entered on the diaries compared to times collected by actigraphy. The sleep diary and actigraphy both provided highly consistent results for bed time, awake time, sleep onset and sleep off set; however, consistency was higher with the sleep diary for total time in bed, sleep latency, and total sleep time compared to the actigraphy. Discrepancies in these results might be explained by the occurrence of wake bouts that are not recorded by participants completing the sleep diary as they may not remember these momentary awakenings in order to write them down. The participant was consistent about writing in the sleep diary and pushing the actigraph event marker resulting in highly consistent bedtimes, wake times, sleep onsets, and sleep offsets. However, discrepancies in these results were influenced by actigraphic estimations of the actual sleep latency, the total sleep time, and time in bed that included these wake bouts. As other research has reported, these wake bouts may not actually be arousals, but instead may be related to tendencies of the actigraph to record motion or movement and interpret it as being awake (Ancoli-Israel et al., 2003; Sack et al., 2007a, 2007b). This may be one explanation for the gross differences in sleep times between the methods. The significance of these wake bouts requires more research to determine if they contribute to sleep fragmentation leading to poor sleep quality. The benefit to investigators using actigraphy lies in its ability to estimate these times and to detect individual disturbances in sleep patterns that contribute to any discrepancies. This

research confirmed our expectation that actigraphy and sleep diaries were highly consistent methods for estimation of sleep times, as well as it emphasized its ability to detect inter-night and intra-individual differences within the study participant.

Another aim of this dissertation was to determine the most efficient way to quantify circadian period from these data. Four techniques for determining the period were compared: Cosinor analysis, Enright's periodogram, Fast Fourier Transformation (FFT), and Linear Regression of Onsets. Each method has benefits and limitations as noted in Chapter five. In this research, the task of quantitatively determining the period could be accomplished using any of the methods except Fast Fourier Transformation. As discussed previously, Fast Fourier Transformation converts data in the time domain to the frequency domain and is useful for identifying the period that mostly represents the circadian wave not necessarily the quantity of the period. Examination of histograms plotted for all three methods showed that FFT violated the assumption of normality and therefore, was not the optimal method for quantification of the circadian period. Instead, FFT is recommended for examination of seasonal fluctuations or circadian pattern recognition, but not quantitative reporting (Calandre, Hildalgo, & Rico-Villademoros, 2007). In this study, participants varied their total sleep time, which included less time in bed through the week with longer times in bed on the weekend or on days off. This trend initially discovered in the differences between circadian periods calculated using seven days of data compared to those obtained with the first and last days removed might be better evaluated using FFT. FFT used to examine the influence of the work schedule or social effect in participants would reveal these altered patterns better than quantifying the circadian period.

The final aim of this dissertation was to identify predictors of FM impact. A review of the literature noted in Chapter six shows that pain, fatigue, sleep alterations, muscle pain, and weakness are all contributors to lower levels of functioning in persons with FM (Bennet, Jones, Turk, Russell, & Matellana, 2007; Rutledge, Jones, & Jones, 2007); however, none of these studies examined the impact of circadian periodicity as a predictor. Using a multiple regression model, pain, fatigue, circadian period, and age predicted 61% of the variance in the FIQ scores. Previous longitudinal research conducted in persons with FM has noted pain level as a significant correlate of disease severity, but no prior research has used the same factors as these nor linked activity-based circadian period alterations with FM impact. Considering the heterogeneous nature of FM, these results confirm that poor sleep quality related to circadian rhythm alterations, unmanaged pain, and unrelenting fatigue contributes to the impact of FM. Given this knowledge, health care professionals may be able to implement strategies to reduce pain and enhance efforts to help their clients improve their sleep using actigraphy.

An interesting side note was that impact from FM decreased with age in this sample. This conclusion may be due to older women being less likely to work fulltime or possibly that they developed self management strategies that they used to improve their symptoms; although all of these conclusions require further examination.

Another interesting finding was that there were no differences in FIQ scores between participants using pain medications, sleep medications, those exercising or taking naps, compared to those who did not use these medications or exercise, although this may also be due to the small sample size. Further, when examining the FIQ scores and ratings of sleep quality by the participants (0 = refreshed, 1 = somewhat refreshed, 2

= fatigued), there was no significant difference between the participant sleep quality ratings and FIQ scores.

A final note of interest was the comparison of sleep quality ratings to the number of co-morbid conditions besides FM. The more conditions that these women suffered, the more likely they were to rate their sleep as un-refreshed, pointing out that that the complaint of poor sleep quality may be conflated by these other conditions.

Limitations

Limitations are noted throughout the various chapters. Briefly, this study was conducted with a small convenience sample using mostly self-report measures in primarily Caucasian females. Cross-sectional self-report surveys were used in addition to seven days of actigraphy in a non-clinical sample. The participants were not examined physically nor were the American College of Rheumatology diagnostic criteria for the number of tender points verified with their physician. Pain assessments and impact from FM were not cross validated by a practitioner skilled in the assessment of FM due to the design of the study.

Another limitation was that the women were allowed to continue their daily medications and continue their usual level of activity during the study which may have influenced the results, but overall this design and sampling represented a real life snapshot into these women's' lives as they live with FM.

Another limitation was the length of the study. The study was conducted over seven days, but this time frame may not be sufficient to actually determine disturbances in circadian rhythm that may occur/resolve over time or that are related to seasonal occurrences, e.g., occupational or lifestyle demands. Actigraphic studies may need to be

conducted over longer periods than seven days to capture true disturbances in sleep patterns and adaptations in circadian period.

Other disturbances in sleep may have co-existed in this sample of women. Actigraphy has been useful for estimating sleep times similar to polysomnography; however by itself, it is not capable of detecting other conditions that might contribute to poor sleep quality, e.g. obstructive sleep apnea, restless leg syndrome, etc., that may be a pathologic and/or a dangerous cause of sleep disturbance in these women. Measurement of depression or mood was not conducted in this study, which may have dramatically influenced the results considering that more than half the women were taking antidepressants.

Depression could influence the impact from FM and affect sleep quality. Regardless of these limitations, these papers add to the vast information available to practitioners that care for persons with FM and are encouraging. These results provide information that has not been addressed in the literature before, that actigraphy may be a useful strategy to help their clients achieve better sleep. Many of the participants in this study noted that they felt better by the end of the week and that they had slept better during the study week. One participant was concerned that her results would not be helpful since she did not experience poor sleep quality during the study. This unexpected information may be due to the participants having paid more attention to their sleep habits while in the study.

Conclusion

By using limb actigraphy to assess sleep patterns and then later used to encourage adherence to more regular sleep habits, practitioners have a new economical method for evaluation of the complaint of poor sleep quality. Strategies to decrease pain, fatigue and

improve poor sleep habits will help these persons start to feel better and reduce the impact of their FM.

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Appendix

Appendix A. Informed Consent

Consent to Participate in a Research Study

Sleep Disturbance and Sleep Quality in Women with Fibromyalgia Syndrome

WHY ARE YOU BEING INVITED TO TAKE PART IN THIS RESEARCH?

You are being invited to take part in a research study about sleep in persons with fibromyalgia. You are being invited to take part in this research study because you have been diagnosed with fibromyalgia. If you volunteer to take part in this study, you will be one of about 50 people to do so.

WHO IS DOING THE STUDY?

The person in charge of this study is Suzette Sewell (PI) a PHD student from the College of Nursing at University of Kentucky (Affiliation). Suzette is being guided in this research by Dr. Lynne Hall, Dr. Barbara Phillips, Dr. Sherry Warden, and Dr. Mary Kay Rayens. There may be other people on the research team assisting at different times during the study.

WHAT IS THE PURPOSE OF THIS STUDY?

The purpose of this study is to compare results of questionnaires you fill out about sleep to other measures of sleep like the actigraph-a wrist watch like device that measures sleep and wakefulness. By doing this study, we hope to learn new information about sleep problems in people with diseases like Fibromyalgia.

WHERE IS THE STUDY GOING TO TAKE PLACE AND HOW LONG WILL IT LAST?

The research procedures will be conducted in a private office of the investigator or by mail. You will need to come to office 2 times during the study. Each of those visits will take less than 1 hour. The total amount of time you will be asked to volunteer for this study is one week.

WHAT WILL YOU BE ASKED TO DO?

If you agree to be in this study, you will be asked to provide information about your health. A study nurse will review this history with you. Your vital signs including your weight and height will be measured. You will be asked to complete 4 questionnaires about your health. This will take about 20 minutes. For 5-7 days, you will be asked to wear a wrist watch like device. This device will measure your movement during the day and the number of times awake during the night. This device records movement only and will be worn for no more than 7 straight days. Also during this time, you will be asked to complete a study diary. This diary will have questions about being awake and going to

sleep. The diary will also record information about your daily pain, daily fatigue and your general health from day to day. It will take less than 1 minute a day to complete the study diary. This is a table of the visits for the study.

Study Schematic

	<i>Screening Visit Day 0</i>									<i>End of Study Visit (Day 7)</i>
<i>Informed Consent</i>	X									
<i>Medical History</i>	X									X
<i>Study Questionnaires</i>	X									X
<i>Vital Signs, Ht, Wt</i>	X									X
<i>Instructions and application of the Actiwatch for 7 days</i>	X									<i>Return of Actiwatch Equipment for analysis</i>
<i>Actiwatch at home</i>										
<i>Study Diary at home</i>										<i>Collection of Study Diary</i>

ARE THERE REASONS WHY YOU SHOULD NOT TAKE PART IN THIS STUDY?

You will not be able to be in the study if you:

- Have untreated obstructive sleep apnea.
- Work third shift employment.
- Cannot complete the study requirements.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

- *There are no risks to you in participating in this study.*
- *There is no discomfort usually while wearing the Actiwatch. The device is similar to a wrist watch. It is waterproof and will not interfere with your activities.*

WILL YOU BENEFIT FROM TAKING PART IN THIS STUDY?

You will not get any personal benefit from taking part in this study. Your willingness to take part, however, may, in the future, help us to better understand and/or treat others who have sleep problems.

DO YOU HAVE TO TAKE PART IN THE STUDY?

If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any benefits or rights you would normally have if you choose not to volunteer. You can stop at any time during the study, but the actigraph must be returned to the study coordinator.

WHAT WILL IT COST YOU TO PARTICIPATE?

There is no cost to you. The study seeks volunteers for this sleep study.

WHO WILL SEE THE INFORMATION THAT YOU GIVE?

We will keep private all research records that identify you to the extent allowed by law.

Your information will be combined with information from other people taking part in the study. When we write about the study to share it with other researchers, we will write about the combined information we have gathered. You will not be identified in these written materials. We may publish the results of this study; however, we will keep your name and other identifying information private.

We will make every effort to prevent anyone who is not on the research team from knowing that you gave us information, or what that information is.

CAN YOUR TAKING PART IN THE STUDY END EARLY?

If you decide to take part in the study you still have the right to decide at any time that you no longer want to continue. You will not be treated differently if you decide to stop taking part in the study. In the event that you stop, arrangements for return of the actigraph are necessary.

The individuals conducting the study may need to withdraw you from the study. This may occur if you are not able to follow the directions they give you or if you have a serious medical condition that prevents you from being part of the study.

WILL YOU RECEIVE ANY REWARDS FOR TAKING PART IN THIS STUDY?

You will not receive any rewards or payment for taking part in the study.

WHAT IF YOU HAVE QUESTIONS?

Before you decide whether to accept this invitation to take part in the study, please ask any questions that might come to mind now. Later, if you have questions about the study, you can contact the investigator, Suzette Sewell RN .

If you have any questions about your rights as a volunteer in this research, contact the staff in the Office of Research Integrity at the University of Kentucky at 859-257-9428 or toll free at 1-866-400-9428. You will be given a signed copy of this consent form to take with you.

WHAT ELSE DO YOU NEED TO KNOW?

You will be told if any new information is learned which may affect your condition or influence your willingness to continue taking part in this study.

If you would like to be in this study, please sign and date below.

Signature of person agreeing to take part in the study

Date

General Instructions

The watch will be applied at the screening visit. Please do not remove it unless it is necessary or if you do not wish to participate any further. The watch does not record specific activities only movement associated with being awake and being asleep.

The actigraph equipment must be returned if you decide not to participate at no cost to you. If you wish to stop being in the study, please contact Suzette Sewell at the number listed in the Frequently asked Questions.

During the study, you will be asked to keep a diary that can be used to record specific information that is valuable to this study. Information like night time awakenings, naps, use of caffeinated products, exercise, etc. can be recorded in the diary and when used with the watch will give us a picture of your sleeping habits and activity over a week.

The small button on the side can be used to mark specific notations made in the sleep diary. It is especially important to push the button when you turn the lights out for bed and when you get up in the morning. These times are also written in the sleep diary.

FREQUENTLY ASKED QUESTIONS ABOUT THE ACTIWATCH AND THE STUDY

Who should I call if I have questions?

Call the investigator

Should I take it off for baths or swimming?

No, the actigraph is water resistant. Please try to wear the watch the entire week.

What is the little button for?

This button is pushed at bedtime and awake time to let the research know what time you went to bed and got up. This button can also be used with the sleep diary to note naps, and awakenings at night. It can also be used to mark when medications are taken or when a specific event is recorded in the diary.

Do I write things other than sleep times in my diary?

All information that you provide about the week is valuable. Our study is looking at your sleep compared to the activity of your Fibromyalgia. This includes fatigue, pain and sleep, but it also looks at whether you are taking naps, how active you are during the day and whether you take medications.

What do I do if I forget to fill out my diary?

Just write down as much as you can remember. If you know the answer, complete it. If you can't remember, just write "I can't remember"

Appendix B. FIBROMYALGIA IMPACT QUESTIONNAIRE (FIQ)

Name: _____ Date: ____ / ____ / ____

Directions: For questions 1 through 11, please circle the number that best describes how you did overall for the past week. If you don't normally do something that is asked, cross the question out.

0 = Always 1 = Most of the time 2 = Occasionally 3 = Never

Were you able to:

- Do shopping? 0 1 2 3
- Do laundry with a washer and dryer? 0 1 2 3
- Prepare meals? 0 1 2 3
- Wash dishes/cooking utensils by hand? 0 1 2 3
- Vacuum a rug?..... 0 1 2 3
- Make beds? 0 1 2 3
- Walk several blocks? 0 1 2 3
- Visit friends or relatives? 0 1 2 3
- Do yard work?..... 0 1 2 3
- Drive a car? 0 1 2 3
- Climb stairs? 0 1 2 3

Of the 7 days in the past week, how many days did you feel good?

0 1 2 3 4 5 6 7

How many days last week did you miss work, including housework, because of fibromyalgia?

0 1 2 3 4 5 6 7

Directions: For the remaining items, mark the point on the line that best indicates how you felt overall for the past week.

When you worked, how much did pain or other symptoms of your fibromyalgia interfere with your ability to do your work, including housework?

● ___ I ___ I ___ I ___ I ___ I ___ I ___ I ___ I ___ ●

No problem with work Great difficulty with work

How bad has your pain been?

● ___ I ___ I ___ I ___ I ___ I ___ I ___ I ___ I ___ ●

No pain Very severe pain

How tired have you been?

● ___ I ___ I ___ I ___ I ___ I ___ I ___ I ___ I ___ ●

No tiredness Very tired

How have you felt when you get up in the morning?

● ___ I ___ I ___ I ___ I ___ I ___ I ___ I ___ I ___ ●

Awoke well rested Awoke very tired

How bad has your stiffness been?

● ___ I ___ I ___ I ___ I ___ I ___ I ___ I ___ I ___ ●

No stiffness Very stiff

Fibromyalgia Impact Questionnaire (continued)

How nervous or anxious have you felt?

● ___ I ___ I ___ I ___ I ___ I ___ I ___ I ___ I ___ I ●

Not anxious Very anxious

How depressed or blue have you felt?

● ___ I ___ I ___ I ___ I ___ I ___ I ___ I ___ I ___ I ●

Not depressed Very depressed

Reference: (Burckhardt, Clark & Bennet, 1991)

http://www.myalgia.com/FIQ/FIQ_scoring_0408.pdf

Fibromyalgia Impact Questionnaire Scoring Guidelines

The FIQ is scored in such a way that a higher score indicates a greater impact of the syndrome on the person. Each of the 10 items has a maximum possible score of 10. Thus the maximum possible score is 100. The average FM patient scores about 50, severely afflicted patients are usually 70 plus. The questionnaire is scored in the following manner:

1. The first item consists of 11 questions that make up a physical functioning scale. The 11 questions are scored and summed to yield one physical impairment score. Each item is rated on a 4 point Likert type scale. Raw scores on each item can range from 0 (always) to 3 (never) -thus the highest total possible raw score is 33. Because some patients may not do some of the tasks listed, they are given the option of deleting items from scoring. In order to obtain a valid summed score for questions 1 through 11, the scores for the items that the patient has rated are summed and divided by the number of items rated (e.g. if the patient completed only 9 items at a score of 2 for each, the final score would be $9 \times 2 / 9 = 2$). An average raw score between 0 and 3 is obtained in this manner.
2. Item 2 is scored inversely - so that a higher number indicates impairment (i.e., 0=7, 1=6, 2=5, 3=4, 4=3, 5=2, 6=1 and 7=0, etc.). Raw scores can range from 0 to 7.
3. Item 3 is scored directly (i.e. 7=7 and 0=0). Raw scores can range from 0 to 7.
4. Items 4 through 10 are scored in 10 increments. Raw scores can range from 0 to 10. If the patient marks the space between two vertical lines on any item, that item is given a score that includes 0.5.
5. Once the initial scoring has been completed, the resulting scores are subjected to a normalization procedure so that all scores are expressed in similar units. The range of normalized scores is 0 to 10 with 0 indicating no impairment and 10 indicating maximum impairment.

In order to maintain a maximum possible score of 100 it is necessary to employ an "equalization calculation" if a patient does not answer all 10 items. If one or more items are missed, the final summative score needs to be multiplied by $10/x$. (i.e. if one question is missed multiply by $10/9 = 1.111$, if 2 questions are missed multiply by $10/8 = 1.25$ etc.)

Fibromyalgia Impact Questionnaire Scoring (continued)

Scale	Item #	Recode	Score Range	Normalization
Physical impairment	1	No	0 - 3	S X 3.33
Feel good	2	Yes	0 - 7	S X 1.43
Work missed	3	No	0 - 7	S X 1.43
Do work	4	No	0 - 10	None
Pain	5	No	0 - 10	None
Fatigue	6	No	0 - 10	None
Rested	7	No	0 - 10	None
Stiffness	8	No	0 - 10	None
Anxiety	9	No	0 - 10	None
Depression	10	No	0 - 10	None

Citation Burckhardt, C.S., Clark, S.R., & Bennett, R.M. (1991). The Fibromyalgia Impact Questionnaire: Development and validation. *Journal of Rheumatology*, 18, 728-734

Appendix C: Sleep Diary

Sleep Diary Investigator Suzette Sewell 502-636-3485

Study Day 1 Date _____ What time is it? _____

The following questions are about last night's sleep and how you felt today.

What time did you go to bed last night? _____

What time did you get up this morning? _____

When I woke up for the day, I felt Refreshed Somewhat Refreshed Fatigued

How many hours of sleep did you get last night? _____

Did you wake up last night? Yes No
if yes, what was the reason? _____

Did you get up out of bed last night? Yes No
if yes, what was the reason? _____

Did you take any naps today? Yes No

Were you active or did you exercise at least 20 minutes today? Yes No

Did you consume caffeine products today? Yes No How many? _____

Other than my normal medications, I took the following medicines today: _____

How much Fatigue have you had today? Please mark on the line below how severe your fatigue was:

No Fatigue _____ Severe Fatigue

How much Pain have you had today? Please mark on the line below how severe your pain was:

No Pain _____ Severe Pain

Remember to push the button on the Actiwatch when you go to bed and when you get up.

Sleep Diary Investigator Suzette Sewell 502-636-3485

Study Day 2 What time is it? _____

The following questions are about last night's sleep and how you felt today.

What time did you go to bed last night? _____

How long did it take you to fall asleep? _____

What time did you get up this morning? _____

When I woke up for the day, I felt Refreshed Somewhat Refreshed Fatigued

How many hours of sleep did you get last night? _____

Did you wake up last night? Yes No
if yes, what was the reason? _____

Did you get up out of bed last night? Yes No
if yes, what was the reason? _____

Did you take any naps today? Yes No

Were you active or did you exercise at least 20 minutes today? Yes No

Did you consume caffeine products today? Yes No How many? _____

Other than my normal medications, I took the following medicines today: _____

How much Fatigue have you had today? Please mark on the line below how severe your fatigue was:

No Fatigue _____ Severe Fatigue

How much Pain have you had today? Please mark on the line below how severe your pain was:

No Pain _____ Severe Pain

Remember to push the button on the Actiwatch when you go to bed and when you get up.

Appendix D. Permission to use Functional Assessment of Chronic Illness

From: hmorrow@facit.org
To: suzettesewell@hotmail.com
Subject: Re: your facit.org request
Date: Mon, 24 Dec 2007 14:44:31 -0600

Hello Suzette Sewell:

Thank you for your interest in the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System. I see that you are interested in the FACIT- F. It should be a fairly simple process (if you have problems please let me know). By becoming a registered user you will be able to download the English scales directly to your system. See: View Questionnaire & Language Availability section and access the third option/button under the FACIT-F, which will allow you to download a copy ready English PDF or Word copy of the scale.

The questionnaire is available to users FREE of charge (English version only) and permission for use is granted given your agreement to a few simple requests. Please consider this official permission to use the scale in your study. Our user's agreement can be found on our website at www.facit.org (See registration & requests: user's agreement). Should you actually decide to include the questionnaire in your research, we would also request that you take the time to complete a Collaborator's Project Information Form on line to submit for our files. We are in the process of updating our website, so, many areas of the site are under construction. We appreciate your patience as we continue to create an efficient and user friendly site. The raw scoring templates will eventually be available on our new website; however, a fee will be associated with this downloadable form. During this transition, we will not be charging a fee. I have attached the scoring and administration guidelines as well as the raw scoring template for the FACIT-F. Please accept them now with our compliments. I hope you will find this information useful. If you have additional questions, please do not hesitate to contact me again.

Thank you,
Helen

Helen A. Morrow, MA
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hmorrow@facit.org
toll free in the US: 877.828.FACT
(Available & will respond to email in the PM)

Appendix E: Functional Assessment of Chronic Illness Therapy—FATIGUE Subscale

By circling (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	Not at all	A little bit	Some what	Quite a bit	Very Much
1. I feel fatigued	0	1	2	3	4
2. I feel weak all over	0	1	2	3	4
3. I feel listless (“washed out”)	0	1	2	3	4
4. I feel tired	0	1	2	3	4
5. I have trouble starting things because I am tired	0	1	2	3	4
6. I have trouble finishing things because I am tired	0	1	2	3	4
7. I have energy	0	1	2	3	4
8. I have trouble walking	0	1	2	3	4
9. I am able to do my usual activities	0	1	2	3	4
10. I need to sleep during the day	0	1	2	3	4
11. I feel light headed (dizzy)	0	1	2	3	4
12. I get headaches	0	1	2	3	4
13. I have been short of breath	0	1	2	3	4
14. I have pain in my chest	0	1	2	3	4
15. I am too tired to eat	0	1	2	3	4
16. I am interested in sex	0	1	2	3	4

Functional Assessment of Chronic Illness Therapy—FATIGUE (continued)

17. I am motivated to do my usual activities	0	1	2	3	4
18. I need help doing my usual activities	0	1	2	3	4
19. I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
20. I have to limit my social activity because I am tired	0	1	2	3	4

FACIT-F Scoring Guidelines (Version 4)

- Instructions:*
1. Record answers in "item response" column. If missing, mark with an X
 2. Perform reversals as indicated, and sum individual items to obtain a score.
 3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
 4. Add subscale scores to derive total scores (TOI, FACT-G & FACIT-F).
 5. The higher the score, the better the QOL.

<u>Subscale</u>	<u>Item Code</u>	<u>Reverse item?</u>		<u>Item response</u>	<u>Item Score</u>
FATIGUE	HI7	4	-	_____	=_____
SUBSCALE	HI12	4	-	_____	=_____
(FS)	An1	4	-	_____	=_____
	An2	4	-	_____	=_____
<i>Score range: 0-52</i>	An3	4	-	_____	=_____
	An4	4	-	_____	=_____
	An5	0	+	_____	=_____
	An7	0	+	_____	=_____
	An8	4	-	_____	=_____
	An12	4	-	_____	=_____
	An14	4	-	_____	=_____
	An15	4	-	_____	=_____
	An16	4	-	_____	=_____

FACIT-F Scoring Guidelines (continued)

Sum individual item scores: _____

Multiply by 13: _____

Divide by number of items answered:

_____ = F Subscale score

*For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on-line at www.facit.org.

Appendix F: Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

0 = No chance of dozing

1 = Slight chance of dozing

2 = Moderate chance of dozing

3 = High chance of dozing

0	1	2	3	Sitting and Reading
0	1	2	3	Watching TV
0	1	2	3	Sitting inactive in a public place (e.g. a theater or a meeting)
0	1	2	3	As a passenger in a car for an hour without a Break
0	1	2	3	Lying down to rest in the afternoon when circumstances permit
0	1	2	3	Sitting and talking to someone
0	1	2	3	Sitting quietly after a lunch without alcohol
0	1	2	3	In a car, while stopped for a few minutes in traffic

Scoring the ESS:

0-8	Normal Function
8 – 10	Mild Daytime Sleepiness
11-15	Moderate Daytime Sleepiness
>16	Severe Daytime Sleepiness

Appendix G: Permission to use Functional Outcomes of Sleep Questionnaire

**FUNCTIONAL OUTCOMES OF SLEEP QUESTIONNAIRE (FOSQ)
CONDITIONS OF AGREEMENT**

This instrument is copyrighted, therefore no question, format or portion of the FOSQ can be adapted or used apart from the instrument as a whole without the express written consent of the author's.

I/we agree to the following conditions for the use of the Functional Outcomes of Sleep Questionnaire (FOSQ) in my/our practice or research:

1. Sign the two enclosed letters of agreement
2. If the FOSQ is being used in research please return the following upon completion of your research (whether published or unpublished):
 - a. How the FOSQ will/was be applied in your research
 - b. Paragraph stating purposes of your study
 1. Instruments used in study
 2. Sample/population to include size, characteristics (i.e., gender, age, health status, where the sample was obtained), and type (e.g., random, convenience, etc.)
 3. Descriptive and inferential statistical results of your study especially, those findings relevant to the FOSQ (including graphs and/or tables if available)
3. If the FOSQ is being applied in practice, please briefly describe the clinic population in which it is being used, and any recommendations that you may have.

Sign and send one copy of this agreement to:

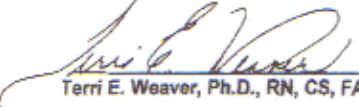
Dr. Terri E. Weaver
University of Pennsylvania
School of Nursing
Philadelphia, PA 19104-6096
215/573-7496 (fax)

The scoring scheme will be sent to you upon receipt of the agreement.

Name: Suzette Sewell RN PhD candidate (type or print)

Address: 3308 Eagle Pass
Louisville KY ~~4020~~ 40213

Signature:  Date: 2/8/2007


Terri E. Weaver, Ph.D., RN, CS, FAAN

Date: _____

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