PREDICTORS OF CLINICAL PAIN IN FIBROMYALGIA: EXAMINING THE ROLE OF SLEEP

By

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LIST OF ABBREVIATIONS

AS	After-sensation
BDI	Beck Depression Inventory
°C	Degrees Celcius
FM	Fibromyalgia syndrome
NMDA	N-Methyl-D-aspartic acid
SD	Standard deviation
SLAP	Sum of local areas of pain
STAI	State-Trait Anxiety Inventory
TP	Tenderpoint
TSSP	Temporal summation of second pain
TST	Total sleep time
TWT	Total wake time

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Clinical pain intensity can be highly variable across patients with fibromyalgia syndrome (FM), and past research has shown that a predictive model of spatial extent of pain, negative mood, and after-sensation accounts for 40-50% of the variance in clinical pain. Poor sleep is hypothesized to have a causal relationship with pain, and over 75% of individuals with FM report disturbed sleep. In the present study, I hypothesized that the existing model of clinical pain in FM would be replicated, and the addition of sleep measures would significantly increase the predictive ability of the model.

Fifty-nine adults with FM participated in the study. Participants indicated the extent of their pain by shading areas on a body diagram, and a sum of pain areas was calculated. Negative mood was measured with the Beck Depression Inventory–II (BDI-II) and State Trait Anxiety Inventory Form Y-1 (STAI). As a proxy measure of central sensitization, ratings of painful after-sensation were obtained 30 seconds following stimulation with a series of heat pulses. Participants also wore an actigraph and kept sleep and pain diaries for 14 days. Data were averaged over the 14 days and 4

measures of sleep were obtained for each participant: average total sleep time and average total wake time (*i.e.* duration of insomnia), each measured objectively (actigraph) and subjectively (diary). Hierarchical linear regression was used to determine the variance in clinical pain (average of 14 daily pain ratings) accounted for by each predictor.

Greater spatial extent (R^2=.21), higher after-sensation ratings (R^2=.07), and higher BDI-II total scores (R^2=.06) were each significant predictors of more clinical pain and together accounted for 34.0% of its variance. Decreased objective total sleep time was the only sleep variable to account for significant additional variance (R^2=.09). The results replicate previous research and suggest that spatial extent of pain, central sensitization, and depressed mood play important roles in FM pain. The data provided limited support for the hypothesis that measures of sleep would improve the predictive ability of the model. Future research should examine the daily, intra-individual variation between sleep and pain in FM to better clarify this relationship.

CHAPTER 1
INTRODUCTION

Fibromyalgia syndrome (FM) is defined by chronic, widespread musculoskeletal pain across the four body quadrants, and decreased pressure pain thresholds. The American College of Rheumatology identified 9 bilaterally paired tender point (TP) sites to characterize this mechanical allodynia (a perception of pain in response to a normally non-painful stimulus like gentle touch); a diagnosis of FM is considered when at least 11 of these 18 points are endorsed as painful during palpation (Wolfe, et al., 1990). While TP counts have diagnostic utility for FM, their correlation with clinical pain is low to modest in both general population (Croft, et al., 1996; Croft, Schollum, & Silman, 1994) and FM samples (Nicassio, Weisman, Schuman, & Young, 2000; Staud, Price, Robinson, & Vierck, 2004; Wolfe, 1997). Clinical pain intensity can be conceptualized as a rating of overall bodily pain, and has strong associations with health care usage and quality of life. Due to the complex interplay between physical, psychological, and social factors involved with this condition, clinical pain intensity can be highly variable across FM patients and is difficult to predict.

In an effort to identify predictors of clinical pain and thereby elucidate potential treatment targets, Staud et al. (Staud, et al., 2004; Staud, Robinson, et al., 2003) found that negative mood, after-sensation (AS) ratings taken during experimental induction of second pain [using a temporal summation of second pain (TSSP) protocol], and a measure of spatial extent of pain [the sum of local areas of pain (SLAP)] were significant predictors of clinical pain intensity in FM patients, and together accounted for 40 – 50% of its variance. The results suggest that physiological and psychological variables are relevant to FM clinical pain. Second pain is the delayed sensation of pain

associated with slower conducting C-fibers, and AS is a type of second pain often conceptualized as pain rating taken 15 – 30 seconds following a pain stimulus. TSSP refers to an increased perception of second pain evoked by repetitive noxious stimuli at constant intensities, and has been found to be mediated by central nervous system processes (Price, Hu, Dubner, & Gracely, 1977). Thus, TSSP and its maintenance (AS) are thought to be proxy measures of a centrally-mediated hypersensitivity to pain stimuli (central sensitization), a mechanism hypothesized to underlie FM and other chronic pain conditions (Yunus, 2007). Relative to normal controls, FM patients show enhanced TSSP as well as prolonged and enhanced AS following repetitive stimulation with thermal heat (Price, et al., 2002; Staud, Cannon, et al., 2003; Staud, Vierck, Cannon, Mauderli, & Price, 2001). Along with widespread pain and allodynia, these psychophysical studies suggest that central sensitization may play an important role in the FM pain experience.

Other subjective health complaints (fatigue, stiffness, irritable bowel syndrome, etc.) represent core syndromal symptoms of FM, and are often considered by clinicians when making a diagnosis. Chief among these complaints are those of poor sleep. In subjective assessments of sleep quality, over 75% of individuals with FM report disturbed and non-restorative sleep (Moldofsky, 2008; Wolfe, Ross, Anderson, Russell, & Hebert, 1995). Objective findings from polysomnagraphic studies demonstrate that FM patients have abnormal sleep architecture, including an increased sleep onset latency (Horne & Shackell, 1991), an increased number of nighttime arousals (Branco, Atalaia, & Paiva, 1994), reduced amounts of restorative stage 3/4 sleep (Branco, et al., 1994), and greater alpha wave intrusion (Moldofsky, Scarisbrick, England, & Smythe,

1975). Poor sleep may have a reciprocal relationship with pain, as there is evidence to suggest that it is both a consequence of (Nicassio, Moxham, Schuman, & Gevirtz, 2002) and a causal or maintenance mechanism (Affleck, Urrows, Tennen, Higgins, & Abeles, 1996; Bigatti, Hernandez, Cronan, & Rand, 2008; Moldofsky & Scarisbrick, 1976) for chronic pain conditions.

The current study built upon the Staud et al. (Staud, et al., 2004; Staud, Robinson, et al., 2003) predictive model of clinical pain in FM (negative mood, AS ratings taken after a TSSP protocol, and SLAP) by examining the role of sleep. I hypothesized that results would replicate those of Staud et al., and that the addition of sleep (measured subjectively and objectively) would significantly increase the predictive ability of the model.

CHAPTER 2
METHODS

Participants

Written informed consent was obtained from all participants before evaluation, and the University of Florida Institutional Review Board reviewed and approved all procedures described in this report. Adults with FM (N = 59) were recruited to participate in a cognitive behavioral treatment trial for pain and insomnia. Details of the intervention are beyond the scope of this report as it examined pre-treatment, baseline data only. Subjects were recruited by television and radio advertising around the Gainesville, Florida area, as well as referrals from tertiary care clinics (Rheumatology, Sleep Disorders Center) associated with the University of Florida. Participants meeting inclusion criteria were those ≥18 years of age who were able to read and understand English and currently suffering from FM. Subjects were excluded from the study if they were unable to provide informed consent, did not endorse at least 11 sites as painful during TP testing, or did not report pain in all four body quadrants. To maximize the generalizeability of findings, comorbid medical or psychiatric conditions were not exclusion factors for this pre-treatment analysis. Medication use was also allowed; however, participants were asked to remain stable on all medications during the study period, and refrain from changing their existing regimen or initiating a new medication.

Demographic characteristics of the sample are presented in Table 2-1. The average age of the sample was 52.4 years. Consistent with population estimates of FM, the majority (93.2%) of participants were female. The racial composition was as follows: 88.1% Caucasian, 10.1% African American, and 1.7% Asian. The marital status of the

sample consisted of the following: 50.8% married, 16.9% single, 20.3% divorced, 3.4% separated, and 8.5% widowed.

Clinical Pain Intensity

Participants provided ratings of current clinical pain intensity once a day in the evening for 14 days. Ratings were made using a visual analogue scale anchored with “no pain sensation” on the left side, and “most intense pain imaginable” on the right side. The visual analogue scale was instantiated on paper as a 10 centimeter horizontal line with the two anchors, and participants indicated their pain level by marking a spot on the line. To obtain a numerical score for this rating, a ruler was used to measure the distance (in centimeters, to the tenth decimal) between the mark and the left end of the line. This value was then multiplied by 10 to rescale it to a 0 – 100 range. The 14 daily values were averaged to get one rating of clinical pain per person.

TP Testing

On day 1 of the 14-day observation period, TP sensitivity was assessed at 9 bilaterally-paired sites as specified by the American College of Rheumatology criteria for FM (Wolfe, et al., 1990). The evaluation was done by trained investigators using a Wagner Force One FDIX Dolorimeter (Wagner Instruments, Greenwich, CT). The rubber tip (7/16 inch diameter) of the Dolorimeter was placed at each TP site and pressure was applied with a force of 1 kg/s until the participant indicated pain, or until 4 kg of force had been reached. The TP was considered positive if pain was indicated at ≤ 4 kg of force. A total number of positive TPs was calculated for each person.

Body Pain Areas (SLAP)

Participants indicated the location of their current pain by shading the corresponding areas on a diagram depicting the front and back of a human body (Figure

2-1.)(Staud, et al., 2004) on day 1 of the observation period. The diagrams were divided into 50 areas, indicated by letters and numbers in the Figure. If any part of an individual body area was shaded, it was scored as 1 (painful). An unshaded area was scored as 0 (not painful). A sum of local areas of pain (SLAP) was calculated for each subject.

TSSP and AS

Subjects underwent quantitative sensory testing using a computer-controlled Medoc Thermal Sensory Analyzer (Model TSA-II; Ramat Yishai, Israel) on day 7 of the observation period. A TSSP protocol was used as trains of 8 heat stimuli were delivered via a contact thermode (30x30mm) placed on the thenar eminence of the palm. Each heat stimulus started at a baseline temperature of 39°C, peaked at 49°C, then returned to baseline with a rise and decline rate of 10°C/s. The duration of each stimulus was 2.4 seconds with an inter-pulse interval (onset to onset) of 3s. Subjects were asked to attend to the peak of delayed pain sensation (*i.e.* second pain) felt after every pulse, and cued to verbally rate the intensity of that second pain after the 2^{nd}, 4^{th}, 6^{th}, and 8^{th} pulses using a numerical rating scale anchored with 0 (no pain sensation) and 100 (most intense pain sensation imaginable). Using the same numerical rating scale, ratings of painful AS were obtained at 15s and 30s following the 8th and final heat stimulus. AS ratings at 30s have been shown to be a strong predictor of FM clinical pain in past research (Staud, Robinson, et al., 2003), and were used as a predictor of clinical pain intensity in the regression analyses. Each subject completed two trials of the TSSP protocol using their non-dominant palm, and the AS ratings from the two trials were averaged. Prior to the two trials, subjects completed one training trial on their dominant palm to familiarize them to the rating system and the range of heat.

Sleep

Insomnia can be divided into 3 stages: early (difficulty falling asleep), middle (waking up in the night), and late (waking too early). Total wake time (TWT) is an aggregate of the time spent in each stage, and can serve as a quantification of insomnia. Total sleep time (TST) is the total time spent asleep. Information obtained from subjectively reported sleep diaries, and objective data from an actigraph was used to calculate TWT and TST.

Subjective Sleep: Diaries

Self-reported sleep diaries were kept daily for 14 days. Each morning participants recorded information about their previous night's sleep, including: bed time, sleep onset latency (number of minutes it took to fall asleep), minutes spent awake after sleep onset, time of last morning awakening, and arise time. TWT (in minutes) was calculated as the sum of sleep onset latency, time spent awake in the night, and the time between the last morning awakening and arise time. TST (in minutes) was calculated as TWT subtracted from the time spent in bed. TST and TWT from the 14 diaries were averaged to obtain 1 mean for each participant, and will be referred to as subjective TST (TST_S) and subjective TWT (TWT_S).

Objective Sleep: Actigraph

Participants wore an actigraph, the Actiwatch 2 (Phillips Respironics), on their non-dominant wrist for the 14 days coincident to completing the sleep diaries. The Actiwatch 2 records data on gross motor activity using a solid-state, piezo-electric accelerometer. The accelerometer continually measures the intensity and frequency of wrist movement at a sampling rate of 32 cycles per second. The sum of all wrist movements in a 30 second interval is recorded as an activity count. The activity counts are downloaded

onto a PC and analyzed using Actiware Sleep Analysis Software v.5.3.2 which classifies each 30-second epoch as a sleep or wake state using validated algorithms. The bedtime and morning arise times reported on the sleep diaries were inserted into the corresponding actigraph day, and represented the time-in-bed period. Actiware determined the start of sleep by searching this time-in-bed period for the first 10 minute interval during which no more than 1 epoch was scored as awake. Similarly, sleep end was signified by the last 10 minute interval containing no more than 1 wake-state epoch. Nightly TWT, as measured by actigraphy, is the sum of all the wake epochs within the time-in-bed period. TST is the sum of all sleep epochs within the time-in-bed period. TST and TWT from the 14 days of actigraph were averaged to obtain 1 mean for each participant, and will be referred to as objective TST (TST_o) and objective TWT (TWT_o).

Negative Mood

Negative mood was assessed with the Beck Depression Inventory II (BDI-II)(Beck, Steer, & Brown, 1996) and the State Trait Anxiety Inventory, State Version - Form Y1 (STAI-Y1)(Spielberger, Gorsuch, & Lushene, 1970). On day 14 of the observation period, participants were asked to think about their mood over the previous 14 days (corresponding to the time period assessed by the sleep and pain diaries) when responding to the questions on the BDI-II and STAI-Y1. The BDI-II is a 21-item self-report inventory that measures the severity of current depressive symptomotology, including cognitive, affective, and vegetative symptoms. Each item consists of a group of 4 descriptive statements centering around one symptom, and participants choose the statement that most accurately characterizes them. Each item is scored on a 0 – 3 scale, and total scores range from 0 to 63. The STAI-Y1 is a 20-item self-report questionnaire that measures current levels of anxiety. Each item consists of a self-

descriptive statement (I feel ___, nervous, calm, etc), and participants rate their agreement with the statement on a 4-point likert scale (1 = “not at all” to 4 = “extremely”). A total score is obtained, ranging from 20 - 80. The BDI-II and STAI have been used extensively in a variety of populations, including those with chronic pain and other medical conditions. The instruments are well-validated, show good reliability (alpha coefficients > .8), and can accurately distinguish between clinical and non-clinical populations.

Statistical Analyses

The Statistical Package for the Social Sciences (SPSS, version 17.0) was used for all statistical analyses. Descriptive statistics were calculated for demographic and clinical variables across the sample. Hierarchical linear regression was used to determine the variance in clinical pain intensity accounted for by AS ratings, SLAP, negative mood (BDI-II and STAI total scores), and sleep. Each independent variable was entered as a separate block in the hierarchical regression, and the associated R2 change value established their unique contribution to the dependent variable, clinical pain intensity. Four hierarchical regression analyses were run. In all analyses, the variables found to be predictive of clinical pain in past research (AS ratings, SLAP, and negative mood) were entered into the first four blocks. Then each of the 4 analyses entered a different sleep variable (TSTs, TWTs, TSTo, or TWTo) into the final block to determine whether measures of sleep increased the predictive ability of the model.

Table 2-1. Demographic characteristics of the sample (N = 59)

	N	%	Years
Mean Age in Years			52.4 (SD = 8.4)
Female Gender	55	93.2	
Race			
Caucasian	52	88.1	
African American	6	10.1	
Asian	1	1.7	
Marital Status			
Married	30	50.8	
Divorced	12	20.3	
Separated	2	3.4	
Widowed	5	8.5	
Single	10	16.9	
Mean Years of Education			14.4 (SD = 2.5)
Employment			
Employed	29	49.2	
Unemployed	30	50.8	

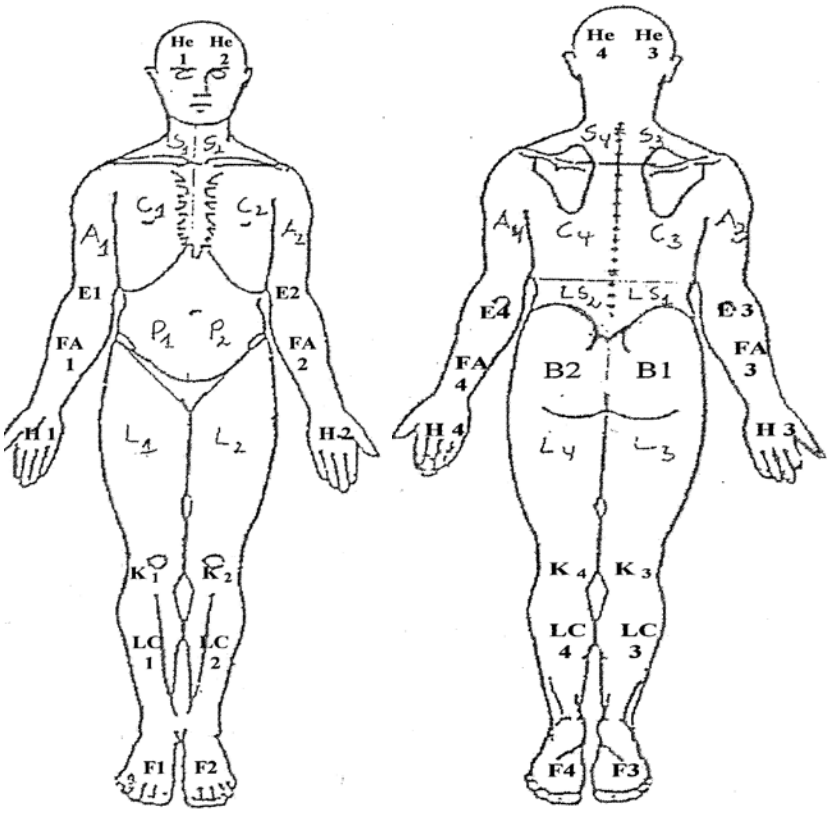

Figure 2-1. Body diagram used by participants to shade areas of current pain. Each shaded area was coded as 1. Each non-shaded area was coded as 0. A sum of shaded areas (SLAP) was calculated for each participant.

CHAPTER 3
RESULTS

Fifty-nine adults with FM provided data for the analysis. Pain, mood, and sleep characteristics of the sample are presented in Table 3-1. The mean rating of clinical pain intensity across the sample was 50.6 (range: 8.7 – 88.5, SD = 19.3). Subjects endorsed an average of 16.0 painful TPs (SD = 2.3), and shaded 21.7 (SD = 11.2) areas of pain on the body diagram. Following experimental induction of second pain, 30 second AS ratings ranged from 0 – 77.5, with a mean of 29.6, SD = 22.6. Participants reported moderate levels of depressive and anxiety symptoms (mean BDI-II: 15.2, SD = 10.5; mean STAI-Y1: 41.8, SD = 12.9).

Self-report data from the sleep diaries indicated that the TST_s across the sample was 397.7 minutes (range: 213.5 – 631.9, SD = 74.1) and the TWT_s was 122.2 minutes (range: 31.9 – 361.3, SD = 67.1). Actigraphy data indicated that the TST_o across the sample was 397.9 minutes (range: 221.6 – 546.6, SD = 58.9), and the TWT_o was 104.0 minutes (range: 39.6 – 305.2, SD = 49.5).

Table 3-2 presents the results of the hierarchical regression analyses. Higher AS ratings (ΔR^2 =.07, p = .05), more bodily pain areas (SLAP) (ΔR^2 =.21, p < .001), and higher BDI scores (ΔR^2 =.06, p = .04) were each significant predictors of higher clinical pain and together accounted for 34.0% of its variance. STAI was not a significant predictor of clinical pain (ΔR^2 =.00, p = .78). Among the four measures of sleep, only lower TST_o was a significant predictor of higher clinical pain (ΔR^2 =.09, p = .01).

Table 3-1. Clinical characteristics of the sample

	Mean	SD	Min – Max
Clinical Pain Intensity	50.6	19.3	8.7 – 88.5
AS	29.6	22.6	0 – 77.5
SLAP	21.7	11.2	4.0 – 50.0
TP Count	16.0	2.3	11.0 – 18.0
BDI Total Score	15.2	10.5	0 – 44
STAI Total Score	41.8	12.9	20 – 78
TST_o	397.9	58.9	221.6 – 546.6
TWT_o	104.0	49.5	39.6 – 305.2
TST_s	397.7	74.1	213.5 – 631.9
TWT_s	122.2	67.1	31.9 – 361.3

Table 3-2. Results of the hierarchical regression predicting clinical pain intensity

Block	Variable	ΔR^2	*F* change	*P*
1	AS	.07	3.98	.05
2	SLAP	.21	15.09	<.001
3	STAI	.00	.08	.78
4	BDI	.06	4.30	.04
5_a	TST_o	.09	7.11	.01
5_b	TWT_o	.01	.35	.56
5_c	TST_s	.02	1.68	.20
5_d	TWT_s	.01	.34	.56
*Full Model		Beta (Standardized)	*T*	*P*
	AS	.23	1.93	.06
	SLAP	.40	3.19	.002
	STAI	-.19	-1.16	.25
	BDI	.34	2.07	.04
	TST_o	-.31	-2.67	.01
	TWT_o	.08	.59	.56
	TST_s	-.15	-1.30	.20
	TWT_s	-.07	-.59	.56

*For blocks 1 – 4, full model = AS, SLAP, STAI, and BDI
For block 5_a, full model = AS, SLAP, STAI, BDI, and TST_o
For block 5_b, full model = AS, SLAP, STAI, BDI, and TWT_o
For block 5_c, full model = AS, SLAP, STAI, BDI, and TST_s
For block 5_d, full model = AS, SLAP, STAI, BDI, and TWT_s

CHAPTER 4
DISCUSSION

The purpose of this study was to determine the predictors of clinical pain intensity in adults with FM, and it represented a replication and extension of work done by Staud et al. (Staud, et al., 2004; Staud, Robinson, et al., 2003). Results confirm that a predictive model of AS, SLAP, and negative mood accounts for significant amount of variance (34.0%) in clinical pain. Only 1 of the 4 measures of sleep (TST_o) accounted for significant additional variance.

Central Sensitization and AS

Central sensitization has been hypothesized to be the primary pathophysiological mechanism for the maintenance of FM pain as well as other musculoskeletal pain conditions (Yunus, 2007). In central sensitization, neurons in the dorsal horn of the spinal cord become hyper-excitable and subsequently hyper-responsive due to prolonged noxious stimuli. These neuroplastic changes are manifested as increased pain sensitivity (hyperalgesia), a perception of pain in response to a normally non-painful stimulus like gentle touch (allodynia), referred or widespread pain (i.e. a lack of spatial localization), and prolonged electrophysiological discharge resulting in post-stimulus pain (Meeus & Nijs, 2007; Yunus, 2007). All of these are relevant characteristics of FM pain.

Most relevant to this analysis, central sensitization is thought to disrupt the endogenous pain inhibitory systems (NMDA receptors and substance P mechanisms, in particular), thereby resulting in prolonged post-stimulus pain due to an inability to adequately stop the pain response (Dickenson & Sullivan, 1991; Meeus & Nijs, 2007). Painful AS ratings taken during experimental heat pain induction are a measure of this

inhibitory dysfunction, and therefore a psychophysical correlate to central sensitization. In this study, higher AS ratings predicted more clinical pain and accounted for 7% of its variance. This result is a confirmation of Staud's findings (Staud, Robinson, et al., 2003), and taken together with findings of abnormal TSSP in FM (Staud, Cannon, et al., 2003), it suggests that central sensitization is an important mechanism in FM clinical pain.

SLAP

Widespread pain is the diagnostic hallmark for FM. It is also an indication of central sensitization, and was measured in this study by SLAP and TP count. SLAP was used as the measure of spatial extent in the analysis and proved to be a powerful predictor of daily clinical pain by accounting for 21% of its variance. This confirms past research suggesting that spatial extent plays an important role in determining clinical pain intensity in FM (Staud, et al., 2004), and complements findings of spatial summation in pain threshold and tolerance during experimental pain induction (Coghill, Mayer, & Price, 1993; Douglass, Carstens, & Watkins, 1992; Price, McHaffie, & Larson, 1989). Additionally, the result supports the clinical utility of shading areas on a body diagram as an indicator of the magnitude of daily pain in FM patients, and to potentially guide localized treatment targets. TP palpation is an evaluation of sensitivity to mechanical stimulation of muscle tissue, and can suffer from measurement error due to inter-rater variability in assessment. Statistically, the usefulness of TP count in predicting FM clinical pain is limited by a restriction of range due to the FM diagnosis requiring at least 11 positive TPs, and due to a hypersensitivity to nociceptive stimulation in FM patients (i.e. most FM patients endorse all or nearly all TP sites as painful). For these reasons, TP count may not be a useful correlate to clinical pain, and

may actually be a better indicator of distress (Wolfe, 1997). Indeed in this study, TP count was significantly correlated with both BDI-II ($r = .32$, $p = .01$) and STAI ($r = .31$, $p = .02$) total scores.

Negative Mood

Higher BDI-II scores predicted more clinical pain and accounted for 6% of its variance. The result confirms Staud's (Staud, et al., 2004; Staud, Robinson, et al., 2003) findings of the importance of negative mood in FM clinical pain, and adds evidence to a large literature linking depression with chronic pain (Bair, Robinson, Katon, & Kroenke, 2003). Longitudinal studies have demonstrated that depression can be both a predictive antecedent to (Leino & Magni, 1993; Magni, Moreschi, Rigatti-Luchini, & Merskey, 1994) and consequence of (Atkinson, Slater, Patterson, Grant, & Garfin, 1991; Brown, 1990) chronic pain. Additionally, the presence of depression portends worse pain outcomes and greater functional limitations in those with a chronic pain condition (Engel, von Korff, & Katon, 1996; Wells, Golding, & Burnam, 1989). Given their frequent co-occurrence, it follows that pain and depression share similar biological and behavioral mechanisms. Regions of the brain involved with emotion regulation (amygdala, hypothalamus, medial prefrontal cortex) are intricately connected to those involved with pain modulation (periaqueductal gray). Thus, the negative expectations and emotions of depression may amplify pain signals, increasing the intensity and duration of pain experienced. Indeed, similar functional and structural changes in limbic formations of the brain (amygdala and hippocampus) have been found in patients with major depression (Frodl, et al., 2008) and FM (Emad, et al., 2008).

Behaviorally, depression is associated with a lack of motivation and physical inactivity. Physical inactivity can contribute to the muscle stiffness experienced by

patients with FM, and conversely, exercise has been shown to have a beneficial effect on symptoms of FM (Fontaine, Conn, & Clauw, 2010; Mannerkorpi, Nordeman, Cider, & Jonsson, 2010). Finally, given the common comorbidity between chronic pain and anxiety (Gureje, 2008) and between anxiety and depression, it is somewhat surprising that STAI total scores did not significantly predict clinical pain. It is possible that the vegetative symptoms of depression (inactivity, fatigue, insomnia) play a more important role in modulating the daily pain of FM than the symptoms of autonomic and psychological arousal that are assessed by the STAI.

Sleep

The examination of sleep represented an extension of Staud's predictive model of clinical pain in FM. Two primary measures of sleep were examined in this study: a measure of sleep duration (TST), and a measure of insomnia duration (TWT), each assessed subjectively and objectively over the course of 14 days. To date, this was the first study to examine TST and TWT as a predictor of clinical pain at the between-person level in an FM population. Only lower TST_o was found to be a significant predictor of more clinical pain, accounting for 9% of its variance. Though the study designs and populations differ, longitudinal within-person findings on the effect of sleep duration on pain are generally supportive of this result. Edwards et al. (Edwards, Almeida, Klick, Haythornthwaite, & Smith, 2008; Edwards, et al., 2009) demonstrated that longer TST predicted better pain inhibitory control the next morning in temporomandibular joint disorder patients, and shorter TST predicted higher next day pain in a general population. Wilson et al. (Wilson, Watson, & Currie, 1998) found that more pain during the day predicted shorter TST at night in a chronic musculoskeletal pain population. And in a study of older adults with insomnia, Dzierzewski et al.

(Dzierzewski, et al., 2010) found that above average TST predicted below average pain the following morning.

Both measures of insomnia (TWT_o and TWT_s) failed to predict clinical pain in our study. This result is contrary to studies demonstrating that disturbed sleep predicts higher pain in an FM population (Wilson, et al., 1998) and in hospitalized burn patients (Raymond, Ancoli-Israel, & Choiniere, 2004). Additionally, laboratory studies in healthy subjects have found that sleep deprivation results in decreased mechanical and heat pain thresholds the following day (Kundermann, Spernal, Huber, Krieg, & Lautenbacher, 2004; Onen, Alloui, Gross, Eschallier, & Dubray, 2001).

Three of the four measures of sleep failed to predict clinical pain, thus giving limited support to the hypothesis that sleep would increase the predictive ability of the model of clinical pain in FM. Several potential explanations exist for the lack of significance in the findings. It is possible that a sleep – pain relationship was washed out at the between-person level using 14-day averages. Rather, it may be that an individual night of poor sleep is followed by a day of higher pain or vice-versa. Indeed, evidence for this daily variation between sleep and pain exists (Edwards, et al., 2008; Edwards, et al., 2009; Raymond, et al., 2004; Wilson, et al., 1998) and two studies have found significant relationships at the within-person level but not at the group level (Affleck, et al., 1996; Dzierzewski, et al., 2010). It also may be that the effects of poor sleep (e.g. daytime fatigue, inactivity, or perceived sleep quality), rather than measures of sleep or insomnia duration, are more important in determining clinical pain. There is evidence that fatigue and pain are related in FM samples (Nicassio, et al., 2002), and the perception of sleep quality has been shown to be a predictor of clinical pain in FM

as well (Raymond, Nielsen, Lavigne, Manzini, & Choiniere, 2001). Finally, it is possible that a sleep – pain relationship is dependent on disruption of specific sleep stages. Muldofsky et al. (Moldofsky & Scarisbrick, 1976) and others (Onen, et al., 2001) have demonstrated that selective disruption of Stage 4, slow wave sleep in healthy subjects resulted in symptoms similar to FM pain (e.g. localized areas of muscle tenderness). Additionally, FM patients have been shown to exhibit abnormal patterns of alpha activity during slow wave sleep compared to normal controls (Roizenblatt, Moldofsky, Benedito-Silva, & Tufik, 2001).

Statistically, TST_s and TWT_s demonstrated weak zero order correlation with the dependent variable, clinical pain intensity, as well as with the other independent variables in the regression analyses. Therefore, it is unlikely that their inability to significantly predict clinical pain can be explained by multicollinearity with other predictors. TWT_o was moderately correlated ($r = .48$) with BDI at the zero order. Thus, depressed mood and objectively-measured insomnia likely shared some variance in the regression analysis, potentially limiting the predictive ability of TWT_o.

Clinical Application

In clinical application, the results of the present study suggest that FM patients may benefit from a three-pronged approach to pain management. The significance of SLAP to clinical pain indicates that peripheral nociceptive sources are playing an important role in the generalized pain hypersensitivity of FM. To decrease the spatial extent of pain, patients may benefit from anesthetic injection to or manual manipulation of myofascial trigger points, or lidocaine injection to local pain areas. To address the implication of central sensitization in the AS finding, treatments should be aimed at normalizing the hyperexcitability of neurons in the central nervous system. Pregabalin

and duloxetine are centrally acting medications that have demonstrated some success in treating FM pain (Arnold, et al., 2005; Crofford, et al., 2005). Finally, psychobehavioral therapies should be considered to treat those with mood dysfunction and maladaptive pain coping. There is evidence to suggest that exercise (Gowans, et al., 2001; Lemstra & Olszynski, 2005) and cognitive behavioral therapy (Lemstra & Olszynski, 2005; Turk, Okifuji, Sinclair, & Starz, 1998) are successful in treating depression as well as improving pain related variables in FM patients.

Limitations

There are several limitations to the current study. The modest sample size limits the generalizeability of findings and may have decreased our power to detect significance in the regression analyses. Due to incomplete data and power considerations, the analyses did not control for the potential effect of sleep medication use among the participants. Use of sleep medications may have an effect on the duration of sleep or insomnia, particularly the time it takes to fall asleep or the time spent awake after sleep onset. Finally, the timing of clinical pain assessment (*i.e.* in the evening before bed) may have affected its relationship with the independent variables. FM pain can vary widely throughout the day, and morning or mid-day pain may have had stronger or weaker relationships with sleep than night pain.

Conclusion and Future Directions

The study confirmed that a model of AS, SLAP, and negative mood is a strong predictor of clinical pain intensity in FM. The data provided limited support to the hypothesis that measures of sleep and insomnia duration would account for additional, significant variance. With an eye toward treatment targets and mechanisms of action, future research should examine other clinical correlates of FM to strengthen the

predictive ability of the model. These might include known correlates like cognitive dysfunction, physical activity level, and symptoms of irritable bowel syndrome, or other sleep-related variables like fatigue, perception of sleep quality, or stage-specific abnormalities during sleep. Future research should also longitudinally examine the intra-individual, daily variation between sleep and pain. This can help to clarify whether a sleep – pain relationship in FM exists on a daily level, and if so, which of the two variables are driving the relationship.

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BIOGRAPHICAL SKETCH

Ryan Anderson received his B.A. in psychology from Washington University in St. Louis in 1999. After graduating, Ryan spent eight years doing research in the Department of Psychiatry at Washington University School of Medicine on depressive and anxiety disorders in patients with diabetes and pre-diabetic obesity. This included work on clinical trials examining the efficacy of various antidepressants in patients with comorbid diabetes and depression, as well as meta-analytic reviews of the prevalence of depression and anxiety in diabetes. In 2009, he began his doctoral study in clinical and health psychology at the University of Florida, and joined Dr. Michael Robinson's Center for Pain Research and Behavioral Health to continue pursuing his interest in medical psychology. Ryan's research interests include the interactions of negative mood, sleep, and pain in patients with chronic pain conditions. His clinical interests are in the assessment and treatment of psychological disorders in patients with medical conditions, and more broadly, in the treatment of adults with depressive disorders.