BIOCHEMICAL MARKERS OF DEPRESSION SUBTYPES IN FIBROMYALGIA

BY

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Abstract

Background: Fibromyalgia (FM) is a common, costly and debilitating chronic pain syndrome diagnosed in nearly 10 million Americans, 90% of whom are women. Conservative estimates place direct and indirect costs of FM at $15.9 billion annually. By definition, people with FM have chronic widespread pain and specified tender point areas at tendon-muscle junctions. Other symptoms associated with FM include disrupted sleep, fatigue, cognitive dysfunction, and mood disorders, mostly depression. The lifetime prevalence of depression in fibromyalgia patients is approximately 60% and suicide is the leading cause of premature mortality. Five distinct subtypes of major depressive disorder have been identified in depressed populations, with atypical and melancholic depressive episodes accounting for 45%-60% of all depression subtypes. There is increasing evidence that supports a biological link between depressive illness and chronic pain. Dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis is one of the most consistent findings in depression research and has been reported in a subset of FM patients. HPA axis dysfunction is the best-defined physiological abnormality in patients with depressive disorders, especially those with melancholic depressive episodes (MDE). It has been hypothesized that the two main depression subtypes, melancholic depressive episodes and atypical depressive episodes (ADE), exist in FM as well and that they exhibit differing levels of HPA axis activation as measured by the dexamethasone suppression test (DST): MDE having increased HPA activation and ADE having reduced HPA activation. In addition, work from our group has reported hypothalamic pituitary

growth hormone (HPGH) axis with low plasma IGF-1 levels --a measure of 48-hour growth hormone (GH) secretion-- in about one third of persons with FM. Further experiments have shown that the reduced GH secretion in FM patients is a result of increased hypothalamic somatostatin tone, which inhibits growth hormone secretion. MDE is associated with increased secretion of corticotropin releasing hormone (CRH), which in turn stimulates the secretion of somatostatin. Thus, it is logical to assume that FM patients with MDE may have reduced levels of GH secretion as evidenced by low plasma IGF-1 levels. It is important to determine if ADE and MDE follow the same clinical and biochemical patterns in a depressed FM population as has been documented in depressed non-FM populations. Research has shown ADE has a preferential response to monoamine oxidase inhibitors (MAOIs) and MDE has a preferential response to CRH antagonists. If it is found that ADE is more prominent in an FM with concurrent Major Depressive Disorder (MDD) population than MDE, this knowledge will support the need to consider more specific prescribing practices based on the need to activate versus attenuate the HPA axis.

Objectives: The purpose of the study was to directly test the hypothesis that MDD subtypes exist in FM and can be identified via clinical characteristics and biochemical assays. In addition, growth hormone production was evaluated for differences among diagnostic groups.

Design: The study was a cross-sectional descriptive study with three groups of patients: (1) non-depressed fibromyalgia patients (FM no MDD), (2) fibromyalgia

patients with melancholic depressive episodes (FM/MDE), and (3) fibromyalgia patients with atypical depressive episodes (FM/ADE).

Setting and Subjects: Invitation letters were mailed to 1582 FM patients selected via a computer generated random numbers table from a tertiary care fibromyalgia clinic data base of over 8,000 FM patients in the Pacific Northwest. Over-sampling for zip codes known to have high ethnic diversity was completed to maximize minority inclusion. The study included men and women between the ages of 20 to 90.

Measurements: The diagnosis of MDD, MDE, and ADE were evaluated by a semi-structured clinical interview using the DSM-IV-TR diagnostic criteria for MDD plus the ADE and MDE subtype criteria. Independent variables of FM, depression, and pain severity; sleep quality; quality of life; and impact of FM on ability to function were also measured using standard instruments with established validity and reliability. HPA axis function as evidenced by plasma cortisol levels was assessed using the DST in all subjects (n=65) and a combined DEX suppression/CRH stimulation test in a subset of subjects (n=19). HPGH axis function was measured via standard laboratory assays of plasma IGF-1.

Analysis: Descriptive statistics were used to characterize demographics (age, gender, race, ethnicity, education, disability status, and marital status) and clinical variables (FM, depression and pain severity; sleep quality; quality of life; and impact of FM on ability to function). Chi square tests and analysis of variance (ANOVA) with Bonferonni and Games-Howell post-hoc tests were used to

determine if significant differences existed among diagnostic groups on demographic and clinical characteristics, pre-CRH stimulation highest mean plasma cortisol levels, post-CRH stimulation peak plasma cortisol levels, and plasma IGF-1 levels.

Results: A higher occurrence of ADE (n=40, 52.6%) versus MDE (n= 27, 35.5%) was found in the sample. No significant differences existed among the three groups on baseline demographic characteristics except for the expected predominance of females to males. Significant differences were found on all clinical characteristics among diagnostic groups except for number of tender points and body mass index. In the DST group, there was a trend in the expected direction for plasma cortisol levels, but no significant differences were found among the diagnostic groups. In the DEX/CRH group, mean peak plasma cortisol levels in the FM no MDD and FM/ADE groups did not significantly differ from each other. However, significant differences did exist between the FM/ADE and FM/MDE groups with the MDE group having the highest pre-CRH stimulation mean cortisol levels (3.24 ng/dl) and post-CRH stimulation highest peak cortisol levels (9.88 ng/dl). Post-hoc analyses demonstrated significant differences in mean plasma cortisol levels between the FM/ADE and FM/MDE groups at the 1545 time point (p= .02), the 1600 time point (p= .004), and the peak plasma cortisol level (p= .001). No significant differences of IGF-1 levels were found among the three groups (p= .31).

Conclusions: This study yielded four novel findings: 1) biological subtypes of major depressive disorder exist in FM and exhibit similar characteristics as those

found in depressed non-FM populations, 2) atypical depressive episodes are more common than melancholic depressive episodes in this FM sample, 3) HPA axis suppression as evidenced by peak plasma cortisol levels are reflective of MDD subtypes, and 4) the use of the combined DEX/CRH stimulation test is feasible in an FM population and may demonstrate more sensitivity and specificity. Further research is needed to replicate the above results in a larger sample and to further evaluate the cost/benefit ratio of the more sensitive and specific combined DEX/CRH stimulation test versus the DST in FM patients with concurrent MDD.

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CHAPTER 1: INTRODUCTION

Introduction

Chapter 1 presents a brief background regarding fibromyalgia (FM) and major depressive disorder (MDD) research in relation to the pertinent research questions, purposes and aims of this study. The gaps in the current literature, the timeliness of this study plus the significance of the problem to nursing and other disciplines conclude Chapter 1.

Fibromyalgia and Major Depressive Disorder

Fibromyalgia is a common, costly, and highly debilitating disorder defined by widespread musculoskeletal pain and muscle tendon junction tenderness. Following the publication of the 1990 American College of Rheumatology (ARC) Classification Criteria for FM, there has been a linear increase in FM research. This research has established the prevailing model that pain in FM is a result of central augmentation. However, FM is more than chronic pain. Most FM patients also have a mood disorder, most commonly MDD. Additionally, many FM patients exhibit a dysregulation of the stress response system, the hypothalamic-pituitary-adrenal (HPA) axis. Recently, Chrousos and Gold proposed that two subtypes of MDD (atypical and melancholic) exist in FM. They further postulated that specific HPA axis abnormalities and clinical correlates could identify these two subtypes. However, they have not tested their model empirically. Multiple lines of evidence support the notion that one component of the HPA axis, specifically the insulin-like-growth factor axis, is abberated in FM patients. Yet no study to date has evaluated IGF-1 in MDD subtypes in FM.

HPA Axis Research in FM and MDD

Multiple research studies have evaluated the HPA axis of FM and MDD separately, but there is a significant gap in the literature regarding the HPA axis in clinically depressed FM patients. The few studies that have measured cortisol (the major stress hormone secreted under acute and chronic stress) in subjects with concurrent FM and MDD have demonstrated inconsistent results. I hypothesized that one possible explanation for these divergent findings is that when plasma cortisol levels from FM subjects with ADE (usual cortisol range </= 5ng/dl) are combined with FM subjects with MDE (usual range >5ng/dl), the mean may be inadvertently suppressed to 5 ng/dl or below if there are more ADE subjects versus MDE subjects in the sample. Conversely, the mean may be inadvertently elevated greater than 5 ng/dl if there are more MDE subjects versus ADE subjects in the sample. To date, no studies have evaluated if MDD subtypes exist in FM and, if so, whether they exhibit the same psychological and physiological characteristics that a depressed non-FM population exhibits. The two principal questions that this study sought to answer were 1) Do the two biological MDD subtypes (ADE and MDE) exist in FM patients with MDD, and if so, do they exhibit similar symptoms of clinically depressed non-FM patients, and 2) Do these two subtypes of MDD in FM patients exhibit the same profiles of dexamethasone suppression as described in the literature in clinically depressed patients without FM? The purpose of the study was to directly test the hypothesis that MDD subtypes exist in FM and can be identified via biochemical assays and clinical characteristics.

Limitations of Prior Research

To control for potential confounding variables experienced in previous research studies, this study incorporated two novel approaches in the design. The first was that participants were evaluated prior to data collection for the presence of MDD, and if present, separated into one of two biochemical subtypes (ADE or MDE). Second, a more highly specific and sensitive test of HPA axis function, the combined dexamethasone/corticotropin-releasing hormone stimulation test (DEX/CRH) was pilot tested in a subset of subjects to evaluate the feasibility of using this test in FM research. To my knowledge, this more sensitive test has not been used in FM research and therefore no data is available on the tolerability, sensitivity, or specificity of the DEX/CRH test in FM populations. Theoretically, it is probable that the increased specificity and sensitivity of the DEX/CRH test would improve detection of altered HPA axis function of ADE and MDE over the standard Dexamethasone Suppression Test (DST) as it has been proven to do in depressed populations. By decreasing the confounding variables that may contribute to inconsistent cortisol findings, we can better understand the biological underpinnings of HPA axis dysfunction in co-occurring FM and MDD.

Specific Aims and Hypotheses

The long-term goal of my program of research is to maximize effectiveness of care, combining psychopharmacological, physiological and psychosocial interventions, in depressed patients with FM. The next critical step is to determine is MDD subtypes exist in FM and to explore their HPA axis

underpinnings. This research may eventually help to identify common pathways that are amenable to pharmaceutical manipulation so that more targeted drug therapies may be developed.

Aim 1

To describe the demographic and clinical characteristics of FM subjects with no MDD, ADE, and MDE.

Hypothesis: There will be significant differences among the three groups on measures of FM severity, depression severity, pain severity, sleep quality, quality of life, impact of FM on ability to function, and body mass index.

Rationale: Research has identified physiological and psychological differences between MDE and ADE in depressed populations and Chrousos and Gold postulate that depressed FM populations will display similar differences.

Aim 2

To determine whether there are significant differences in dexamethasone induced suppression of the HPA axis, as evidenced by mean dexamethasone suppression (MDS) and peak plasma cortisol levels, among FM subjects with no MDD, ADE and MDE.

Hypothesis: The MDS and peak plasma cortisol levels following dexamethasone induced suppression will be </= 5ng/dl in both the FM no MDD and FM/ADE groups. Conversely, the FM/MDE group will have cortisol levels > 5ng/dl, indicating lack of HPA axis suppression.

Rationale: Extensive research of depression subtypes using the DST has identified that persons with MDE have an impaired suppression of the HPA axis

resulting in higher levels of plasma cortisol while persons with ADE and healthy controls have a normal suppression response resulting in normal to low levels of plasma cortisol.

Aim 3

To explore whether there are differences in the serum insulin-like growth factor-1 (IGF-1) levels of FM subjects with MDE compared to FM subjects with ADE and no MDD.

Hypothesis: FM subjects with MDE will have lower IGF-1 levels than FM subjects with ADE and no MDD.

Rationale: Elevated levels of corticotropin-releasing hormone (CRH), as found in MDE, alters the tonic balance of somatostatin and growth hormone-releasing hormone such that growth hormone (GH) release is inhibited. Ultimately, lower levels of circulating GH results in lower levels of IGF-1. Serum levels of IGF-1 have been found to be low for age in about 30% of people with FM, which interestingly corresponds to the prevalence of MDE in a depressed non-FM population.

Significance to Nursing

In diseases such as FM and MDD, where there is significant negative stigmatization and even disbelief that the diseases exist, investigations that confirm the biochemical underpinnings of these diseases are paramount. Nurses encounter FM and MDD patients in all specialties of nursing and are in a unique position to assist patients by generating and disseminating current and accurate scientific knowledge regarding these diseases. For instance, it is validating for

patients to learn that FM and MDD are biochemical in nature versus solely psychogenic and that there are treatments that help to alleviate symptomology, thus affording the possibility of leading a more functional life. In addition, this knowledge will help to develop customized nursing care plans and interventions for each patient based o their specific HPA axis dysfunction. Knowledge from the study is also expected to assist future investigations regarding the effectiveness of differential prescribing practices to target more effective psychopharmacological interventions. This knowledge is eventually expected to decrease the functional, financial, and social losses caused by co-occurring MDD and FM.

Summary of Major Study Findings

This study was the first to confirm biological depression subtypes in FM. It was also the first to test the HPA axis in FM patients with and without subtypes of depression. Furthermore, it was the first to use the more specific and sensitive combined DEX/CRH stimulation test to evaluate HPA axis function in a depressed FM population. Findings of the study demonstrated the existence of two distinct biological subtypes of MDD in FM with a higher occurrence of ADE compared with MDE. There were significant differences in clinical characteristics (FM, MDD, and pain severity; sleep quality; quality of life; impact of FM on ability to function) and peak plasma cortisol after DEX/CRH stimulation testing between the ADE and MDE subtypes. The combined DEX/CRH test was found to be tolerable and feasible in the subset of patients who received this test. While the differences of IGF-1 levels between FM subjects with MDE compared to FM

subject's with ADE and no MDD were not statistically significant (p= .31), the mean IGF-1 levels per group trended in the expected directions.

Organization of Chapters 2 – 5

The remainder of this dissertation is as follows:

Chapter 2 provides a comprehensive review of the literature with critical analyses of classic and more recent research in the individual fields of FM, MDD and co-morbid MDD in FM. The most relevant research to this study is further critiqued in relation to the theoretical framework and the function of the HPA axis.

Chapter 3 discusses research design and methods for the study in relation to the rationale for the study design, choice of setting, selection of sample, data collection methods and all procedures. The validity, reliability and scoring methods for all instruments used in the study are described in detail. The measures of biochemical variables (cortisol and IGF-1) and the efforts made to control for confounding variables are also discussed here. Initial statistical analyses procedures for all data and the rationale for the choice of analyses completes Chapter 3.

Chapter 4 presents a description of the data with respect to the hypothesized relationships. Statistical findings for each aim are reported with the corresponding statistical significance. Findings of exploratory aims are also reported.

Chapter 5 presents interpretations of the statistical significance of the results and discusses the theoretical and practical implications of the findings.

The current findings are further discussed in relation to previous research and divergent findings. The relationships among the problems addressed by this study, review of the literature, theoretical framework, methods, findings, and discussion are summarized here. The clinical and research implications of the findings for nursing and other disciplines, limitations of the study, and suggestions for future directions conclude Chapter 5.

Table 1.1

List of Abbreviations

ACR = American College of Rheumatology	**ACTH** = Adrenocorticotropic Hormone
ADE = Atypical Depressive Episode(s)	**BDI** = Beck Depression Inventory
BMI = Body Mass Index	**CRH** = Corticotropin-releasing Hormone
DEX = Dexamethasone	**DEX/CRH** = Combined Dexamethasone Suppression/ CRH Stimulation Test
DST = Dexamethasone Suppression Test	**FM** = Fibromyalgia
GH = Growth Hormone	**HPA Axis** = Hypothalamic-Pituitary-Adrenal Axis
IGF-1 = Insulin-like Growth Factor-1	**MDD** = Major Depressive Disorder
MDE = Melancholic Depressive Episode(s)	**TSH** = Thyroid Stimulating Hormone
SIGH-ADS = Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement	**SIGH-SAD-SR** = Structured Interview Guide for the Hamilton Depression Rating Scale-Seasonal Affective Disorder-Self Report

CHAPTER 2: REVIEW OF THE LITERATURE AND THOERETICAL FRAMEWORK

Introduction

This chapter presents an in-depth review of the literature with a focus on the processes that underlie the pathophysiology of FM and MDD. The review is separated into discussions of 1) prevalence and burden of FM and MDD, 2) disordered pain processing in FM and its links to MDD, 3) the theoretical framework of stress physiology, 4) an overview of the stress response system, HPA axis and HPGH axis, 5) associations of FM and MDD, 6) the HPA axis in FM and MDD 7) subtypes of FM and MDD, and 8) psychological and physiological differences of ADE and MDE subtypes. Throughout the discussion, emphasis is placed on the pertinent clinical characteristics of the study: FM severity, depression severity, pain severity, quality of sleep, quality of life, functional impairment severity, cortisol, and IGF-1. The theoretical framework will include a description of the constructs of Hans Selye's General Adaptation Syndrome. Psychoneuroendocrinology of FM and MDD will inform this model.

Background and Significance

Prevalence and Burden of Fibromyalgia

Fibromyalgia is a common, chronic debilitating disease characterized by widespread musculoskeletal pain (100%), specified tender points (100%), fatigue (96-100%), sleep disturbances (86%-98%), and co-morbid psychological disorders, including a 60%- 68% lifetime prevalence of depression (Manu, 1999; Neeck, 2002; Rao & Bennett, 2003; Epstein, Clauw, Heaton, Klein, Krupp, Kuck,

et al., 1999). It also exhibits several neuroendocrine system disturbances including the hypothalamic-pituitary-adrenal (HPA), hypothalamic-pituitary-growth hormone (HPGH), and hypothalamic-pituitary-thyroid (HPT) axes.

Fibromyalgia has an estimated economic burden of between $700 million direct costs annually in the United States (Wolfe, Ross, Anderson, Russell, & Hebert, 1995), and $15.9 billion in direct and indirect health care costs (Thorson, 1996). One study in the Netherlands found the annual disease related total societal costs per FM patient to be 7,813 Euros or $10,585 US dollars (Boonen, van den Heuvel, van Tubergen, Goossens, Severens, et al., 2005). Fibromyalgia affects women disproportionately, with 80%-90% of individuals with FM being women between the ages of 30 to 50 years old (Wolf et al., 1995). However, FM is not limited to this age range as it has been diagnosed in children and elders also (Anthony & Schanberg, 2001; Shillman, Jones, Ross & Adams, 2006).

Prevalence and Burden of Major Depressive Disorder

Major depressive disorder, often referred to as depression in lay publications, is also a common chronic debilitating disease characterized by depressed mood; fatigue; sleep, cognitive, and neuroendocrine disturbances; and may also manifest as painful bodily sensations (APA, 2001). Depression is the seventh leading cause of morbidity in the United States and it is expected to be the fourth leading cause by 2020 (CDC, 2002). The total global economic burden of mental illness as compared to all diseases was 10.5% in 1990 and is projected to be 15% by 2020 (Murray & Lopez, 1996). In 1992 dollars, depression was found to account for a $43 billion dollar deficit mostly related to

reduced or lost worker productivity (Nemeroff, 1998). Each year in the United States, 9.5% of American adults, approximately 18.8 million people, have an active depressive illness (NIH, 2004). Like FM, depression also disproportionately affects women compared with men (21% vs. 13% lifetime prevalence) (Kessler, McGonagle, Zhao, Nelson, Hughes, Eshleman, et al., 1994).

It is estimated that 15% of individuals with MDD will successfully complete suicide (APA, 2001). In 2001, suicide was reported as the eleventh leading cause of death (CDC, 2002) and the total number of suicide deaths was 30,622 (NIH, 2004). Individuals with FM also have a nine-fold increased risk of death from suicide (Standard Mortality Ratio= 9.1[95%CI; 3.3-19.8]) (Dreyer, Kendall, Winther, Mellemkjaer, Danneskiold-Samsoe, & Bliddal, 2004). It is imperative that research be conducted to decrease the impact of these two diseases on patients, their families, and society as a whole.

Disordered Pain Processing in FM and Its Links to MDD

An epidemiological review of the literature reveals that nonmalignant chronic musculoskeletal pain is commonly encountered in the general population. In an early survey of 2,034 adults in northern England by Croft and colleagues (1993), prevalence rates for chronic widespread pain were 11.2%. Of these subjects, 21.5% met the American College of Rheumatology's (ACR) 1990 diagnostic criteria for FM: 1) respondents had pain in 11 or more of 18 tender points on digital palpation using 4 kg of pressure in three of four body quadrants, 2) the pain had lasted for greater than three months, and 3) the pain

could not be explained by other mechanisms or diseases. Thus, 2.4% of the general population met diagnostic criteria for FM as per the 1990 ACR criteria. Over the years, studies conducted in different populations have corroborated Croft and colleagues' findings and indicate the prevalence of FM is approaching 7% in some United States populations and as high as 10% in some parts of the world (see Table 2.1).

Table 2.1

Prevalence of FM in Population Studies

Country	**Prevalence (%)**	**Year**	**Study**
United States	2.0	1995	(Wolfe *et al*, 1995)
US (Amish)	7.3	2003	(White & Thompson, 2003)
Canada	3.3	1999	(White *et al*, 1999)
Pakistan	1.5	1998	(Farooqi & Gibson, 1998)
Spain	2.4	2001	(Carmona, 2002)
Italy	2.2	2005	(Salaffi *et al*, 2005)
Mexico	1.4	2002	(Cardiel & Rojas-Serrano, 2002)
Brazil	2.5	2004	(Senna *et al*, 2004)
Sweden	1.3	2000	(Lindell *et al*, 2000)
Sweden	1.0	1989	(Jacobsson *et al*, 1989)
Norway	10.5	1992	(Forseth *et al*, 1999)
Finland	0.75	1991	(Makela & Heliovaara, 1991)
Denmark	0.7	1989	(Prescott *et al*, 1993)

Widespread musculoskeletal pain is the primary symptom of FM yet the mechanisms of this pain are not fully understood. The standard definition of pain by The International Association for the Study of Pain (1979) is "an unpleasant sensory or emotional experience associated with actual or potential tissue damage or described in terms of such damage" (Merskey & Bogduk, 1994). The

symptoms of widespread chronic pain in FM indicate abnormalities in the nociceptive, limbic, and endocrine systems (Neeck & Reidel, 1999).

Acute and Chronic Pain Processing

Physiological pain is modulated by both the central nervous system and the hypothalamic pituitary adrenal axis (Staud & Domingo, 2001). Stress, whether due to physical illness, emotional trauma, or physiologic pain, stimulates the release of corticotropin-releasing hormone (CRH) which increases adrenocorticotrophin hormone (ACTH). Interestingly, ACTH has been found to decrease the perceptions of pain in FM (Pillemer, Bradley, Crofford, Moldofsky, & Chrousos, 1997). Exposure to noxious stimuli leads to a complex and interactive system of pain processing involving peripheral pain receptors and nerve fibers that carry the painful stimuli to the dorsal horn of the spinal column where it undergoes primary processing. The noxious stimuli are then transmitted via the spinothalamic tract to the thalamus for secondary processing. It is also transmitted via the limbic system pathways to other limbic structures (amygdala, cingulated gyrus, hippocampus, hypothalamus) where affective value is assigned to the noxious stimuli (Millian, 1997). The components of the normal pain processing pathways include peripheral receptors; neural pathways; spinal cord mechanisms including ascending and descending neuronal pathways; and brain areas specific to pain processing including the medulla oblongata, thalamus, hypothalamus, cortex, reticular formation, and the limbic system (Cross, 1994).

Nociceptors (peripheral pain receptors sensitive to noxious stimuli) transmit nociceptive (pain) impulses to the central nervous system (CNS) via

primary afferent fibers (PAF). Peripheral stimuli are transmitted via one of three types of PAF's, which originate in the periphery and terminate in the dorsal horn of the spinal cord. *A-delta fibers* are large, thinly myelinated nerve fibers that are triggered by strong mechanical pressure or intense heat. Stimulation of A-delta fibers generates rapid, bright, and localized pain sensations. *C-fibers* are small, unmyelinated, polymodal nociceptors that are triggered by thermal, mechanical, and chemical stimuli and generate slower diffuse pain sensations. *A-beta fibers* are large, myelinated, low-threshold mechanoreceptors which respond to light touch and low-intensity mechanical information (Cross, 1994).

Nociceptive pain (pain due to excessive stimulation of nociceptors) is conducted from the periphery to the dorsal horn via the afferent A-delta and C-fibers (Millian, 1999). The stimuli are then transmitted to the higher brain centers via the supraspinal spinothalamic tract, which goes to the ventrobasal part of the lateral and medial nuclei of the thalamus (Millian, 1999). Noxious stimuli are sent to the lateral thalamus and then to the cortex, where the location of the sensation is assessed. Noxious impulses from the medial thalamus are sent to the reticular formation, hypothalamus, and limbic system. The reticular formation is responsible for motor, sensory and autonomic responses to noxious stimuli, which assists in the rapid withdrawal of the body away from the noxious stimuli (Millian, 1999). The limbic system aids in integrating higher brain function with motivational and emotional connotations to the painful stimuli. It also contains the afferent nerves from the hypothalamus and the brain stem, and receives descending influences from the cortex (Mense, 2003).

Descending inhibitory pain pathways originates from the cortex, thalamus, and brainstem. Nerve fibers connect the organs of the limbic system, including the reticular formation of the medulla to the raphae nucleus where serotoninergic axons descend in the dorsolateral funiculus of the spinal column and release serotonin (Millian, 1999). Serotonin imbalances are known to be associated with increased pain.

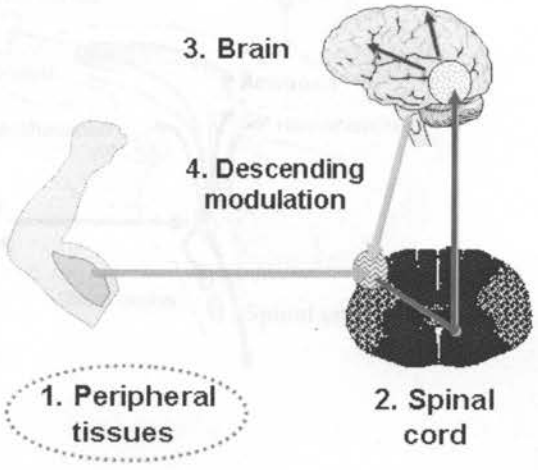
Temporal Summation and Central Sensitization

A review by Staud (2004) reports there are peripheral tissue changes and central nervous system changes that lead to abnormal pain processing in FM. Repetitive stimuli of C-fiber nociceptors leads to sensitization of pain-modulating systems in the central nervous system at both spinal and supraspinal levels. Desmeules and colleagues (2003) found that the nociceptive system (peripheral pain nerves) in patients with FM is centrally hyper-excited. In this hyper-excited state, spinal cord neurons produce an enhanced responsiveness to noxious stimulation (hyperalgesia) and even formally innocuous stimulation (allodynia) (Bennett, 1999). Chronic pain is commonly associated with hyperalgesia (an increase in the pain elicited by a noxious stimulus) and/or allodynia (an increase in the pain elicited by normally innocuous stimulus). Staud, Cannon, Mauderli, Robinson, Price, and colleagues (2003) determined that repetitive muscle stimulation produced significantly greater temporal summation (wind-up pain) in FM patients compared with healthy controls, supporting the supposition that FM patients have an exaggerated response to painful stimuli. Staud and colleagues (2003 & 2006) concluded that persistent nociception could lead to neuronal

plasticity and increased hyperalgesia and allodynia, which not only initiates, but also perpetuates central sensitization. This persistent stimulation of C fibers may cause a local reaction consisting of vasodilatation and increased capillary permeability with the subsequent release of substance P and calcitonin gene-related peptide. In response, potassium, acetylcholine, histamine and bradykinin may be released which leads to the release of prostaglandin and leukotriene. These chemicals have been found to contribute to sensitization of the high-threshold mechanoreceptors in muscle tissue and may lead to neurogenic inflammation (see Figure 2.1).

Figure 2.1

Pain Pathways in FM

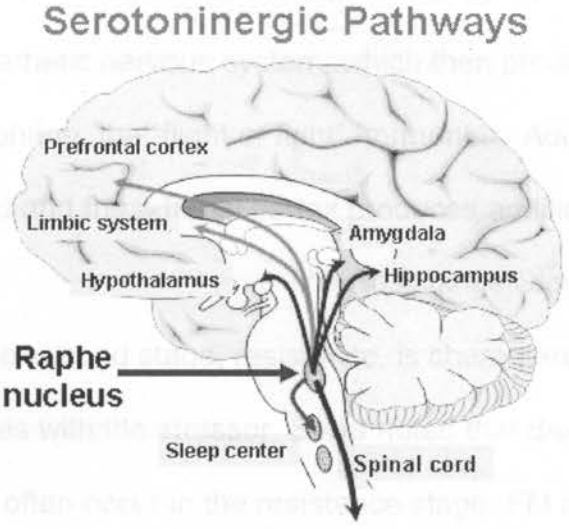


Repetitive stimulation of the nociceptive system also induces the release of central transmitters in the spinal column including substance P and serotonin (Millian, 1999). Painful sensations are transmitted to the limbic system and

stimulate the serotonin pathways. Alterations of serotonin are strongly associated with MDD symptomology and are thought to be associated with the painful sensations often experienced in clinical depression devoid of peripheral or visceral pain generators (Stahl & Briley, 2004). Serotonin also plays an important role in the regulation of the HPA axis as it stimulates the secretion of ACTH during stress, which then influences other HPA axis functions including increasing serum cortisol levels (see Figure 2.2).

Figure 2.2

Serotonergic pathways involved in central sensitization.



Theoretical Framework of Stress Physiology

The theoretical framework that is used to inform this study is the General Adaptation Syndrome (GAS) model, as the concepts of stress, stress adaptation, and system exhaustion are key concepts in the model and correlate with the

main concepts of this study. FM and MDD have been identified as stress-related disorders that have biochemical commonalities, including a maladaptive stress response. Hans Selye postulated in his GAS model that disease was a result of dysfunction of the body's general adaptation response to stress (Selye, 1978). More recent research support this theory (Chrousos, 1998). Selye first described the GAS in 1936 (Selye, 1946). It involves three progressive stages of response to stress: alarm, resistance (adaptation), and exhaustion.

The Alarm Reaction Stage

The first stage, the alarm reaction, is characterized by psychological and physiological responses when a person is exposed to a stressor, such as physical pain or emotional trauma. The body reacts to the stressor by activating the sympathetic nervous system, which then produces epinephrine and norepinephrine, the "flight or fight" hormones. Additionally, the HPA axis is stimulated and the adrenal cortex produces additional cortisol.

The Resistance Stage

The second stage, resistance, is characterized by adaptation, whereby the body copes with the stressor. Selye noted that diseases precipitated or caused by stress often occur in the resistance stage. FM and MDD are two diseases that follow this pattern; others include diabetes, cardiovascular disease, and infectious diseases. The adaptive stage continues until the stressful situation is resolved and a rapid return to homeostasis occurs. However, in the presence of long-term exposure to a stressor, the third stage, exhaustion, is entered.

The Exhaustion Stage

This stage is manifested by altered levels of CRH, ACTH, and cortisol. An imbalance of these hormones leads to a loss of sensitivity of the HPA axis negative feedback mechanisms, which in turn contributes to the development of clinical symptoms of FM and MDD including fatigue, depression, inability to concentrate, poor memory, weakness, obesity, muscular pain and tenderness (Tintera, 1955). This final stage is the focus of this study and is examined in more detail below. Interestingly, Arnold and colleagues (2006) found that symptoms of psychiatric disorders often preceeded symptoms of FM by more than one year.

Overview of the Hypothalamic Pituitary Adrenal (HPA) Axis

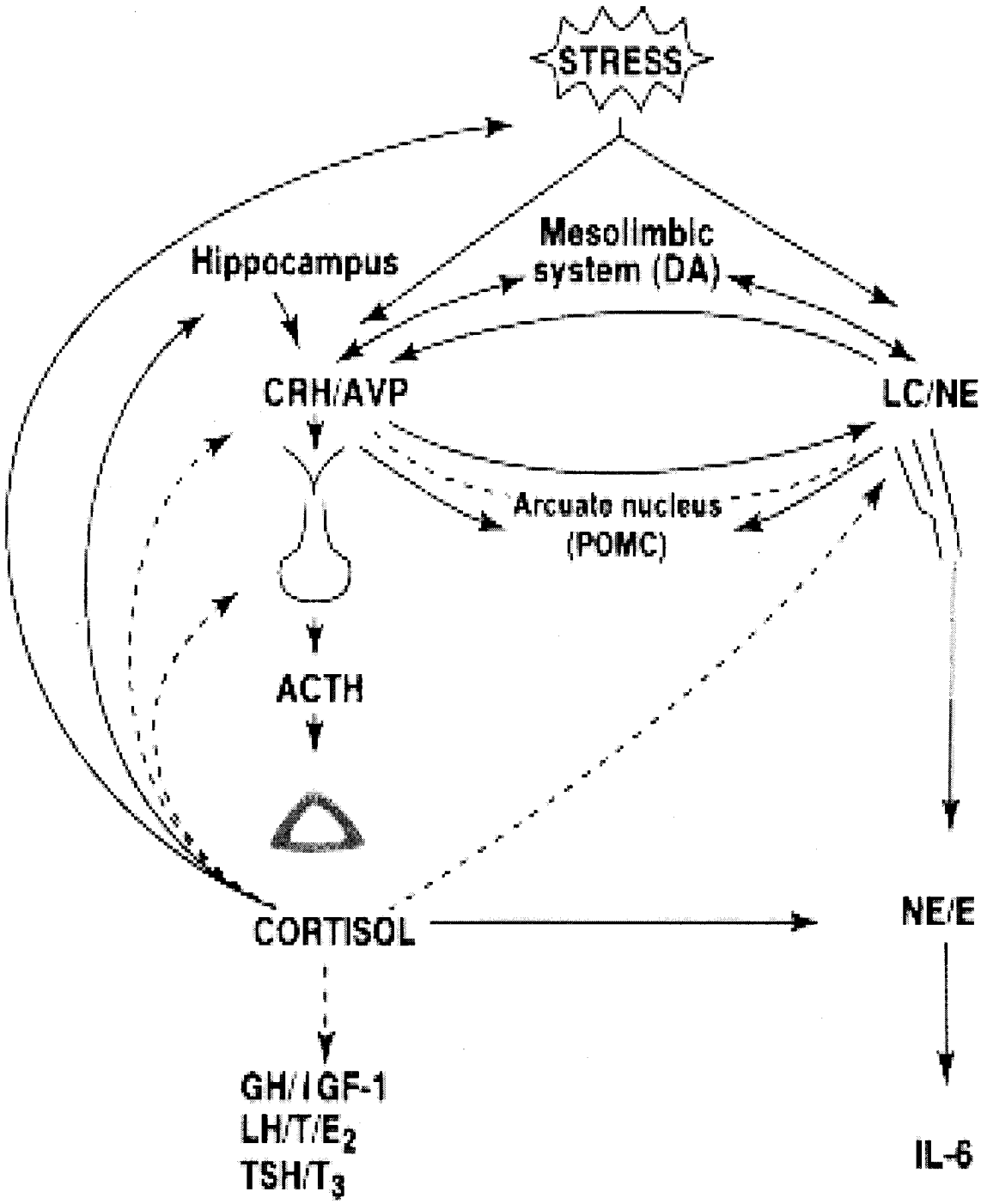
The stress response system is governed by the HPA axis, which is the primary endocrine stress axis in humans. The main role of the HPA axis is to coordinate the physiological adaptation to stressful stimuli thus assisting the body to maintain homeostasis. Acute stress stimulates chemical cascades that increase the brains ability to discern potentially threatening environmental stimuli thus enhancing alertness and vigilance and increasing the chances of survival. Prolonged stress causes a dysregulation of the HPA axis with resulting dysregulation of several other hormonal systems (see Figure 2.3).

The HPA system is regulated by a complex system of long and short feedback loops that control the release of the various hormones involved in the stress response. The main components of the stress system are the CRH system and the locus ceruleus/norepinephrine (LC/NE) systems. The CRH and LC/NE systems regulate multiple bodily processes and interact with other axes,

including the hypothalamic pituitary growth hormone (HPGH) axis and the immune system. The CRH neurons and central catecholaminergic neurons of the LC/NE system reciprocally innervate and activate each other. Activation of the HPA axis and subsequent increases in cortisol leads to suppression of the GH/IGF-1, lutenizing hormone/testosterone/estradiol (LH/T/E_2) and the thyroid stimulating hormone/ triiodine-thyronine (TSH/T_3) axes (Cook, Ludlam, & Cook, 2000). Activation of the sympathetic nervous system also increases IL-6 secretion. A simplified schematic representation of the central and peripheral components of the stress system, their functional interrelations and their association with other central systems involved in the stress response are depicted in Fig. 2.3 (solid lines indicate stimulation; dashed lines indicate inhibition.)

Figure 2.3

Brain circuits of the stress response.



(Reprinted with permission from Chrousos and Gold, 2002).

Overview of the Hypothalamic Pituitary Growth Hormone (HPGH) Axis

The HPA axis is the mechanism by which the brain responds to acute and chronic stress. Prolonged stress causes a dysregulation of the HPA axis with resulting dysregulation of several other hormonal systems including the HPGH axis (see Figure 2.4). Painful stimuli and associated stressors increase the release of CRH, which can act as a neurotransmitter and can inhibit, but mostly activates CRH neurons (Neeck, 2000). Increased plasma CRH levels in turn increase the secretion of ACTH and somatostatin. Increased plasma ACTH levels activate the release of cortisol, which then increases the release of somatostatin. Increased somatostatin tone inhibits the secretion of growth hormone and TSH. This physiological process explains in part the abnormally low levels of GH/IGF-1 in approximately 30% of patients with FM (Bennett, Cook, Clark, Burckhardt, & Campbell, 1997). Because GH is released in minute pulsatile bursts throughout the day, IGF-1, a long lasting marker of 24-hour GH release, is assessed as an indirect measure of 24 hour GH release.

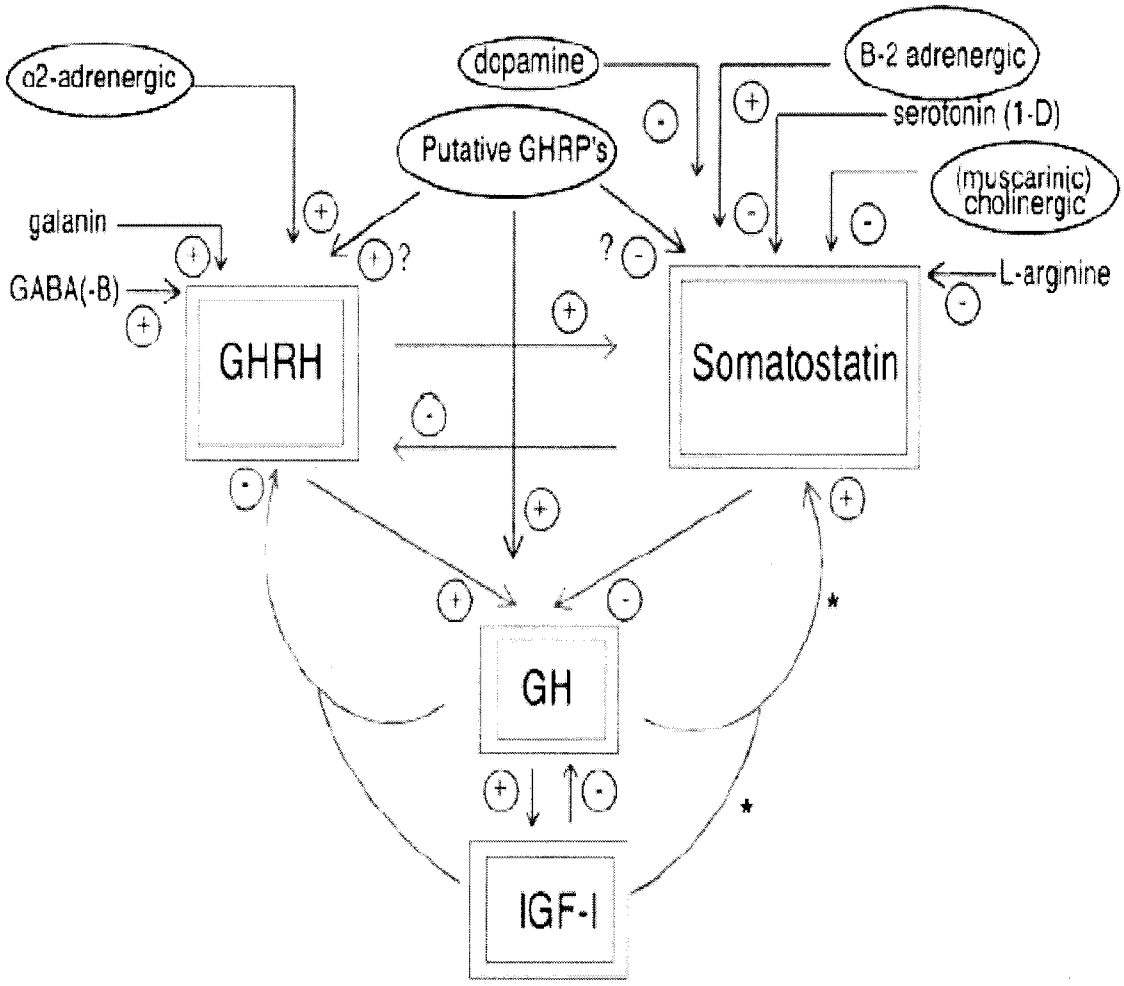
In adults, GH is responsible for multiple processes including normal muscle tissue repair, carbohydrate metabolism, and maintaining adequate energy stores (Cuneo, Salomon, McGauley & Sonksen, 1992). Growth hormone deficiency symptoms in adults are similar to symptoms commonly reported by patients with FM: fatigue, muscle weakness, poor exercise tolerability with retrograde pain, loss of lean body mass, and sleep disturbances (Bennett, 2002). Bennett and colleagues (1997) reported that of 500 FM patients, approximately 30% had abnormally low serum IGF-1 levels.

Growth hormone is mainly produced during deep sleep stages and in response to exercise. Deep sleep (Stage III and Stage IV) is disrupted by alpha-delta wave intrusion in persons with FM and is thought to contribute to low serum GH/IGF-1 levels in FM patients. Landis and colleagues (2001) demonstrated that mean serum concentrations of IGF-1 were lower in women with FM compared to healthy controls, even when the groups did not differ on amounts of sleep or wake stages on the night of testing.

Paiva and colleagues (2002) evaluated GH production in response to exercise and found that 20 patients with FM failed to produce an increase in GH as compared to 10 age-matched healthy controls. Subsequent research found pyridostigmine, which inhibits hypothalamic tone thus increases GH release, reversed reduced GH response to strenuous aerobic exercise in FM patients with both normal and abnormal IGF-1 levels (Paiva, Deodar, Jones & Bennett, 2002). To further evaluate the effect of pharmacologic and physiologic manipulation of the HPGH/IGF-1 axis, Jones and colleagues (2007) conducted a double blind, placebo controlled study, which randomized 165 FM subjects to one of four arms: pyridostigmine/exercise, pyridostigmine/diet recall, placebo/exercise, or placebo/diet recall. Although six months of daily oral pyridostigmine and triweekly exercise failed to improve the IGF-1 levels of patients with FM, there was significant improvement in anxiety and sleep in the pyridostigmine group and decreased fatigue in the exercise group.

Figure 2.4

Diagrammatic representation of modulation of the HPGH/IGF-1 axis



Asterisks denote that 2 or more loci of action are recognized. Not shown are numerous other metabolic and hormonal effectors that also activate multiple pathways, (e.g., sex steroids, age, glucocorticoids, diabetes mellitus, obesity, T4, etc.). An unproven role for a putative (as yet unidentified) GHRP-like endogenous ligand is also noted, given that receptors for GHRP ligands are expressed in the hypothalamus and pituitary gland.

(Adapted from Müller, Locatelli, & Cocchi, 1999)

Association of Fibromyalgia with Major Depressive Disorder

Multiple studies have confirmed that the HPA, HPGH, and HPT axes are all involved in FM and MDD and that HPA axis dysregulation plays an important role in the shared neurobiology of FM and MDD (Neeck, 2002; Gold & Chrousos, 2002; Neeck, 2000; Tsigos & Chrousos, 2002; Nestler, Barrot, DiLeone, Eisch, Gold, & Monteggia, 2002; and Schule, Baghai, Zwanzger, Eser, Padberg, Holler, & Ruprecht, 2003). A meta-analysis of observational studies by Henningsen and colleagues (2003) evaluating the commonalities between FM and MDD confirmed there was a definite increase of MDD in patients with FM compared with healthy controls or patients suffering from diseases of similar etiology, e.g. rheumatoid arthritis (see Table 2.2). In 2006, Arnold and colleagues found there was a substantial increase in lifetime psychiatric comorbidities in persons with FM compared to persons with RA including mood disorders, anxiety disorders, eating disorders, substance use disorders, somatoform disorders and psychotic disorders. Specifically, compared to individuals with RA, those with FM were significantly more likely to have comorbid bipolar disorder (12.8% vs. 0%), major depressive disorder (61.5% vs. 27.5%), or major mood disorder (74.4% vs. 27.5%). Individuals with FM were 4.3 times more likely (CI=1.8 to 10) than those without FM to have major depressive disorder (Arnold et al, 2006). Interestingly, there was also an approximate four-fold increase in the prevalence of bipolar disorder in FM subjects compared with RA subjects.

Studies have found both hypoactive and hyperactive HPA axis function in FM and MDD. Crofford and colleagues (1998) and Neeck (2002) found a

hyperactive HPA axis in FM subjects, yet Adler and colleagues (2002) documented research supporting that FM is related to decreased HPA activity and a lowered level of CRH (see Table 2.2). Tsigos and Chrousos (2002) point out that while melancholic (nervous) depression is associated with increased HPA axis activity in depressed non-FM populations, atypical (vegetative) depression is associated with decreased HPA axis activity. They further postulate that a depressed FM population would have similar depression subtype variations in HPA axis function. Yet, to date, no empirical research has been conducted to determine if this is true in a depressed FM population (see Table 2.2).

Table 2.2

Literature review of the neuroendocrine commonalities of FM and MDD

AUTHOR(S) YEAR	TYPE/ DESIGN	SAMPLE SIZE	FINDINGS	COMMENTS
Crawford et al, (1998).	Summary article.	N/A 45 references.	Summarized the neuroendocrine axes that are important in FM and depression. Endorsed findings of a hyper aroused HPA axis and elevated CRH in FM and the common pathways of depression and FM.	The prevalence of FM affecting women 9:1 was discussed and linked to the HPG axis, specifically estrogen alterations.
Neeck, (2002).	Summary article.	N/A 68 references.	Supports the hypothesis that enhanced HPA axis activity and CRH neuron activity in FM and depression is the primary final pathway for symptoms of both disorders. Purports that negative feedback mechanism of glucocorticoids to the pituitary and the brain is impaired.	
Tsigos & Chrousos, (2002).	Summary article.	N/A 47 references.	Separates out melancholic depression as a result of an increased HPA axis and atypical depression as a result of a decreased HPA axis. Lists FM as a result of decreased HPA activity. Contradicts two of the leaders in the field of FM.	Link between the HPG axis dysregulation and the overrepresen-tation of females who suffer from FM and MDD discussed.

Table 2.2 (Continued)

Literature review of the neuroendocrine commonalities of FM and MDD

AUTHOR(S) YEAR	TYPE/ DESIGN	SAMPLE SIZE	FINDINGS	COMMENTS
Adler et al, (2002).	CME review article.	N/A. 98 references	Purports a hypoactive HPA axis in both CFS and FM.	Discussed prevalence of CFS affecting women 1.8 times more than men and non whites more often than whites. Discussed FM prevalence 7:1 in women, 2% of pop., with increasing risk as age increases.
Henningsen et al, (2003).	Meta-analysis of observational studies.	Varied; from n=11 to n=18,690. From 2667 kept 244 studies. Effect sizes were highly significant, e.g.: FM and amount of depression sx's 0.287-0.481.	Meta-analytic integration confirmed pt's dx'ed with FM suffer from depression at a higher rate than controls or pt's with similar diseases of known pathology. Supports the common pathways of FM and depression.	HPA axis addressed, but no statement regarding dysregulation made. States depressive sx's that are in common with FM cannot be globally defined as the bodily manifestation of depression nor can they be defined as due solely to FM.

While the above studies have laid the theoretical groundwork for supporting the hypothesis of shared biological underpinnings of these two diseases, there is still a significant gap in the literature regarding how co-morbid FM and MDD directly affect the HPA axis. Only one study to date has empirically evaluated the common biochemical dysregulation of the HPA axis hormones of FM patients with concurrent MDD.

Ataoglu and colleagues (2003) conducted a study to see if there was a neurobiological connection between FM and MDD. They hypothesized that if there was a connection, FM patients without MDD should, like depressive patients, fail to suppress cortisol after dexamethasone administration. Their findings showed that the dexamethasone-suppression test (DST) failed to discern a significant difference in plasma cortisol levels between healthy controls and FM subjects and thus concluded no neurobiological relationship between FM and MDD related to the HPA axis existed. It bears pointing out that the sample size was relatively small and the study did not control for different cortisol levels between ADE versus MDE subtypes. Theoretically, if depression subtypes are not identified prior to data analysis, collapsing data for all depressed subjects into one pool for analyses could erroneously result in either decreased or increased cortisol levels. Therefore, it is possible the non-significant findings of the study conducted by Ataoglu and colleagues may have been due in part to not separating subjects into MDD subtypes prior to analyses.

Hypothalamic Pituitary Adrenal (HPA) Axis in FM and MDD

Charney and Manji concluded in their 2004 review of the leading theories

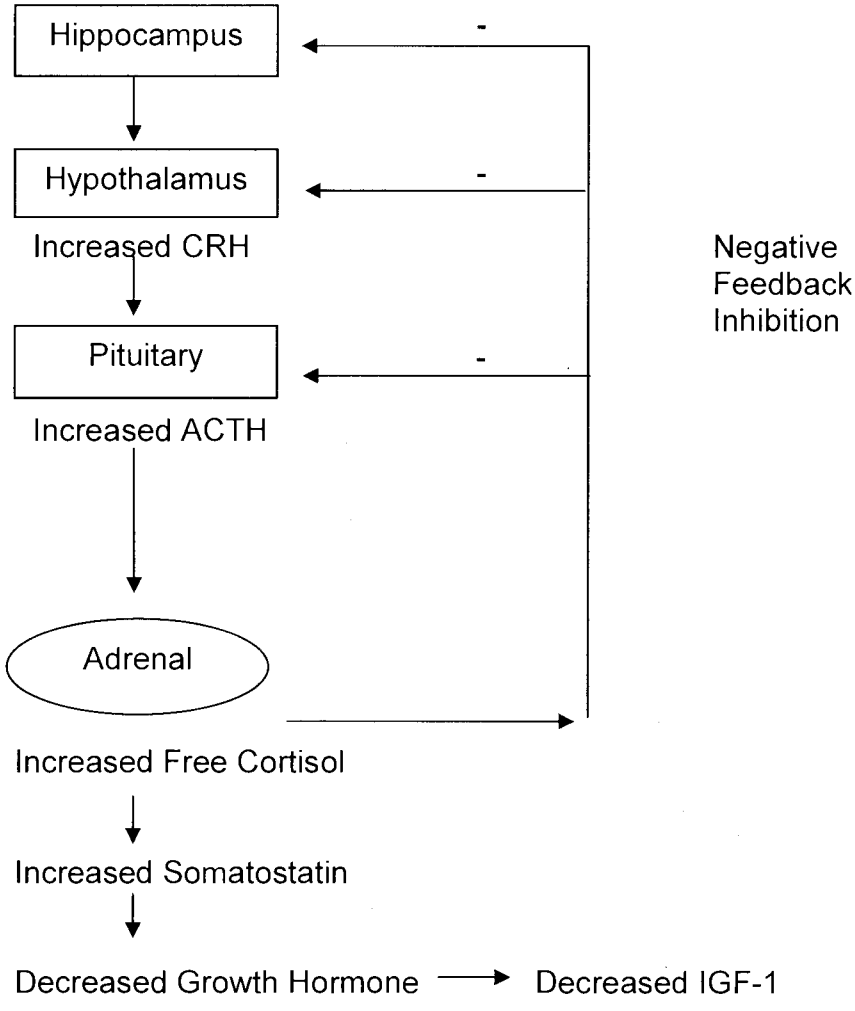
of the etiology of depression that there are multiple factors involved in the development of depression symptoms, among them alterations in the serotonergic, noradrenergic, and the stress systems (HPA axis); genetics; and neural plasticity. Holsboer (2000) reviewed the evidence regarding the corticosteroid hypothesis of depression and found there was extensive evidence to support that the HPA and related axes are significantly altered in depressive disorders. For the purposes of this discussion, the focus will be narrowed to an overview of the HPA and HPGH axes; the serotonin and norepinephrine pathways in the limbic system; and genetics as it pertains to glucocorticoid receptor polymorphisms and impaired glucocorticoid resistance in the HPA axis.

Encompassed in the limbic system are the serotonin (5HT-2) and norepinephrine (NE) pathways. Serotonin interacts with the HPA axis to modulate expression of hormones and also interacts with the NE system. Serotonin-producing neurons project from the raphi nucleus in the brain stem to several other areas in the central nervous system and are involved in emotional affect as well as pain modulation (Nemeroff, 1998; Bennett, 1999) (see Figure 2.2). Norepinephrine neurons project from the LC to various areas in the brain and are also involved in emotional affect as well as pain modulation (Nestler et al, 2002; Bennett, 1999). Serotonin and NE innervate all of the limbic structures in the brain including the hippocampus, hypothalamus, and the amygdala. Decreased serotonin and NE levels result in increased pain sensations. These pathways also innervate the HPA axis organs in the brain (hypothalamus, anterior pituitary) and secondarily the full HPA and related axes.

The hypothalamus contains paraventricular neurons (PVN) that secrete and release CRH during stress (Gutman, Gutman, & Nemeroff, 2003). CRH is transported to the anterior pituitary and stimulates the pituitary gland to secrete ACTH into the bloodstream. The release of ACTH stimulates the production and release of cortisol from the adrenal cortex resulting in elevated cortisol levels (Gutman, et al., 2003), which lead to decreased GH and IGF-1 levels. In an intact HPA axis, elevated cortisol levels inhibit CRH and ACTH release at the level of PVN and pituitary gland thus returning the system to homeostasis (Nemeroff, 1998). In brief, the hypothalamic-pituitary-adrenal, hypothalamic-pituitary-growth hormone, and hypothalamic-pituitary-thyroid axes are all involved in MDD as well as FM.

CRH is the main mediator of the HPA axis (Tsigos & Chrousos, 2002). It is a 41-amino-acid neuropeptide that regulates the behavioral, immune, and autonomic aspects of the stress response (Gutman, Gutman, & Nemeroff, 2003). Vale and colleagues initially discovered CRH in 1981, and subsequent research has produced strong evidence that links CRH, cortisol, and growth hormone/IGF-1 imbalances to FM and MDD (Gutman, et al., 2003; Neeck, 2002). In addition, CRH stimulates the release of somatostatin from the hypothalamus, which decreases pituitary release of GH secretion (see Figure 2.5).

Figure 2.5. HPA axis feedback loop dysregulation in FM and MDD.



In an intact HPA axis, the above process works to rebalance the system by communicating to the hypothalamus to decrease CRH release, which brings the HPA system back into homeostasis. In the dysfunctional HPA axis, the negative feedback mechanisms become blunted and are not able to keep the system in homeostasis. This contributes to further alterations of other hormonal systems and affects other processes as well. For instance, decreased sensitivity to cortisol and other glucocorticoids is thought to be related to glucocorticoid

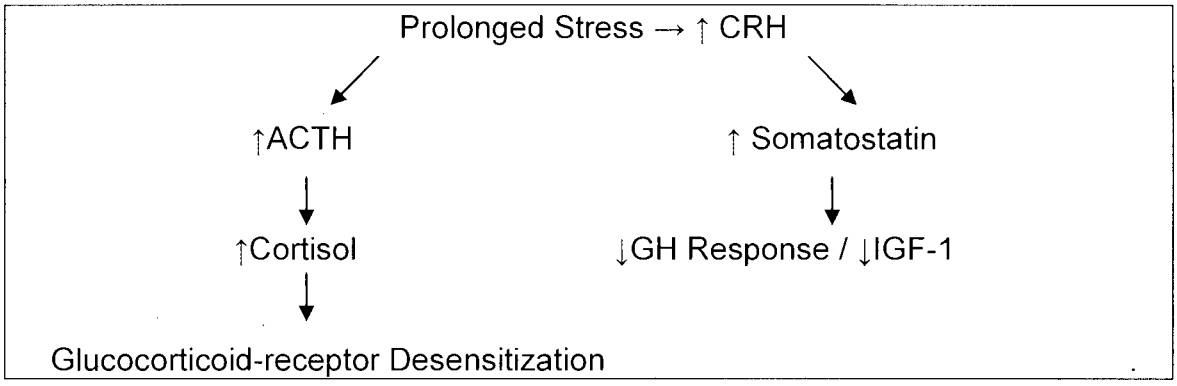
receptor gene dysfunction.

Glucocorticoid Receptor System

Clinical studies have demonstrated HPA axis impairment and elevated levels of cortisol in patients with FM and MDD, which is thought to be due, in part, to an impairment of the GR-mediated negative feedback mechanism (see Figure 2.2) (Holsboer, 2000; Pariante & Miller, 2001). This two-tiered corticosteroid-receptor system is comprised of high and low affinity receptors, the minerocorticoid receptor (MR) and the glucocorticoid receptor (GR), which modulates the effects of cortisol during stress on both central and peripheral systems (de Kloet, Vreugdenhil, Oitzl, & Joels, 1998). Glucocorticoid actions are exerted through the glucocorticoid receptor, which is a member of the steroid/thyroid/retinoic acid nuclear receptor family (Bamberger, Schulte, & Chrousos, 1996; Kino, DeMartino, Charmandari, Mirani & Chrousos, 2003.) Several GR-gene variants and polymorphisms have been discovered and are relatively common in humans (Huizenga, De Lange, Pols, Stolk, Burger, Grobbee, et al, 1998; van Rossum, Binder, Majer, Koper, Ising, Modell, et al, 2006; van Rossum & Laberts, 2004; van Rossum, Roks, de Jong, Brinkmann, Pols, et al, 2004).

Figure 2.6

CRH Driven HPA Interactions in FM and MDD



The clinical implications of GR-gene polymorphisms, which contribute to the dysregulation of the HPA axis, is that they are beginning to be considered as primary targets of new drug research for the treatment of stress related disorders (DeRijk, Schaaf, & de Kloet, 2002; van Rossum et al, 2006). Tsigos and Chrousos (2002) recommended that research into medications that may attenuate the HPA axis are necessary to decrease the symptoms of depression, anxiety and other related diseases such as FM. Gupta and colleagues (2007) recently developed a model of depression including the glucocorticoid receptor and the HPA axis. This work resulted in a biologically plausible model in which to investigate mechanisms underlying disorders of the HPA axis, including FM and MDD.

Fibromyalgia Subtypes

The importance of considering patient heterogeneity in the FM population has become a topic of much interest. In Thieme, Turk and Flor's (2004) investigation to determine the prevalence as well as predictors of psychiatric

disorders in patients with FM, they determined that there are three distinct psychological subgroups in FM based on coping styles. The three groups were designated Dysfunctional (DYS), Interpersonally Distressed (ID), and Adaptive Copers (AC). The DYS group mainly demonstrated anxiety while the ID group mostly demonstrated depression, and the AC group showed little co-morbidity of psychiatric disorders. In conversation with Dr. Dennis Turk (personal communication, November, 2005) supported the theoretical basis of there being other potential subtypes of FM based on biochemical markers of depression subtypes in FM.

This research informed the current study in that it supported a basis for the need of a broader conceptualization of patients with FM. It also supported those patients with mood disorders demonstrate the highest levels of emotional distress and thus are in need of psychosocial as well as pharmacological interventions.

Major Depressive Disorder Subtypes

Although five different subtypes of depression are discussed in the literature, the DSM-IV-TR (APA, 2001) only identifies two subtypes of MDD: melancholic depressive episodes (MDE) and atypical depressive episodes (ADE). These two subtypes combined represent approximately 60% of all MDD cases (Levitan, Lesage, Parikh, Goering, & Kennedy, 1997). Research by Gold and colleagues (2002) supports that there are two different HPA axes dysfunctions occurring in depression – *hyperactivity* (suggestive of melancholic depressive episodes) and *hypoactivity* (suggestive of atypical depressive

episodes). The two subtypes are biologically distinct and exhibit differential biochemical markers and clinical characteristics (see Table 2.3). The MDE subtype has been found to correlate with a *hyperactive* HPA axis and *elevated* plasma CRH and cortisol levels (Gold, Graby, Yasuda & Chrousos, 2002). The ADE subtype has been found to correlate with a *hypoactive* HPA axis and *low* CRH and cortisol levels (Gold et al., 2002). Between the two subtypes, it can be argued that the majority of clinical symptoms observed in FM more closely resemble ADE and would thus support the findings of low CRH and plasma cortisol levels found in these two disorders (see Table 2.3). Upon consultation with Dr. George Chrousos (2005), the theoretical framework for this study was found to be scientifically sound and consistent with the current knowledge base in FM/MDD research.

Table 2.3

Physiological and psychological differences of MDE compared to ADE.

Symptom/ Characteristic	**Melancholic Episode**	**Atypical Episode**
Level of Arousal	*Hyper*aroused	*Hypo*aroused, Apathetic
Anxiety Level	Anxious	Generally not anxious
Mood Reactivity	Unreactive to environment	Brightens with positive events
Energy Level	Overt energy level variable	Marked lethargy and fatigue
Cognition	Decreased concentration	Loss of focus
HPA Axis	Centrally-activated *(Hyperactivity)*	Centrally-mediated *(Hypoactivity)*
GH Axis (IGF-1)	Suppressed (Decreased)	Suppressed (Decreased)
CRH Levels	Increased	Decreased
Cortisol Levels	Increased	Decreased
Body Mass Index (BMI)	Normal	Higher fat to muscle ratio
Sleep	Decreased, poor quality	Increased, poor quality
Appetite	Decreased, loss of weight	Increased, weight gain

(Adapted from Gold & Chrousos, 2002)

The existence of subtypes of MDD in depressed populations is well established (see Table 2.4) (Anisman et al, 1999; :Levitan et al, 2002; Young et al, 2001; de Winter et al, 2003; Ataoglu et al, 2003).

Table 2.4

Review of literature related to the psychoneuroendocrinology of FM and MDD

1. Authors **2. Research Question / Hypothesis** **3. Purpose** **4. Framework**	**1. Study design** **2. Time period** **3. Sample** **4. Setting**	**1. Measurements** **2. Variables**	**1. Results**	**1. Major findings** **2. Limitations** **3. Implications / Future Research**
1. Ataoglu, S., Adnan, O., Yildiz, O. & Ataoglu, A (2003). Evaluation of dexamethasone suppression test in fibromyalgia patients with or without depression. *Swiss Medical Weekly. 133(15-16):241-4.* 2. If there is a neurobio-logical connection between FM and MDD, FM patients without depression should, like depressive patients, fail to suppress cortisol. 3. To investigate whether the DST reveals any neurobiological relation-ship between FM and depression r/t the HPA axis. 4. Physiological.	1. Experimental design using chemical assay to measure the levels of cortisol after a DST challenge in subgroups of people with FM. 2. Over 6 days. 3. 26 FM patients without depression, 20 FM patients with depression, and 20 healthy controls. 4. Inpatient basis in Turkey- no further information.	1. 17 item Hamilton Depression Rating Scale; DST measuring cortisol suppression. 2. The presence of depression and FM; intake of NSAIDS and/or antidepressants; and cortisol suppression rates.	1. Cortisol levels were found to be significantly higher in response to the DST in FM patients with depression versus FM patients without depression and healthy controls. Cortisol level differences between FM patients without depression and the control group was not significant.	1. Findings show that the DST reveals no neurobiological relationship between FM and depression related to the HPA axis. 2. Did not control for Atypical versus Melancholic Depression; relatively small sample size; use of the DST versus the combined DST/CRH stimulation test; and did not discuss the hypoactive HPA axis in FM supported by other studies.

Table 2.4 (Continued)

Review of literature related to the psychoneuroendocrinology of FM and MDD

1. Authors **2. Research Question / Hypothesis** **3. Purpose** **4. Framework**	**1. Study design** **2. Time period** **3. Sample** **4. Setting**	**1. Measurements** **2. Variables**	**1. Results**	**1. Major findings** **2. Limitations** **3. Implications / Future Research**
1. Levitan RD. Vaccarino FJ. Brown GM. & Kennedy SH (2002). Low-dose dexamethasone challenge in women with atypical major depression: pilot study. *Journal of Psychiatry & Neuroscience. 27(1):47-51.* 2. Compared matched normal control group to women with ADE to see if would exhibit hyper-suppression of cortisol after low doses of DEX. 3. To determine if ADE may be associated with hyper-suppression of the HPA axis. 4.: Physiological.	1. Experimental design to determine the optimal dosage of dexamethasone when measuring cortisol suppression in atypical depression. 2. 1 week. 3. 11 controls and 8 consecutive female outpatients diagnosed with atypical depression matched on age and body mass index. 4. Consecutive outpatients presenting to the Depression Clinic who met the DSM-IV criteria for Major depression with atypical features (MD-AF). Controls were recruited via posters and newspaper ads at the University of Toronto.	1. 29-item Structured interview Guide for the Hamilton Depression Rating Scale (SIGH-SAD) with an eight item subscale to assess atypical symptoms of depression; DST test; 2. Age, body mass index, presence or absence of MD-AF, cortisol.	1. The results of the 0.5 mg dose of DEX on the mean suppression of morning cortisol levels was greater in patients with ADE (91.9%, SD= 6.8%) than that of the controls (78.3%, SD= 10.7%, $p<0.01$). The results of the 0.25 mg dose were not significant. Results suggest that ADE may be a biologically distinct mood disorder.	1. Adds to the growing body of knowledge that suggests that atypical depression may be associated with exaggerated negative feedback regulation of the HPA axis unlike melancholic depression. 2. Small sample size; use of the DST versus the combined DST/CRH stimulation test; did not assess for the confounding variable of childhood trauma. 3. Need to add an interpersonal trauma questionnaire to rule out childhood trauma as the potential reason for low cortisol levels.

Table 2.4 (Continued)

Review of literature related to the psychoneuroendocrinology of FM and MDD

1. Authors **2. Research Question / Hypothesis** **3. Purpose** **4. Framework**	**1. Study design** **2. Time period** **3. Sample** **4. Setting**	**1. Measurements** **2. Variables**	**1. Results**	**1. Major findings** **2. Limitations** **3. Implications / Future Research**
1. Anisman, H., Ravindran, A.V., Griffiths, J., & Meral, I. Z (1999). Endocrine and cytokine correlates of major depression and Dysthymia with typical or atypical features. *Molecular Psychiatry, 4*, 182-188. 2. Unstated. 3. To determine whether cytokine alterations associated with depression were related to the neurovegetative symptom profile or to the chronicity of the illness. 4. Framework: Physiological.	1. Experimental design using observational methods to measure and correlate levels of cytokine alteration with subtypes of depression. 2. Varied based on washout periods from one to seven weeks. 3. 27 controls, 14 depressed subjects, 31 atypical depressed subjects, 14 dysthymic subjects, and 15 atypical-dysthymic subjects. 4. Consecutive referrals (outpatient) to the Mood Disorder Clinic of the Royal Ottawa Hospital.	1. HAM-D, MADRAS, & BDI. 2. Chronicity of illness, subtype of depression, ACTH, cortisol, IL-1, and IL-2.	Atypical depressive's plasma ACTH was elevated while cortisol was reduced relative to controls. IL-1beta production was increased in Dysthymic patients, and was highly correlated with age-of-onset and duration of illness. IL-2 production was reduced in each of the groups, although less so among atypical major depressives.	1. Circulating cytokines influence neuroendocrine functioning and may affect neurovegetative features. A role for interleukins may exist with respect to the pathophysiology of certain subtypes of depression. 2. None identified at this point. 3. Further research regarding IL needs to be conducted before the full impact on subtypes of depression can be identified.

Table 2.4 (Continued)

Review of literature related to Major Depressive Disorder Subtypes

1. Authors **2. Research Question / Hypothesis** **3. Purpose** **4. Framework**	**1. Study design** **2. Time period** **3. Sample** **4. Setting**	**1. Measurements** **2. Variables**	**1. Results**	**1. Major findings** **2. Limitations** **3. Implications / Future Research**
1. Young, E.A, Carlson, N.E., & Brown, B. (2001). Twenty-four-hour ACTH and cortisol pulsatility in depressed women. *Neuropsychopharmacology 25*(2), 267-276. 2. Does an increased ACTH secretion occur in women with depression and if so are there changes in the pulsatile components of ACTH secretion? 3. To determine if any of the CNS controlled HPA axis rhythms differed between depressed patients and controls matched for age and menstrual cycle day. 4. Physiological	1. Experimental biological assessment using matched controls. 2. 24 hour evaluation of ACTH/Cortisol with 10 minute serum sampling. 3. 25 pre-menopausal depressed women (20-50) matched with non-depressed women by age and menstrual cycle day. 4. Recruited from pt.'s presenting to University of Michigan Mood Disorders Program. Admitted to the GCRC at UM for 26 hours.	1. Structured Clinical Interview for DSM-IV (SCID-IV), Structured Clinical Interview – non-patient version (SCID-NP), Hamilton Depression Rating Scale (Ham-D), hormone assays of ACTH and Cortisol, 24-hour urinary free cortisol. 2. Depressed versus non-depressed, subtype of depression, age and menstrual cycle day.	1. As a group, the depressed women demonstrated a trend towards increased cortisol secretion, but it was not significant. Women with AD demonstrated cortisol levels reflective of matched controls. Women with endogenous (MD) depression had a slightly higher cortisol level, however it was also not statistically significant. There was no evidence of changes of pulsatility freq. of cortisol over 24 hrs.	1. Data suggest that the pulsatile and circadian components of the HPA axis are normal in premenopausal depressed women and that only 24% of depressed women demonstrate hyper-cortisolemia (MD subjects.) This corresponds to prior research studies. Also validated by other studies is the finding that age affects cortisol secretion. 2. Small sample size of subgroups. Did not to identify the subgroups. 3. Future research is needed to examine the HPA axis (and cortisol and other hormone levels) in an open loop state to elucidate the origins of HPA axis dysfunction.

Table 2.4 (Continued)

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1. de Winter, R.F. P., van Hemert, A. M., DeRijk, R.H., Zwinderman, K.H. et al (2003). Anxious-retarded depression : Relation with plasma vasopressin and cortisol. *Neuropsychopharmacology, 28*, 140-147. 2. Elevated AVP levels will be demonstrated in a sub-category similar to melancholic depression and cortisol levels will also be elevated. 3. To determine whether the plasma AVP level would be elevated in anxious-retarded depression, melancholic depression, and anxious-retarded melancholic depression and if the cortisol levels were correlated to this elevation. 4. Physiological.	1. Correlational cross-sectional prospective follow-up study. 2. 2 years. 3. 81 patients with major depression. 4. Recruited from an outpatient university clinic in The Netherlands (Rijneest Groep).	1. Psychopathological assessment measured by a semi-structured interview. Plasma AVP and total plasma cortisol were measured via biochemical assay procedures. 2. Subtypes of depression, AVP and cortisol levels.	1. Patients with anxious-retarded depression had a highly significant AVP-cortisol correlation. Log-transformed mean plasma AVP values were higher in patients with anxious-retarded depression than in patients with nonanxious-retarded depression. Patients with anxious retarded melancholic depression also had a significantly elevated level of plasma AVP and a highly significant correlation between plasma AVP and cortisol levels. The correlation was low in patients w/ melancholic depression.	1. Anxious-retarded depression may be a useful refinement of the melancholic subcategory with regard to dys-regulation of the HPA axis and plasma AVP release. 2. People left on all medications. Did not discuss the common features of newly defined subcatagories and atypical depression. 3. Need further research to determine if this is a viable subtype of depression. 4. The 2-dimensional refinement of the MDE subcategory may be useful in future to further define AVP-related dysfunction of the HPA axis.

Currently, there is renewed controversy regarding the validity of the diagnostic criteria for the atypical depressive episode subtype as defined in the DSM-IV-TR (APA, 2001). A study by Posternak and Zimmreman (2002) found only weak to modest associations between most of the atypical symptoms, and found no association between the mandatory criteria of mood reactivity (DSM-IV-TR Criteria A). They did report a strong association between anxiety and atypical depression, but it was unclear if this was associated with the presentation of the ADE symptomology or whether it was more representative of a personality disorder separate from ADE. One study by Parker and colleagues (2002) found the mandatory DSM-IV-TR criteria of mood reactivity did not show specificity in relation to any of the other four criteria. While the authors presented a strong critique of the current criteria and postulated the need to define a more clinically and heuristically useful set of diagnostic criteria, more research and discussion is needed to produce such a viable alternative (Parker, Roy, Mitchell, Wilheim, Malhi, Hadzi-Pavlovic & Dusan, 2002). Therefore, the current criteria were used as it is the prevailing method for the diagnosis of ADE.

Psychological Characteristics of ADE Compared to MDE

The DSM-IV-TR (APA, 2001) defines a *melancholic depressive episode* as having either a loss of pleasure in all, or almost all, activities or a lack of mood reactivity to usually pleasant stimuli. In addition, one must also experience at least three of the following: depressed mood which is regularly worse in the morning; early morning awakening; marked psychomotor retardation or agitation; anorexia or weight loss; or excessive or inappropriate guilt. An a*typical*

depressive episode is defined by the DSM-IV-TR (APA, 2001) as having mood reactivity (mood brightens when positive events occur) and two or more of the following: increased appetite or weight gain; hypersomnia; leaden paralysis; or longstanding patterns of interpersonal rejection sensitivity that results in significant social or occupational impairment (see Table 2.5).

Table 2.5

DSM-IV-TR Diagnostic criteria for MDE and ADE

MDE CRITERIA	ADE CRITERIA
A. Either loss of pleasure in all, or almost all, activities	***Exclusionary Criteria*** Criteria not met for MDE during the same episode.
A. Lack of reactivity to usually pleasurable stimuli (does not feel much better, even temporarily, when something good happens.	A. Mood reactivity (i.e., mood brightens in response to actual or potential positive events)
B. distinct quality of depressed mood (i.e., the depressed mood is experienced as distinctly different from the kind of felling experienced after the death of a loved one)	B. Significant weight gain or increase in appetite
B. depression regularly worse in the morning	B. hypersomnia
B. early morning awakening (at least two hours before usual time of awakening)	B. leaden paralysis (i.e., heavy leaden feelings in arms or legs)
B. marked psychomotor retardation or agitation	
B. significant anorexia or weight loss	
B. excessive or inappropriate guilt	

Physiological Characteristics of ADE Compared to MDE

A review of the literature reveals significant evidence that supports the distinct physiological characteristics of MDD subtypes, and more specifically the

subtypes of ADE and MDE. Levitan and colleagues (2002) found that atypical depression is associated with an exaggerated negative feedback regulation of the HPA axis resulting in lower cortisol levels (see Table 2.4). Anisman and colleagues (1999) demonstrated that people with ADE had elevated plasma ACTH while cortisol was reduced relative to controls plus that there was a role for interlukins with respect to the pathophysiology of MDD subgroups. De Winter and colleagues (2003) investigated whether elevated plasma arginine vasopressin (AVP) levels in anxious-retarded depression (ADE), melancholic depression (MDE) and anxious-retarded melancholic depression would be related to cortisol levels. They found that patients with ADE had highly significant AVP-cortisol ratio correlations versus patients with MDE.

Further investigation is needed to clarify the differences reported by these innovative thought leaders. Although some of the divergent findings may be due to differences in study design, settings, and sample sizes, an alternative rationale is that differences in cortisol levels in prior research stem from different neuroendocrine processes that occur in depression subtypes of persons with FM and concurrent MDD.

Also, the DST has traditionally been used to measure HPA function in depression research versus the more sensitive and specific combined DEX/CRH stimulation test. However, the sensitivity of the DEX/CRH test for major depression has been found to be approximately 80%, while the average sensitivity of the DST is approximately 44% (Hueser et al, 1994). Using the combined DEX/CRH stimulation test versus the DST to measure HPA axis

function in an FM population may lead to a more accurate reflection of HPA axis function and therefore more significant differences in cortisol levels between depression subtypes. Consultation with Dr. Florian Holsboer, a senior researcher of HPA axis function from the Max Plank Institute in Germany, supported the scientific rationale of this theoretical conjecture (F. Holsboer, personal communication, May, 19, 2007).

No prior study has used the combined DEX/CRH stimulation test to measure HPA axis function in an FM population based on depression subtypes. Therefore, there is little information available to assess if its use in an FM population is feasible or if using this test when assessing HPA axis function in a depressed FM population will lead to more significant findings. As the commercially available ovine corticotropin-releasing hormone, Acthrel, costs approximately $400 per dose, the cost/benefit ratio of using the more expensive DEX/CRH test needs to be explored. To address these gaps in our knowledge base, this study incorporated two novel approaches to evaluate the neurobiological relationship between FM and MDD focusing on the HPA and HPGH axes. I hypothesized separating MDD subtypes and using the combined DEX/CRH stimulation test would eliminate potentially confounding variables other studies have experienced.

Summary

In conclusion, a thorough literature review and four consultations with leading researchers in the fields of FM and MDD (Bennett, Chrousos, Turk, & Holsboer) revealed a significant gap in the literature regarding studies identifying

the specific neuroendocrine associations between FM and MDD. The divergent findings of cortisol levels further complicate the interpretation of the limited data available. Gold and Chrousos (2002) postulated separating biological subtypes of depression, such as ADE and MDE, would facilitate the clarification of mechanisms that underlie depression. To my knowledge, no study to date has explored biological subtypes of MDD in an FM population. This represents an important gap in our knowledge base. As discussed in detail elsewhere (Ross & Laraia, 2003), prior research has demonstrated MDD subtypes respond best to different psychopharmacological interventions based on the need to activate or attenuate the HPA axis to correct the underlying dysfunction. Therefore, the current study separated MDD subtypes and pilot tested the newer combined DEX/CRH stimulation test to determine if differences in cortisol levels among non-depressed FM subjects, FM subjects with ADE, and FM subjects with MDE existed. The following specific aims will be investigated: 1) To describe the demographic and clinical characteristics of FM subjects with no MDD, ADE, and MDE, 2) To determine whether there are significant differences in dexamethasone induced suppression of the HPA axis, as evidenced by mean dexamethasone suppression and peak plasma cortisol levels, among FM subjects with no MDD, ADE and MDE, and 3) To explore whether there are differences in the serum insulin-like growth factor-1 (IGF-1) levels of FM subjects with MDE compared to FM subjects with ADE and no MDD.

CHAPTER 3: METHODS

Introduction

This chapter details the study's research design and methods. Particular attention will be devoted to the design, setting, sample, protection of human subjects, inclusion/exclusion criteria, power analysis, selection of measures for study constructs, subject recruitment with sampling strategies, sequence and procedures, and statistical procedures.

Design

This study used a cross sectional, descriptive design. The first aim of the study was tested using a standardized interviewer-administrated structured interview to determine MDD subtype. The second aim was tested using standardized laboratory assays to evaluate HPA axis response, as evidenced by plasma cortisol levels, to dexamethasone and/or corticotropin-releasing hormone stimulation. The third aim was tested using standardized laboratory assays to evaluate plasma IGF-1 levels.

Setting

This study was conducted at an academic medical center in the Pacific Northwest. Subjects attended orientation sessions at the School of Nursing and completed the laboratory protocol at the General Clinical Research Center.

Sample

A convenience sample was selected from a Rheumatology clinic database of over 8,000 FM patients. Preliminary over-sampling of patients from neighborhoods known to be ethnically diverse was done to increase minority

inclusion. Patient flow is detailed under recruitment procedures. Subjects 18 years old and above were recruited for the study. The broad age range increased inclusiveness and heterogeneity of the sample, which allows for generalization to a larger population. This study targeted primarily women as they represent 80%-90% of individuals affected by FM (Wolfe, Anderson, Harkness, Bennett, Caro, et al, 1997; Bennett, Jones, Turk, Russell, & Matallana, 2007). However, men were also included in the sample as they present with FM in Rheumatology practices also.

Inclusion and Exclusion Criteria

English speaking men and women of all ethnic groups were recruited to participate in this research study. Efforts were made to approach communities in areas of Portland, Oregon with a diverse population to increase the potential recruitment of ethnic minorities. As Portland is predominantly white (82.6%), the Hispanic/Latino (3.2%), African American (5.3%), Asian American (5.3%), and Native American or Alaskan Native (1.2%) populations were over-sampled to obtain as close to a representative sample as possible (U.S. Census Bureau, 2000).

Potential subjects were excluded if they had severe depression or suicidal ideation. They were also excluded if they had any medical condition or were taking any medication that might have had confounding effects on the HPA axis. Table 3.1 lists further inclusion and exclusion criteria with rationale.

Table 3.1

Inclusion and exclusion criteria with rationale

Inclusion Criteria	Rationale
1. Female or male aged 18 and above.	1. It was appropriate to include women and children over 18 in the study as FM occurs in these groups. It also occurs in children under 18, but IGF-1 is age dependent and their inclusion in this study would have potentially confounded results for the third aim.
2. Diagnosis of FM as per the 1990 ACR criteria for 3 or more years.	2. Necessary criteria for group characteristics. A 3 year limit was chosen based on previous research experience by the team as they note that patient soften alter their medications extensively during the first 3 years of diagnosis. Such medication changes could potentially alter the HPA and GH Axis, confounding aims 2 and 3.
3. Willing to maintain a steady treatment regime during the 4 weeks of the study.	3. Changes in treatment regime may introduce confounding variables.
4. Able to speak and read English at a sixth grade level.	4. The interviews and forms are in English thus requiring this skill.
Exclusion Criteria	**Rationale**
5. A BDI score greater than 31.	5. A score of 31 and above indicates potentially severe depression. It was unethical and unsafe to enroll severely depressed people into a study and ask them to maintain their treatment regime without changes for 4 weeks when there are antidepressant treatments that have been proven efficacious in FM.
6. Any medical disorder that alters the HPA axis or puts the person at increased risk related to DEX/CRH testing.	6. Contraindications of DEX use are current untreated infections such as viral, fungal, or tuberculosis diseases of the eyes. Dr. Bennett, the study's medical director, screen for medical contraindications to study inclusion.
7. Suicidal ideation.	7. Suicidal ideation is a psychiatric emergency and may require changes in medication regimes or hospitalization.
8. Pregnant or nursing mothers.	8. Dexamethasone is a pregnancy category C drug and it is not known if it crosses into breast milk therefore represents a risk to the child.
9. Abnormal thyroid stimulating hormone (less than 0.28uIU/ml or greater than 5.00uIU/ml).	9. Abnormal thyroid function potentially alters GH/IGF-1 levels and symptoms of hyper and hypothyroidism may mimic depression.
10. Planned elective surgery during the 4 weeks of the study period.	10. Prior studies by the FM Research Team at OHSU have lost subjects to attrition due to elective surgery.
11. Weight change of 15 pounds or more during the 3 months prior to the study or active weight loss as a result of a weight loss regime.	11. Significant weight loss or gain prior to and during the 4-week trial could influence IGF-1 levels.

Protection of Human Subjects

The human subjects as described in Appendix D included adult men and women ages 18 and older diagnosed with FM. Some also met diagnostic criteria for major depressive disorder. The inclusion of depressed subjects with FM was necessary as the purpose of the study was to evaluate MDD subtypes in FM. The benefits of this research were determined by the OHSU IRB to outweigh the minimal risk of the study. Persons less than 18 years old were excluded because of the significant difference in FM manifestation, HPA function, and treatment of depression in this age group. Pregnant women were excluded due to the potential risk from dexamethasone and corticotropin-releasing hormone to harm the fetus. Nursing mothers were also excluded. Pregnancy status was determined via self-report of potentially being pregnant at the time of the study. For women who were capable of reproduction, confirmation of pregnancy status was offered using a standard urine pregnancy test. However, all women of childbearing ages denied the possibility of being pregnant thus no pregnancy tests were administered.

Power Analysis

There are no reports in the FM literature regarding depression subtypes in FM. Therefore the study was powered on the second aim. A power level of 0.80 and an alpha of 0.05 are generally thought to be adequate for the behavioral sciences (Cohen, 1988). An alpha level of 0.05 indicates that the probability is less than 5% on any one test of the null hypothesis that the relationship between the variables is due to chance alone. No study to date had measured cortisol

levels in subjects with FM based on subtypes of MDD. Therefore, to estimate the sample size required to detect a significant effect, the power analysis was based on data from two separate studies (see Table 3.2). A study by Young and colleagues (2001) evaluating the plasma levels of cortisol between women with ADE, MDE, and non-ADE/non-MDE was used to determine the differences in cortisol levels between ADE and MDE subjects (non-FM). A study by Ataoglu and colleagues (2003) evaluating the levels of cortisol among healthy controls, FM subjects with no MDD, and FM subjects with MDD was used to determine the differences in cortisol levels between FM subjects with and without MDD.

Based on the data from Young and colleagues' research (2001) on plasma cortisol levels with MDE, ADE, and non-MDE/ADE subjects, this study had 98% power to detect an effect size difference of d=1.27 between groups with 20 subjects in each group and an alpha level of .05. Based on the data from Ataoglu and colleagues' study (2003), this study had 89% power to detect an effect size of d=1.09 with 20 subjects in each of three groups and an alpha level of .05. Regarding the specific comparison of plasma cortisol levels between individuals with FM and MDD and those with FM and no MDD, this study had 79% power to detect an effect size difference of d= .68 among these groups with 27 subjects in each group and an alpha level of .05. As this was a novel pilot project, I intended to recruit the target sample size of 30 subjects per diagnostic group to allow for attrition or exclude outliers.

Table 3.2

Mean plasma cortisol levels (SD) in FM and MDD subtypes

AUTHORS	DIAGNOSTIC GROUP	MEAN CORTISOL (ng/dl) (SD)	N
Young et al (2001)	Atypical depression Melancholic depression Non-atypical / Non- melancholic	8.3 (1.9) 12.17 (4.0) 8.7 (1.9)	6 7 7
Ataoglu et al (2003)	FM with depression FM with no depression Healthy Controls	3.72 (2.31) 2.49 (1.11) 2.11 (0.7)	20 20 26

Study Measures

Baseline demographics, clinical characteristics, and biochemical outcomes were measured using three demographic/clinical data collection forms: Current Medication Report, Demographic Data Form, Clinical Data Form; five self-report measures: Beck Depression Inventory- 1973 Revision (BDI), Structured Interview Guide for the Hamilton Depression Rating Scale- Seasonal Affective Disorder- Self report (SIGH-SAD-SR), Fibromyalgia Impact Questionnaire (FIQ), Quality of life Scale (QOLS), Jenkins Scale; one physical exam: Tenderpoints / Cumulative Myalgic Scale (CMS); three serum assays: Thyroid Stimulating Hormone (TSH), Cortisol, Insulin-like Growth Factor-1 (IGF-1); and one interviewer-administered structured interview: Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement (SIGH-ADS). The variables of interest were measured as described in Tables 3.3 and 3.4.

Table 3.3

Instrument/test(s) used to measure study constructs and scale reliability in this sample of FM

Construct (Measure Type)	**Instrument/Test: Number of Questions (Potential Range) (Sample Question)**	**Reliability (Cronbach's α)**
MDD subtype: ADE vs. MDE (Screening and Clinical Measure)	**DSM-IV-TR Diagnostic Criteria** 13 question structured interview (count: 0= no; 1= yes) (Presence of: insomnia/hypersomnia, anorexia/hyperphagia, leaden paralysis, psychomotor agitation/retardation, interpersonal rejection sensitivity, excessive guilt)	**N/A**
MDD severity (Screening and Clinical Measure)	**Beck Depression Inventory-II (1973 Revision) (BDI)** 21 questions (0-63: lower scores= lower depression severity) (I do not feel sad/ I feel sad/ I am sad all the time and I can't snap out of it/ I as so sad or unhappy that I can't stand it)	**R= .87**
MDD severity (Clinical Measure)	**Beck Depression Inventory- Adjusted (BDI-A)** 18 questions (0-52: lower scores= lower depression severity) (Same as BDI except questions re: fatigue, sleep disturbance, and effort to get things done removed.)	**R= .85**
MDD severity (Clinical Measure)	**SIGH-ADS** 21-item Hamilton Depression Scale, 8-item ADS, and 2-item supplement (0-88: lower scores reflect lower depression severity) (What has your mood been like over the past 7 days compared to when you've felt well or ok?)	**R= .87**
MDD severity (Clinical Measure)	**SIGH-SAD-SR** 29 questions (0-88: lower scores reflect lower depression severity) (I have not been down or depressed at all/ I have been feeling somewhat down/ …feeling quite down/ I have been feeling or looking very depressed (others have said so)/ I haven't been able to think about anything else except how bad or depressed I feel.)	**R= .78**
Pain severity (Clinical Measure)	**Tenderpoints/Cumulative Myalgic Scale (CMS)** Physical exam of amount of tenderness at each of the ACR defined 18 standardized tender points (0-54: lower scores reflect lower pain levels) (0-54: lower scores reflect less pain)	**R= .90**

Table 3.3 (Continued)

Instrument/test(s) used to measure study constructs and scale reliability in this sample of FM

Functional impairment FM severity MDD severity Pain Severity (Clinical Measure)	**Fibromyalgia Impact Questionnaire (FIQ)** 10 questions (0-100: lower scores reflect lower impact of FM on functional ability) (Were you able to: Do shopping? Prepare meals? Vacuum a rug? Visit friends or relatives?) (How many days last week did you miss work, including housework, because of fibromyalgia?) (How depressed or blue have you felt overall for the past week?) (How bad has your pain been overall for the past week?)	**R= .85**
Quality of life (Clinical Measure)	**Quality of Life Scale (QOLS)** 16 questions (16-112: lower scores reflect worse quality of life) (How satisfied are you at this time with: Health? Work- job or in home? Material comforts?)	**R= .92**
Quality of sleep (Clinical Measure)	**Jenkins Scale** 4 questions (0-20: lower scores reflect better sleep quality) (How often in the past month did you: have trouble falling asleep? Wake up several times during the night? Wake up after your usual amount of sleep feeling tired or worn out?)	**R= .80**

Table 3.4

Laboratory assays used to measure biochemical markers of interest to study

Plasma **TSH** by Chemiluminescent Assay (Screening Measure)	HPT axis function
Plasma **Cortisol** by Radioimmunoassay (Biological Measure)	HPA axis function
Plasma **IGF-1** levels by Immunoradiometric Assay (Biological Measure)	HPG axis function

Screening Measures

After obtaining informed consent, subjects were screened for eligibility based on overall depression severity measured by the *Beck Depression Inventory- 1973 Revision* (Beck & Steer, 1987). The BDI-II-R is a 21-item scale that assesses intensity of depression in clinical and normal patients and has a reliability of .92 (Beck & Steer, 1987). Each item is a list of four statements arranged in increasing severity about a particular symptom of depression (0= neutral severity and 4= maximum severity) with a maximum score of 63. A score of 31 or higher on the BDI-II-R was chosen as an exclusion criterion as this score indicates potentially severe depression and could necessitate immediate treatment. The BDI-R-II (see Appendix A for all instruments) has been widely used in depression research and has been adapted for use in FM by removing three items from the total score: fatigue, sleep disturbance, and effort to get things done. These symptoms correspond to FM and therefore do not correlate well with MDD and overestimate the level of depression. This adaptation, the BDI-A, has better sensitivity (74%-85%) and specificity (45%-65%) in a FM population than the original (Burckhardt, O'Reilly, Wiens, Clark, Campbell, & Bennett, 1994). A score of 13 or higher indicates a moderate level of depression, while scores above 21 are fairly specific for MDD in FM patients (Burckhardt, et al, 1994). Reliability for scale items of the BDI-R-II was determined to be a Cronbach's alpha of .87 in this sample. Cronbach's alpha for the BDI-A was .85 in this sample (see Table 3.3 for more information regarding instruments used to measure study constructs).

The subtypes of MDD were measured via the criteria set forth in the Diagnostics

and Statistical Manual, 5th edition, (2001) and the *Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement (SIGH-ADS).* This interviewer-administered questionnaire reflects the DSM-IV-TR (APA, 2001) criteria differentiating ADE and MDE. It is based on the 21-item Hamilton Depression Rating Scale (HAM-D) plus includes an 8-item addendum to the scale for atypical neurovegetative symptoms. This scale is a refined version of the Structured Interview Guide for the Hamilton Depression Rating Scale- Seasonal Affective Disorder version (SIGH-SAD). The SIGH-ADS includes all the questions of the SIGH-SAD, and two un-scored questions regarding difficulty awakening and temperature discomfort that indicate ADE. Stewart and colleagues (1998) refined the wording on selected questions from the SIGH-SAD to increase patient understanding, which was expected to increase the reliability of the instrument (CET Organization, personal communication, 2004). The intra-class correlation coefficients were determined to be r=0.95 for the SIGH-SAD, r=0.91 for the Hamilton scale, and r= 0.94 for the atypical symptom scale (Terman, Terman, & Ross, 1998). In this sample, the reliability for scale items as measured by Cronbach's alpha was established to be r= 0.83 for the SIGH-ADS, r= 0.82 for the 21-item Hamilton scale, and r= 0.71 for the atypical symptom scale. While removal of one item would have increased the reliability alpha of the scale to r= .82, removing the item would have decreased the integral meaning of the concept of leaden paralysis and limited the ability to compare results to prior research studies using the full scale. A self-report version (SIGH-SAD-SR) was also administered close to the visit during which the SIGH-ADS was completed to provide a valuable check on interviewer ratings. If greater

than a two-point difference between the SIGH-SAD-SR and the SIGH-ADS was detected, the interviewer questioned the subject further for final scoring. This increased the validity of the interviewer rating.

Urine HCG testing was offered to all females of childbearing age who had the potential of being pregnant. Upon questioning, all female subjects denied the potential of being pregnant (not sexually active, hysterectomy, postmenopausal) and thus no urine HCG testing needed to be performed.

Abnormal levels of *thyroid stimulating hormone* (TSH) are indicative of hypothalamic pituitary thyroid axis perturbations, which may affect HPA axis functioning. Therefore, TSH was measured to eliminate this possible confounding variable. Thyroid stimulating hormone was collected during the laboratory session and analyzed using a chemiluminescent assay on the automated imulite system (Diagnostic Products Corporation, Los Angeles, CA). The analytic sensitivity is .002 uIU/ml. The mean intra-assay precision (coefficient of variation) obtained from four points within the calibration range is 7.1%. The mean inter-assay precision obtained form four different points within the calibration range are 11.1%. Subjects were screened for a TSH of less than 0.28uIU/ml or greater than 5.00uIU/ml with the intent to exclude their data from statistical analyses of cortisol and IGF-1. No abnormal TSH levels were found, thus no cases were excluded based on this criteria.

Primary Outcome Variables

Demographic and Clinical Characteristics

The *Demographic Data Form* collected data regarding age, education,

race/ethnicity, degree of disability, and number of years diagnosed with FM. Clinical data were obtained using an investigator derived *Clinical Data Form,* which assessed past medical history, subjective review of systems, and anthropometric data (height, weight, and body mass index). Height and weight were measured in inches and pounds using a calibrated standing scale (Detecto, Brooklyn, New York). Body mass index was calculated from height and weight.

The *American College of Rheumatology 1990 criteria for confirmation of FM and tender point scores* were collected at the laboratory visit with a standard front and back body pain diagram and a physical exam indicating 11 or more tender points. Eighteen tender points were palpated manually and compared to control sites, exerting 4 kg of pressure to each site per standardized protocol (Wolfe, Smythe, Yunus, Bennett, Bombardier, Goldenberg, et al, 1990).

The *Tenderpoints / Cumulative Myalgic Scale* (CMS) is an eighteen item scale that diagnoses FM as per the ACR 1990 criteria plus rates the amount of pain associated with 4 kilograms of pressure applied to 18 tenderpoints commonly found in FM as described in the ACR 1990 FM criteria (Wolfe et al., 1990). Pain severity was measured by having the subject rate their pain level on a 0-3 scale (0= no pain, 1= some pain, 2= ouch, 3= moves away) when 4 kg of pressure was applied at each site. Higher scores indicate more pain, with a total possible score range of 0 to 54. Number of tender points and total myalgic score were recorded. The principal investigator acknowledges that tender point scores have been called a "sedimentation rate for distress" by some FM investigators (Wolfe, et al., 1997; Cohen, 1999), but I elected to

keep the CMS as 1) the majority of FM trials still employ them, 2) they were the defining criteria that differentiated FM from other chronic pain syndromes in the 1990 ACR criteria, 3) they require minimal examiner time, 4) they provide somewhat objective pain data and 5) did not add to subject burden as number of tenderpoints had to be confirmed for subject entry. Reliability for scale items of the CMS as measured by Cronbach's alpha was established to be .90 in this sample.

The *Fibromyalgia Impact Questionnaire* (FIQ) is an assessment and evaluation instrument developed to measure FM patient status, response to treatment, and outcomes in interventional studies (Burckhardt, Clark & Bennett, 1991). It is designed to measure the components of health status believed to be most affected by FM. The FIQ also includes a single item pain measurement, thus was used in conjunction with the Tenderpoints / Cumulative Myalgic Scale to measure pain severity. Pain is measured by a 10-point visual analogue scale (VAS) anchored by "no pain" and "very severe pain." The test-retest reliability has been documented to range from 0.56 on the pain score to 0.95 for physical function (Bennett, 2005). Internal consistency as measured by Cronbach's alpha, has been established to range from 0.72 to 0.93 in seven translated versions of the FIQ (Bennett, 2005). High construct and convergent validity has been demonstrated in relation to the Arthritis Measurement Scale, the Stanford Health Assessment Questionnaire, Centre for Epidemiological Studies- Depression, and the State-Trait Anxiety Inventory (Burckhardt, Clark & Bennett, 1991; White, Nielson, Harth, Ostbye & Speechley, 2002). Discriminant validity occurs when an instrument discriminates between groups that are known to be different. The FIQ has been shown

to discriminate between healthy controls (people who did not have any chronic painful illness), untreated FM patients, and was sensitive to change in FM patients who completed a 6-month multidisciplinary treatment program or an exercise intervention (Bennett, Burckhardt, Clark, O'Reilly, Wiens, & Campbell, 1996; Jones, Burckhardt, Clark, Bennett, & Potempa, 2002). Reliability for scale items of the FIQ as measured by Cronbach's alpha was established to be .85 in this sample.

The *Quality of Life Scale* (QOLS) is a16-item Likert-type scale that assesses multiple areas of well-being and life satisfaction (Flannigan, 1978). Quality of life is measured on a continuum where 1= terrible and 7= delighted continuum. The possible range of scores is from 16 to 112, with higher scores indicating better well being and quality of life. It has been validated in an FM sample with an internal consistency reliability alpha equaling .82 to .88 and test-retest reliability of .84 (Burckhardt, Woods, Schultz, & Ziebarth, 1989; Burckhardt, Clark, & Bennett, 1991). Reliability for scale items of the QOL as measured by Cronbach's alpha was established to be .92 in this sample.

The *Jenkins Scale* is a 4-item scale that measures the quality of sleep obtained over the proceeding month (Jenkins, Stanton, Niemcryk & Rose, 1988). The scale has a possible range of scores from 0 to 20. Higher scores indicate poorer quality of sleep and restorative processes of sleep. Utilizing data from 6 and 12-month follow-up studies with cardiac surgery patients, the test-retest reliability of the three-item scale was found to be 0.59. Internal consistency coefficients for the three and four-item scales were 0.63 and

0.79 respectively (Jenkins et al., 1988). Reliability for scale items of the Jenkins Scale as measured by Cronbach's alpha was established to be .80 in this sample.

Plasma Cortisol Levels

To test for levels of HPA axis suppression, plasma cortisol levels were measured after pre-treating with 1.5 mg of dexamethasone at 11 p.m. the night before the administering either the standard DST or the combined DEX/CRH stimulation test. The combined DEX/CRH stimulation test is one of the most reliable neuroendocrine function tests for the investigation of HPA system dysregulation in depression (Hueser, Yassouridis & Holsboer, 1994). Deuschle and colleagues (1998) concluded that the combined DEX/CRH stimulation test is more closely associated with the activity of the HPA system than is the DST in healthy and depressed subjects. The sensitivity of the DEX/CRH test for major depression has been found to be approximately 80%, while the average sensitivity of the DST is approximately 44% (Hueser et al, 1994).

A positive DST or DEX/CRH test indicates non-suppression of cortisol (increased levels) thought to be an effect of a *hyperactive* HPA axis, which corresponds to MDE. A negative DST or combined DEX/CRH test indicates suppression of cortisol (decreased levels); it is thought to be an effect of a *hypoactive* HPA axis, which corresponds to ADE. Six blood samples were collected at six different time points over the course of 90 minutes (1445, 1500, 1530, 1545, 1600, 1615) via an intravenous catheter using a commercially available radioimmunoassay (ICN, Cersa, California). Essentially, the DST was conducted using the 1500 time point on all participants who attended the laboratory visit. A subset of 19 subjects also underwent the protocol for the combined DEX/CRH

stimulation test: they received 100 mcg of Acthrel at 1502). The inter- and intra-assay coefficients of variation (CV) are below 7% at an average concentration of 40 ng/ml. All biochemical markers were analyzed at the university's General Clinical Research Center's core laboratory in compliance with standard testing methods.

Insulin-like Growth Factor-1 (IGF-1)

Insulin-like growth factor-1 was collected during the laboratory visit as a measure of daily GH secretion. Plasma was analyzed using an immunoradiometric assay (IRMA, Diagnostic Systems Laboratories, Webster, Texas). The sensitivity of the assay was 0.80ng/dl. The mean intra-assay CV was 2.6% and mean inter-assay CV was 4.5%.

Subject Recruitment

Initially, purposive sampling of existing patient clinical records from the Rheumatology Clinic was conducted. One thousand clinical records from this group were randomly selected via a computer generated random numbers table. The selection of 1000 clinical records was based on a population prevalence rate of 20%-30% for current MDD in persons with FM; and a 30% prevalence rate of ADE and 30% prevalence rate of MDE in persons with MDD.

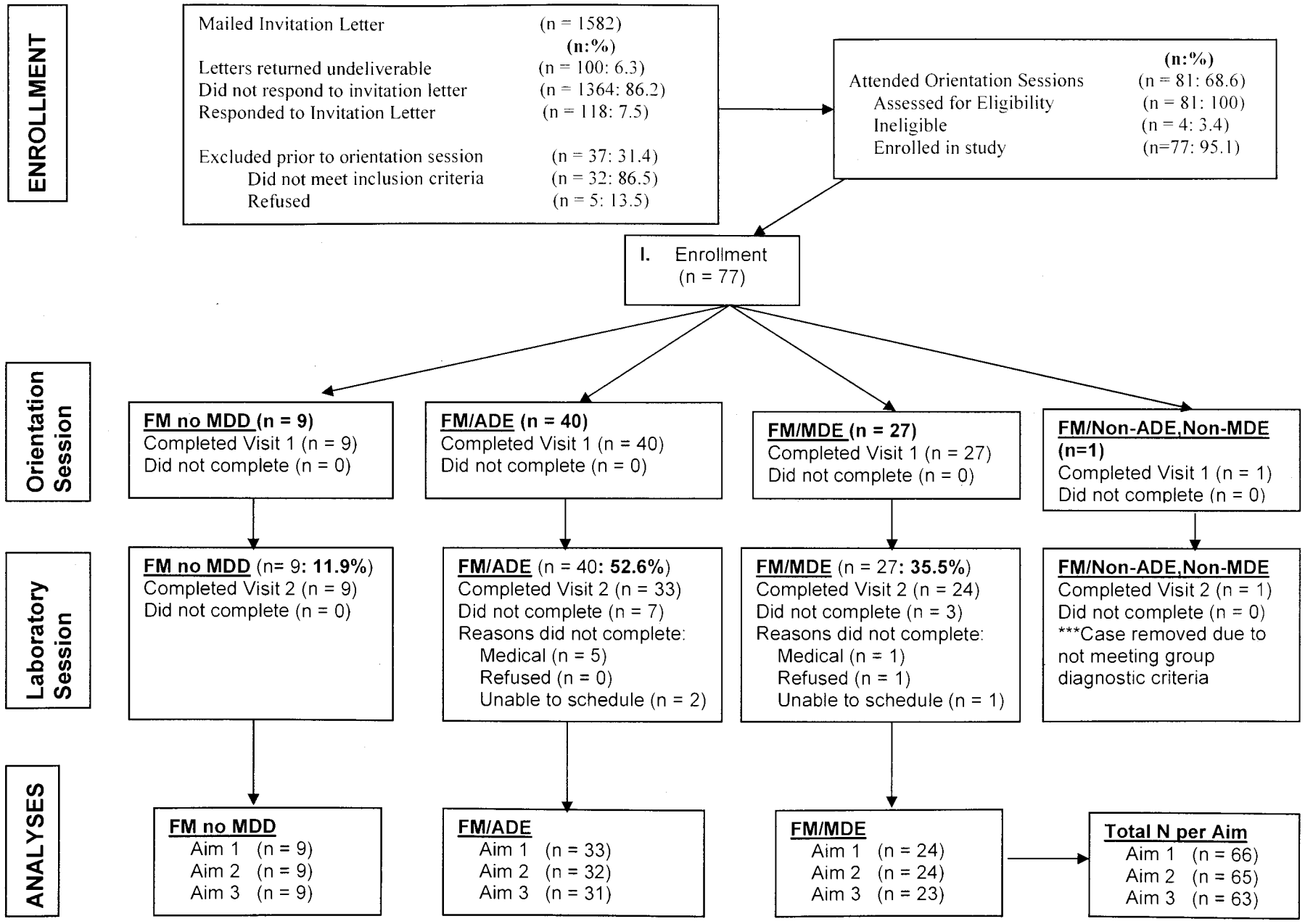
Two hundred twenty FM subjects' records were manually screened for positive responses to an abbreviated DSM-IV MDD criteria checklist taken from the PRIME-MD mood module collected as part of the FM clinic initial assessment profile. Other data gathered were name, address, and abnormal laboratory values. After reviewing 220 charts, 105 potential subjects were identified and mailed an invitation to attend an orientation session. Only four of the 105 potential subjects attended the first orientation

session. Thus, after consultation with the dissertation committee, the recruitment procedure was amended and convenience sampling was used. Recruitment was then opened up to inclusion of all potential FM subjects living within a 120-mile radius of the university.

Recruitment strategies for convenience sampling included handing out recruitment flyers to local FM support groups; placing recruitment flyers in the waiting area of the university rheumatology clinic and a mental health clinic in Salem, Oregon; and a link on the www.myalgia.com site with contact information for the study coordinator.

Prior studies in the FM population at this university have demonstrated a 72% response rate, a 40% participation rate, and a 9% attrition rate in a six-month drug and exercise intervention (Jones, et. al., 2007). A 7-step protocol was then used to invite subjects to enter the study (Reiner & Jones, 2004). Briefly, potentially eligible subjects were mailed an invitation letter. This invitation letter, which included a description of the study and contact information for the principal investigator in case of further questions, was mailed to prospective subjects. All interested persons were invited to attend an orientation session that would inform them of the study design, procedures, risks, and benefits. This strategy resulted in an 8% response rate of mailed invitation letters and a 95.1% participation rate of those who attended the orientation sessions. An attrition rate of 13% was achieved, of which 60% (6/10) was due to medical issues unrelated to participating in the study and 30% (3/10) was due to the subject's inability to schedule the laboratory visit (see Figure 3.1).

Figure 3.1: CONSORT Enrollment Flowchart



Sequence and Procedures

Orientation Sessions

An overview of the study's rationale and the potential risks, benefits and alternatives were explained to potential subjects who attended an orientation session. All subjects completed a university approved informed consent process. The protocols for the DST and the combined DEX/CRH stimulation test (see Appendix B) were explained to subjects and they were educated regarding the need to take a 1.5 mg dexamethasone tablet at 2300 the night before the test. It was further explained that for those who had no contraindications to receiving the CRH stimulating hormone, an injection of Acthrel would be given via an intravenous catheter the day of the laboratory testing. Informed consent was obtained from those subjects who were interested in joining the study. Informed consent was verified by the principal investigator who also obtained consent to call the subject the night before the test at 2255 hours to remind them to take the dexamethasone tablet. A Beck Depression Inventory, Current Medication Report Form, Demographic Data Form and Clinical Data Forms were then given to consented subjects and time was allotted for them to complete these questionnaires. See Table 3.5 for sequence of study instruments and biochemical assays preformed.

Table 3.5
Study timeline with sequence of instruments and biochemical assays

WEEK -4 TO -1: Preliminary recruiting
Identification of Potential Subjects
Mailed Invitation Letter

WEEK 1: Two-hour Orientation Session (5 sessions offered 1/07-8/07)
Informed Consent
Presentation of study design, procedures, risks, and benefits
Inclusion/Exclusion Criteria Checklist
Demographic Data Form
Beck Depression Inventory
Current Medication Report Form
Clinical Data Form Page 1
SIGH-SAD-SR

WEEK 2-3: Four-hour Laboratory Session (Individually scheduled)
SIGH-ADS
Urine HCG Testing as needed
Clinical Data Form Page 2
FM Impact Questionnaire
Jenkins Scale
ACR Criteria Form
Tenderpoints/Myalgia Score
Plasma TSH
Plasma IGF-1
DST Testing with plasma cortisol levels X 6 over 90-minutes
(1445, 1500, 1530, 1545, 1600, 1615)
DEX/CRH Testing with plasma cortisol levels X 6 over 90-minutes
(1445, 1500, [CRH given IV push @ 1502], 1530, 1545, 1600, 1615)

A 4-hour laboratory appointment was scheduled during the luteal phase for menstruating females or within fourteen days of the orientation session for males and non-menstruating females. The subjects were scheduled to arrive at the clinic at 1200 the day of the testing. Although drawing TSH levels during the orientation session was considered, the percentage of altered TSH levels in an actively managed FM population is less than 2%, thus did not warrant adding

another venous puncture to patient burden. Therefore, all biochemical assays were drawn the day of the laboratory visit.

Structured Interview

Upon arrival to the clinic, the patient version of the Structured Interview Guide for the Hamilton Depression Rating Scale-Seasonal Affective Disorder-Self Report (SIGH-SAD-SR) was obtained from the subjects who were instructed to complete it the day before or the day of the testing. The principal investigator administered the SIGH-ADS and then compared the self-report version scores with the SIGH-ADS scores to verify the consistency and validity of the answers. If there were any differences of two or more points on any question, the principal investigator discussed the question with the subject in further detail for clarification. After this interview was completed, the subject was introduced to the General Clinical Research Center's (GCRC) nursing staff.

Laboratory Visit and Procedures

Vital signs. After being oriented to the GCRC and room amenities, height, weight, and vital signs were obtained. Vital signs were also obtained at 1530 for the subset of 19 subjects who received Acthrel at 1502, and at 1630 for all subjects after the last blood draw was obtained and the indwelling catheter was removed.

IV insertion. A registered nurse inserted a peripheral venous catheter in either the subject's hand or forearm. To ensure the vein was patent, 5-10 cc of normal saline flush was given. If the vein became inpatent, a second peripheral venous catheter was placed as an alternative sight.

Blood drawn. Plasma samples of glucose, TSH, IGF-1, and initial cortisol levels were drawn at 1445 and 1500 after a 30-minute rest period. Theoretically, stressful events may increase cortisol secretion, thus the rest period was designed to allow the HPA axis to recover from the venopuncture and novelty of the situation. Blood was drawn from the indwelling catheter on all subjects at four additional time points: 1530, 1545, 1600, and 1615.

Self-report measures. No study to date has indicated that psychological testing such as the Quality of Life Scale or the Fibromyalgia Impact Questionnaire acutely elevates cortisol levels or affects IGF-1 levels, so to maximize the use of subjects' time, self-report measures were completed during the 30 minute rest and 90 minute plasma sampling period.

CRH stimulation. After the 1500 cortisol was drawn, ovine corticotropin-releasing hormone (Acthrel) was administered to a subset of 19 subjects at 1502 per standardized endocrine protocol as described elsewhere (Heuser et al, 1994). Acthrel 100 mcg (Ferring Pharmaceuticals, Inc., Suffern, New York) was diluted in normal saline and injected via an intravenous catheter. Acthrel was not given to those subjects with potential contraindications to CRH administration (cardiac complications, mitral valve prolapse, medications with potential interactions, etc).

Data Analyses

All data analyses were conducted using the Statistical Programs for Social Sciences (SPSS) version 14.0. Missing values were handled conservatively. For returned self-report scales missing more than 5% of data, the subject's data were

not utilized in the specific analysis (n=2). Returned self-report scales were missing less than 5% of the total possible questions (only 3.3%). The statistical tests were computed using available data only. No subjects were excluded from analysis because of missing cortisol or IGF-1 levels.

Basic Assumptions of Parametric Testing

There are three basic assumptions of parametric testing: 1) groups have equal sample sizes, 2) variables are normally distributed in each group and 3) variances of group means are equal. To assure the correct statistical tests were utilized in the data analyses, violations of assumptions were tested prior to running further statistical tests.

Equal Sample Sizes Chi-square tests were used to determine if distribution of the FM/MDD diagnostic groups were equal in size.

Normal Distribution of Variables The distribution of nominal and ordinal demographic variables (gender, education, employment status, occupation, receiving disability payments, marital status, ethnicity, race) was examined for normality using histograms. Screening for normal distribution for interval level demographic variables (age, BMI, number of years with FM symptoms and number of years diagnosed with FM) was conducted using the Shapiro-Wilks W test. The Shapiro-Wilks W test is the standard test for normality. When W=1 the given data are perfectly normally distributed. When W is significantly less than 1, the assumption of normality is not met. Skewness and kurtosis values with histograms were also examined for normality of distribution for both nominal/ordinal and interval level data.

Homogeneity of Variance The assumption of equal variance was tested using the Levine's test of homogeneity of variance on cortisol, IGF-1, and interval level clinical variables (age; BMI; number of years with FM symptoms; number of years diagnosed with FM; FM, MDD, and pain severity; quality of life, sleep quality, number of tenderpoints, impact of FM on ability to function).

Statistical Analyses

Although analysis of variance (ANOVA) is based on the assumptions of normality and homogeneity of variance, it is a robust statistical procedure and the assumptions frequently can be violated with relatively minor effects (Howell, 2002). This is especially true for the normality assumption (Howell, 2002). In general, if the sample can be assumed to be symmetrical and if the largest variance is not more than four times the smallest, the ANOVA is most likely to be valid (Howell, 2002). Therefore, ANOVA with Bonferroni post hoc tests were used to determine differences among the three FM/MDD groups with equal variances of interval level variables. For those variables that violated the Levine's test, Welch's robust test of equality of means with Games-Howell post-hoc tests was used.

The differences between groups on nominal and ordinal level variables were measured using the chi-square (χ^2) test.

Cases Excluded for Aims 1, 2 and 3

Thyroid stimulating hormone plasma levels were within normal ranges for all subjects thus did not need to be controlled for. One subject, who did not meet diagnostic criteria for any of the three groups, was deleted from all further

analyses. This screening error was due to non-disclosure on the self-report forms of psychotic depression, which was excluded from this study due to the potentially confounding effects on the HPA axis. Ten subjects did not complete the laboratory visit: six due to non-study related medical reasons; three were unable to schedule the four hours needed to complete this visit; and one withdrew from the study after the first visit citing health issues and displeasure due to her personal expectations of the protocol not being met. Upon follow-up interview regarding the reason for withdrawal, the subject notified the principal investigator that she was displeased the protocol did not examine and diagnose her with FM at the first session and that she felt one of the study personnel did not exhibit professional decorum. Sixty-six subjects (87% of the original sample recruited) completed the study as detailed on the CONSORT enrollment flowchart (see Figure 3.1).

We were unable to obtain serum samples on one subject due to difficulty accessing and maintaining a patent vein, thus this case was excluded from analyses for aims 2 and 3. One subject's last four cortisol levels (post- Acthrel stimulation) were greater than four standard deviations above the group means and thus increased the potential of making a Type II error (the probability of accepting the null hypothesis when it is indeed false). Therefore, these four data points were deleted from the analyses for Aim 2. One subject's IGF-1 level was 5.8 standard deviations above the group means for the range of age-normed IGF-1values and thus increased the potential of making a Type I error (the probability of rejecting a null hypothesis when it is true). Therefore, the subject's

IGF-1 level was excluded from the analyses for Aim 3.

Completers versus Non-completers

In total, 66 subjects' data were used in the analyses of demographic and clinical characteristics for Aim 1, 65 subjects' data for Aim 2, and 63 subjects' data for Aim 3. Due to unequal variance and sample sizes less than 30, Chi-square with Kuskal-Wallis tests were used to measure significant differences of baseline characteristics between subjects who completed the study compared to those who did not complete the study. No significant differences were noted between completers and non-completers as noted in Table 3.6.

Table 3.6

Differences between completers vs. non-completers on baseline characteristics

Baseline Characteristics	χ^2 **Sig.**
Age in years	.86
Sex	.47
Education	.30
Employment status	.61
Occupation	.15
Receiving disability payments	.24
Number of years with FM symptoms	.31
Number of years diagnosed with FM	.85
Marital status	1.0
Ethnicity	.14
Race	.93

CHAPTER 4: RESULTS

The purpose of the present study was to directly test the hypothesis that MDD subtypes exist in FM and can be identified via biochemical assays and clinical characteristics. Subjects were separated into one of three groups based on the DSM-IV-TR diagnostic criteria for MDD: FM no MDD, FM/ADE, or FM/MDE (APA, 2001).

Assumption of Equal Sample Sizes

Chi-square (χ^2) tests were used to determine if the distribution of FM/MDD diagnostic groups were equal in size. Chi-square tests determined the sample sizes of the groups were significantly unequal ($\chi^2 < .001$), thus the assumption of equal sample sizes was violated. However, as nonparametric testing does not require equal sample sizes and analysis of variance is a robust test minimally affected by sample size, no correction was needed.

Assumption of Normality

The distribution of nominal and ordinal demographic variables (gender, education, employment status, occupation, disability status, marital status, ethnicity, race) was examined for normality using histograms. The assumption of normality was partially violated on two nominal level variables: gender was predominantly female and race was predominantly Caucasian. However, as these were expected deviations from normality due to FM disease characteristics (disproportionately affecting females 9:1 compared to males) and the greater population available for sampling was 82.6% Caucasian, no correction was possible.

Screening for normal distribution for interval level demographic variables (age, BMI, number of years with FM symptoms and number of years diagnosed with FM) was conducted using the Shapiro-Wilks W test. Age (SW= .97) and BMI (SW= .95) were normally distributed with skewness values between -2 to 2 (indicating a normal distribution). Number of years with FM symptoms were normally distributed in the FM no MDD and FM/MDE groups ($p > .05$), but positively skewed in the FM/ADE group ($p < .001$). Number of years diagnosed with FM was also positively skewed. As this is a common finding in FM, no correction for skewness was required. Kurtosis values ranged from .85 to 1.62 on the above variables indicating there were no peaks or valleys in distribution, thus no correction was required for kurtosis.

Assumption of Homogeneity of Variance

The assumption of equal variance was tested using the Levine's test of homogeneity of variance on interval level clinical variables, cortisol levels, and IGF-1 levels. The following variables met the assumption of equal variance: number of years diagnosed with FM, age, BMI, pain severity, quality of life, sleep quality, MDD severity, and IGF-1. The following variables did not meet the assumption of equal variance: number of years with FM symptoms, number of tenderpoints, impact of FM on ability to function, and cortisol levels.

Sample Description

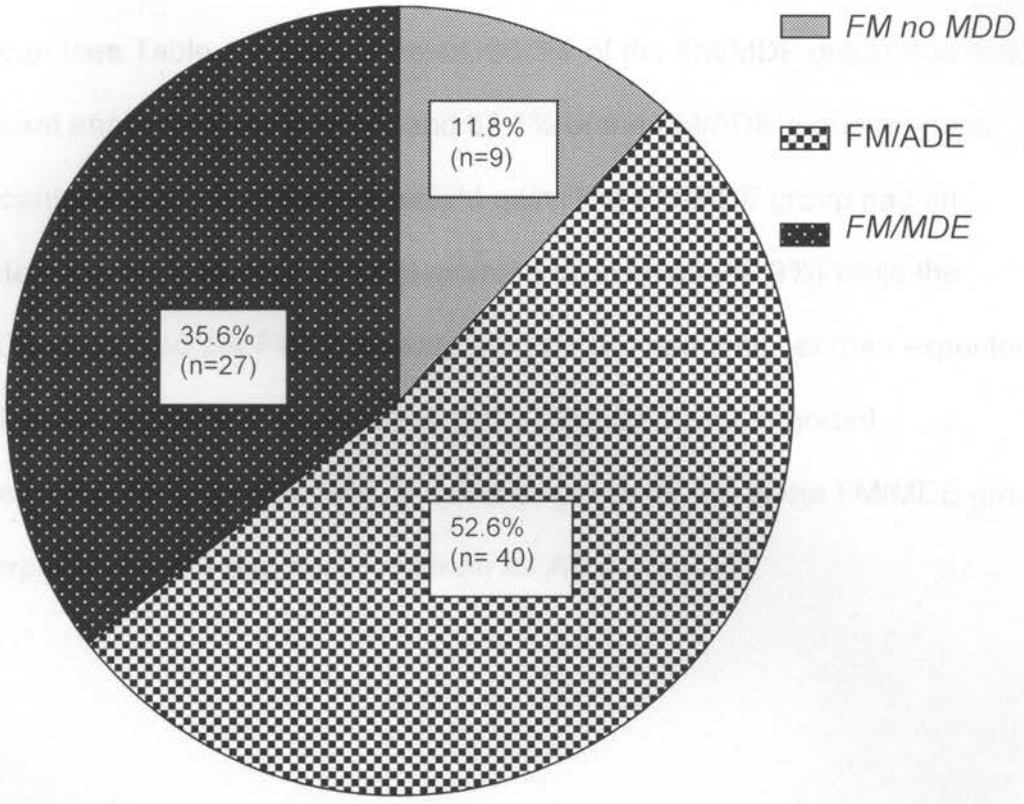
Seventy-six subjects (73 females= 96.1%, 3 males= 3.9%) signed informed consent and completed visit 1. The sample was primarily Caucasian (89.5%), married or living with a significant other (61.8%) and well educated. Fifty-five point two percent (55.2%) of subjects had attended trade school or some college, while 18.4% had completed an Associates or Bachelor's degree and 18.4% had completed a Master's degree or higher. Subjects were on average 54 years old (SD= 12.67), had experienced FM symptoms for an average of 18 years (SD= 12.83), and had been diagnosed with FM for an average of 8 years (SD= 6.12). Fifty-eight out of 73 women (79.5%) were between the ages of 30 and 60, with 12 (16.4%) being 65 or older and 3 (4.1%) being 29 or younger.

Distribution of Diagnostic Groups

Chi-square tests determined that the distribution of FM/MDD diagnostic subtypes across groups was unequal ($\chi^2 = 14.0$, $p < .001$) and thus violated the assumption of equal sample sizes. Nine of 76 subjects (11.8%) met diagnostic criteria for FM no MDD, 40 of 76 (52.6%) for FM/ADE, and 27 of 76 (35.6%) for FM/MDE (see figure 4.1).

Figure 4.1

Percent of subjects per diagnostic group: FM no Depression, FM with Atypical Depressive Episodes, and FM with Melancholic Depressive Episodes



Distribution of Criteria for Diagnostic Groups

The sample's diagnostic groups met the general diagnostic criteria as defined in the DSM-IV-TR for the ADE and MDE subtypes (see Table 4.2). Seventy four percent of the FM/MDE group experienced anhedonia while none of the FM no MDD group and only 12.5% of the FM/ADE group met this criteria. Twenty nine percent (29.6%) of the FM/MDE group reported lack of reactivity to

usually pleasurable stimuli while only 11.1% of the FM no MDD group and none of the FM/ADE group reported experiencing this criteria. One hundred percent of the FM/ADE group reported mood reactivity, a mandatory criteria for ADE, yet 74.1% of the FM/MDE and 44.4% of the FM no MDD group also met this criteria. The majority of the sample reported leaden paralysis irrespective of diagnostic subgroup (see Table 4.1). As expected, 33.3% of the FM/MDE group reported significant anorexia or weight loss and 67.5% of the FM/ADE group reported significant increase in appetite or weight gain. The FM/MDE group had an expectedly high prevalence of early morning awakening (88.9%) while the FM/ADE group and the FM no MDD group (33.3%) had a higher than expected prevalence rate. As expected, 71.1% of the FM/ADE group reported interpersonal rejection sensitivity, but unexpectedly 48.1% of the FM/MDE group also experienced this diagnostic criterion for ADE.

Table 4.1

Prevalence rates of DSM-IV (TR) diagnostic criteria for MDD subtypes: No MDD, MDE and ADE

MDE CRITERIA	FM no MDD	FM/ADE	FM/MDE
Anhedonia (loss of pleasure in all, or almost all, activities)	0/9= 0%	5/35= 12.5%	7/27= 74.1%
Lack of reactivity to usually pleasurable stimuli	1/9= 11.1%	0/39= 0%	8/27= 29.6%
Distinct quality of depressed mood	0/9= 0%	34/40= 85%	27/27= 100 %
Depression regularly worse in the morning	1/9= 11.1%	13/41= 32.5%	17/27=63%
Early morning awakening (at least two hours before usual time of awakening)	3/9= 33.3%	17/40= 42.5%	24/27= 88.9%
Marked psychomotor retardation or agitation	0/9= 0%	13/40= 32.5%	19/27= 70.4%
Significant anorexia or weight loss	1/9= 11.1%	3/40= 7.5%	9/27= 33.3%
Excessive or inappropriate guilt	0/9= 0%	16/40= 40%	23/27= 85.2%
ADE CRITERIA	**FM no MDD**	**FM/ADE**	**FM/MDE**
Criteria met for MDE during the same episode.	0/9= 0%	0/40= 0%	27/27= 100% (Exclusionary Criteria)
Mood reactivity	4/9= 44.4%	40/40= 100%	20/27= 74.1%
Significant weight gain or increase in appetite	0/9= 0%	27/40= 67.5%	10/27= 37%
Hypersomnia	0/9= 0%	14/40= 35%	5/27= 18.5%
Leaden paralysis	4/9= 44.4%	40/40= 100%	26/27= 96.3%
Interpersonal rejection sensitivity	0/9= 0%	27/38= 71.1%	13/27= 48.1%

Aim 1

The first aim of this research was to describe the demographic and clinical characteristics of FM subjects with no MDD, ADE and MDE. I hypothesized no differences would be found among the three groups on demographic

characteristics (age; BMI; gender; race; ethnicity; marital, employment, and disability status; education level; occupation; number of years with FM symptoms; number of years diagnosed with FM), but that there would be significant differences among the three groups on clinical characteristics (FM, depression, and pain severity; sleep quality; quality of life; impact of FM on ability to function).

Demographic Characteristics

Chi square tests were used on the seven nominal and ordinal level demographic variables to determine if they differed among the three diagnostic groups ($\chi^2 = 9.14$; p= .01). As depicted in Table 4.3, the only variable that differed was gender: the FM no MDD group had two men, the FM/ADE group had one man, and the FM/MDE group had no men.

Levine's test for homogeneity of variance was conducted on the four interval level demographic variables to determine if there were equal variances of means among the three FM/MDD diagnostic groups. The assumption of homogeneity of variance was supported for age (p= .76), BMI (p= .96) and number of years diagnosed with FM (p= .42). Therefore, ANOVA and Bonferroni post hoc tests, with an adjusted alpha of .02, were conducted on these three variables. As I hypothesized, no significant differences were found among the three groups on age and number of years diagnosed with FM as noted in Table 4.3. Although it was hypothesized there would be significant differences on BMI among the three groups, differences did not reach statistical significance (p=.28).

Table 4.2

BMI percentage by depression subtype

		BMI percentage			Total %
		<25	>25	>30	
Depression subtype	not depressed	2 (22.2%)	3 (33.3%)	4 (44.5%)	9 (100)
	atypical depressive episode	5 (16.7%)	8 (26.6%)	17 (56.7%)	30 (100)
	melancholic depressive episode	5 (21.7%)	10 (43.5%)	8 (34.8%)	23 (100)
Total FM Sample		12 (19%)	21 (34%)	29 (47%)	62 (100)

Number of years with FM symptoms was found to have statistically significant differences in variance among the three diagnostic groups ($p < .001$) and thus violated the test of homogeneity of variance. Therefore, Welch's robust tests of equality of means with Games-Howell post hoc tests were used to measure the differences among groups for this variable. There was a trend toward significant differences ($p = .09$) with the FM/ADE and FM no MDD groups having had symptoms of FM for approximately six years longer than the FM/MDE group (see Table 4.3).

Table 4.3

Demographic data for total sample and by diagnostic group: count (%) for nominal and ordinal data and mean (SD) for interval data

DEMOGRAPHIC VARIABLES		Total Sample (n= 76) 100%	FM no MDD (n=9) 11.9%	FM/ADE (n=40) 52.6%	FM/MDE (n=27) 35.6%	Statistic	Sig.
Gender	Female	73 (96.1%)	7 (77.8%)	39 (97%)	27 (100%)	χ^2	.01
	Male	3 (3.9%)	2 (22.2%)	1 (2.5%)	0		
Ethnicity	Hispanic/Latino	5 (6.6%)	0 (0%)	3 (7.5%)	2 (7.4%)	χ^2	.34
	Non-Hispanic/ Non-Latino	67 (88.2%)	8 (88.9%)	35 (87.5%)	24(88.9%)		
	Not reported/Unknown	4 (5.3%)	1 (11.1%)	2 (5.0%)	1 (3.7%)		
Race	Black/African American	2 (2.6%)	0	0	2 (7.4%)	χ^2	.23
	Asian	1 (1.3%)	0	1 (2.5%)	0		
	American Indian/ Alaskan Native	5 (6.6%)	2 (22.2%)	1 (2.5%)	2 (7.4%)		
	White	68 (89.5%)	7 (77.8%)	38 (95%)	23 (85.3%)		
Educational Level	Grade 10-12	6 (7.9%)	0	3 (7.5%)	3 (11.1%)	χ^2	.80
	High School/GED	9 (11.8%)	0	6 (15%)	3 (11.1%)		
	Some college or trade school	33 (43.4%)	6 (66.7%)	14 (35%)	13 (48.1%)		
	College Degree	14 (18.4%)	2 (22.2%)	10 (25%)	2 (7.4%)		
	Graduate Degree or higher	14 (18.4%)	1 (11.1%)	7 (17.5%)	6 (22.2%)		
Marital Status	Married	39 (51.3%)	6 (66.7%)	24 (60%)	9 (33.3%)	χ^2	.14
	Living Together	8 (10.5%)	3 (33.3%)	2 (5%)	3 (11.1%)		
	Separated	3 (3.9%)	0	1 (2.5%)	2 (7.4%)		
	Single	22 (28.9%)	0	11 (27.5%)	11 (40.7%)		
	Other	4 (5.3%)	0	2 (5%)	2 (7.4%)		
Employment Status	Works Full Time	16 (21.1%)	3 (33.3%)	8 (20%)	5 (18.5%)	χ^2	.92
	Works Part Time	8 (10.5%)	0	4 (10%)	4 (14.8%)		
	Not employed out of home	52 (68.4%)	6 (66.7%)	28 (70%)	18 (66.7%)		
Receiving disability	No	53 (69.7%)	7 (77.8%)	27 (67.5%)	19 (70.4%)	χ^2	.83
	Yes	23 (30.3%)	2 (22.2%)	13 (32.5%)	8 (29.6%)		
Age (years)		54.36 (12.67)	52.22 (11.16)	55.20 (12.95)	53.81 (13.05)	ANOVA	.79
Number of years with FM symptoms		18.05 (12.83)	20.11 (10.78)	20.36 (15.07)	14.11 (8.82)	Welch's	.09
Number of years diagnosed with FM		7.72 (6.12)	10.22 (8.20)	7.40 (6.10)	7.35 (5.36)	ANOVA	.43
BMI		30.55 (19.69)	29.51 (6.97)	32.05 (7.35)	29.08 (6.57)	ANOVA	.28

Clinical Characteristics

Levine's test for homogeneity of variance was conducted to measure the differences among diagnostic groups on clinical measures. Analysis of variance with Bonferroni post hoc tests (adjusted alpha= .01) were conducted on the interval level variables that did not violate Levine's test (pain severity, p= .33; MDD severity, p= .08; quality of life, p= .17; sleep quality, p= .09). For those variables that violated the assumption of equal variance (number of tenderpoints, p< .001; impact of FM on ability to function, p= .02), Welch's robust test of equality of means with Games-Howell post-hoc tests were used to identify where differences occurred (see Table 4.4).

As hypothesized, there were significant differences among the three groups on depression severity, pain severity, quality of sleep, quality of life, and impact of FM on ability to perform activities of daily living, but not on number of tender points. As depicted in Table 4.4, depression severity was significantly different among all three groups. The FM no MDD group appropriately had significantly less depression than the FM/ADE and FM/MDE groups (p< .001). The FM/MDE group had the worst depression severity of the three groups (p< .001).

Table 4.4

Mean scores with (SD) for clinical characteristics per diagnostic group

Clinical Characteristics Construct (Instrument)	**FM no MDD (n=9) A**	**FM/ADE (n=33) B**	**FM/MDE (n=24) C**	**Significance Level**	**Sig. Level BTW groups**
Number of tender points (Physical Exam)	16.33 (2.50)	17.55 (1.00)	17.63 (.82)	ANOVA F(2) 63=3.91;p= .35	NS
Depression severity (HamD-17)	4.89 (3.72)	16.70 (5.78)	22.25 (3.93)	ANOVA F(2) 63= 40.73; p< .001	a-b***, a-c***, b-c***
Pain severity (Myalgia score) (FIQ #15- VAS)	34.67 (11.70) 4.11 (2.52)	43.72 (8.29) 6.58 (1.87)	44.42 (8.65) 7.54 (1.74)	ANOVA F(2) 63= 4.31; p= .018 F(2) 63= 4.31; p< .001	a-b*, a-c*
Quality of sleep (Jenkins)	7.89 (7.52)	14.15 (4.78)	14.00 (4.78)	ANOVA F(2) 63= 5.50; p= .006	a-b**, a-c**
Quality of life (Flannigan)	95.56 (8.23)	69.58 (15.72)	63.83 (15.71)	ANOVA F(2) 63= 14.91; p< .001	a-b***, a-c***
Impact of FM (FIQ)	31.45 (18.57)	64.04 (17.72)	68.70 (10.75)	Welch's F(2) 63= 20.85; p< .001	a-b***, a-c***

* p <= 0.05 ** p <= 0.01 ***p <= 0.001

Post hoc analyses found pain severity, as measured by the Cumulative Myalgic Score, was higher in the FM/ADE and FM/MDE groups compared to the FM no MDD group (see Table 4.4). However, no statistical difference existed between the FM/ADE and FM/MDE groups. The visual analogue scale item for pain in the FIQ (Question # 15) supported there was a significant difference between the FM no MDD and FM/ADE groups ($p = .003$), and the FM no MDD and FM/MDE groups ($p < .001$), but no significant differences existed between the FM/ADE and FM/MDE groups. Quality of sleep was the best in the FM no MDD group compared to the FM/ADE ($p = .007$) and FM/MDE groups ($p = .01$). No significant differences were found between the FM/ADE and FM/MDE groups on sleep quality. Quality of life was better in the FM no MDD group compared to the FM/ADE and FM/MDE groups and impact of FM on ability to function was much worse in the FM/ADE ($p = .001$) and FM/MDE ($p = .001$) groups than the FM no MDD group. No significant differences were found between the FM/ADE and FM/MDE groups on functional ability as measured by the FIQ. The hypothesis for aim 1 was supported with the exception that no differences were found between diagnostic groups on BMI or number of tenderpoints.

Aim 2

The second hypothesis of this study was that the mean dexamethasone-suppressed cortisol value (MDSCV) following DST testing and the mean peak plasma cortisol value following DEX suppression/CRH stimulation testing would be low to normal ($\leq$ 5ng/dl) in both the FM no MDD and FM/ADE groups. Conversely, I hypothesized the FM/MDE group would have elevated cortisol

values (> 5ng/dl), indicating lack of HPA axis suppression.

Cortisol Levels per Diagnostic Group

In the dexamethasone-suppressed (DST) group, Levine's test of homogeneity of variances found the assumption of equal variance was violated for all six plasma cortisol sample draws and the highest plasma cortisol value of those draws. Therefore, Welch's robust test of equality of means was conducted with Games-Howell post hoc tests to determine where significant differences existed among the three diagnostic groups on the six mean plasma cortisol values and the group mean for the highest plasma cortisol value of each individual (see Table 4.5).

Significant differences in mean dexamethasone-suppressed cortisol values only existed at the 1530 time point among the three diagnostic groups (p=.05). However, there was a trend in the expected direction for the 1545 (p= .07), 1600 (p= .06) and the group mean for the highest plasma cortisol value of each individual (p= .08). Overall, the FM/MDE group had the highest group means across all six time points, while the FM no MDD and FM/ADE groups did not differ significantly.

Post hoc analyses using the Games-Howell test determined that there were significant differences at 1530 between the FM no MDD group (μ=.17; SD= .41) and the FM/MDE group on mean cortisol values (p= .05) with the FM/MDE group having the highest mean (μ= 3.41; SD= 4.37). As hypothesized, no significant differences were found between the FM no MDD and FM/ADE groups. There was a trend towards significance between the FM/ADE (μ= .31; SD= .84)

and the FM/MDE groups (p= .06) at 1530.

Although technically there were no significant differences between diagnostic groups at the other five plasma cortisol sample time points as measured by Welch's robust test of equality of means, post hoc analyses did show significant differences in mean dexamethasone-suppressed cortisol values between the FM no MDD group and the FM/MDE group at 1545 (p= .05), 1600 (p= .05) and the group mean of the highest individual cortisol value per six time points (p= .05). There were significant differences between the FM/ADE and FM/MDE groups at 1600 (p= .05), trended toward significance at 1545 (p= .06) and the mean of the highest individual cortisol value per six time points (p= .07).

Table 4.5

Mean dexamethasone-suppressed cortisol values following DST testing between diagnostic groups across 6 time points and the highest of the 6 samples

Time Cortisol Drawn (Welch's Sig.)	**DST** FM No MDD A (n=6)	**DST** FM/ADE B (n=25)	**DST** FM/MDE C (n=14)	**Post Hoc Significance Level Between Groups**
1445 (n=45) Welch's= .21	.40 (.62)	.36 (.62)	1.89 (2.94)	NS
1500 (n=46) Welch's= .22	.35 (.54)	.48 (1.01)	2.02 (3.28)	**NS**
1530 (n=44) Welch's= **.05**	.17 (.41)	.31 (.84)	3.41 (4.37)	a-c*; p=.05 b-c; p=.06 **(TR)**
1545 (n=43) Welch's= .07	.18 (.45)	.25 (.51)	3.16 (4.03)	a-c*; p=.05 b-c; p=.06 **(TR)**
1600 (n=44) Welch's= .07	.37 (.57)	.32 (.62)	3.35 (4.01)	a-c*; p=.05 b-c*; p=.05
1615 (n=43) Welch's= .13	.38 (.60)	.25 (.52)	2.67 (3.86)	**NS**
Highest of 6 Draws (n=46) Welch's= .08	.57 (.63)	.68 (1.04)	3.66 (4.56)	a-c; p=.06 **(TR)** b-c; p=.07 **(TR)**

* $p \leq 0.05$ ** $p \leq 0.01$ ***$p \leq 0.001$

TR=Trend toward significance; $p \leq 0.10$ **NS** = Not significant; $p > 0.10$

In the DEX/CRH group, Levine's test of homogeneity of variances found the assumption of equal variance was violated for the 1500 (p= .001), 1545 (p= .02), 1600 (p= .009) and 1615 (p= .006) DEX/CRH time-points. Therefore, Welch's robust test of equality of means with Games-Howell post hoc tests were conducted to on the 1500, 1545, 1600 and 1615 mean plasma cortisol levels. ANOVA with Bonferroni post hoc tests were conducted to determine where significant differences existed among the three diagnostic groups on the 1445, 1530 mean plasma cortisol values as well as the group mean or the highest individual peak plasma cortisol values as depicted in Table 4.6.

There was a significant difference in the 1545 cortisol level between the FM/ADE and FM/MDE groups (p= .02), 1600 cortisol level between the FM/ADE and FM/MDE groups (p= .004), and the peak cortisol level between the FM/ADE and FM/MDE groups (p= .001). As hypothesized, no significant differences were found between the FM no MDD and FM/ADE groups on mean cortisol levels. In summary, the hypothesis for Aim 2 was supported in the DEX/CRH testing group, but not the DST testing group.

Table 4.6

Mean peak plasma cortisol values following DEX/CRH testing between diagnostic groups across 6 time points

Time Cortisol Drawn (ANOVA/ Welch's Sig.)	**DEX/CRH** FM No MDD N=3 A	**DEX/CRH** FM/ADE N=6 B	**DEX/CRH** FM/MDE N=10 C	**Post Hoc Significance Level Between Groups**
1445 (pre-CRH) n=18;ANOVA= .76	.33 (.58)	.46 (.63)	1.09 (2.41)	**NS**
1500 (pre-CRH) n=19;Welch's= NS	.00 (.00)	.57 (62)	3.24 (4.77)	**NS**
1530 (post-CRH) n=17;ANOVA= .14	2.33 (1.50)	.88 (.87)	4.87 (4.50)	**NS**
1545 (post-CRH) n=17;Welch's= **.05**	3.07 (2.14)	1.18 (.97)	6.46 (4.39)	b-c*; p=.02
1600 (post-CRH) n=17;Welch's= **.02**	3.97 (3.19)	1.12 (1.59)	9.71 (5.56)	b-c**; p=.004
1615 (post-CRH) n=17;Welch's= .15	4.90 (4.03)	1.42 (1.93)	6.91 (6.79)	**NS**
Peak (post-CRH) n=19; Welch's= **.02**	4.90 (4.03)	1.58 (1.75)	9.88 (5.15)	b-c***; p=.001

* $p \leq 0.05$ ** $p \leq 0.01$ ***$p \leq 0.001$

TR=Trend toward significance; $p \leq 0.10$ **NS** = Not significant; $p > 0.10$

Effects of Type of Test Performed on Cortisol Levels

A post hoc examination was conducted to examine the effect of using the more sensitive and specific combined DEX/CRH stimulation test compared to the standard DST test in an FM population. As depicted in Tables 4.5 and 4.6, the standard DST testing was done on 46 out of 65 subjects (70.8%) and the DEX/CRH testing was done on 19 out of 65 subjects (29.2%). The groups did not differ on type of test done (χ^2 = .33).

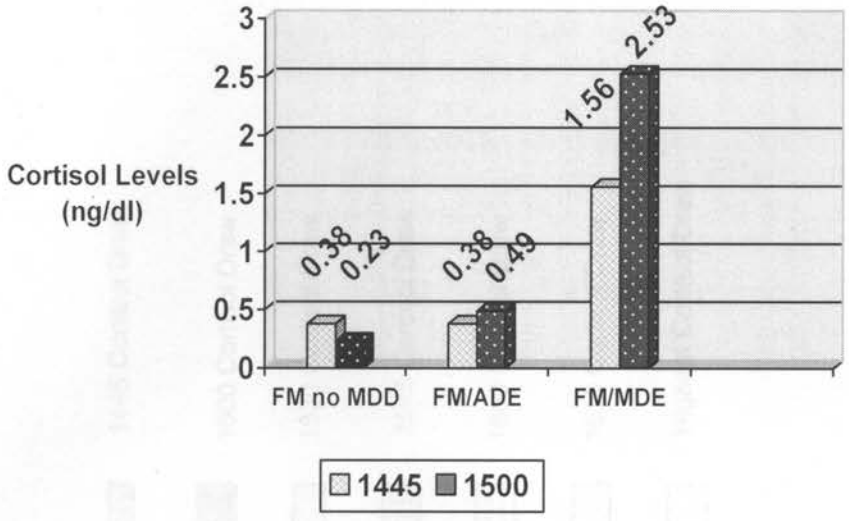
The group mean for the highest individual plasma cortisol value after DST testing was below 5 ng/dl for the FM no MDD group (μ= .57; SD= .63), FM/ADE group (μ= .68; SD= 1.04) and also for the FM/MDE group (μ= 3.66; SD= 4.56) (see Table 4.5).

The mean peak plasma cortisol value after DEX/CRH testing was below 5 ng/dl for the FM no MDD group (μ=4.90; SD= 4.03) and FM/ADE group (μ= 1.58; SD= 1.75) groups, but was above 5 ng/dl for the FM/MDE group (μ= 9.88; SD= 5.15) (see Table 4.6).

As hypothesized, the mean 1445 and 1500 (post-dexamethasone, pre-CRH) cortisol values were highest in the FM/MDE group as compared to the FM no MDD and FM/ADE groups (see Figure 4.2). The mean cortisol values for all six time points in the DST and the DEX/CRH groups were consistently highest in the FM/MDE group and lowest in the FM/ADE groups (see Figures 4.3 and 4.4).

Figure 4.2

Mean pre-CRH cortisol levels by diagnostic group



The percentage of subjects with a 1500 cortisol value above 5 ng/dl for the DST group was 29% higher in the FM/MDE group than in the FM no MDD and FM/ADE groups. The percentage of subjects with a 1500 cortisol value above 5 ng/dl for the DEX/CRH group was 47% higher in the FM/MDE group than in the FM no MDD group and 80% higher than in the FM/ADE group (see Table 4.7).

Table 4.7

Number of subjects with cortisol levels above or below 5 ng/dl at1500 time point

TYPE OF TEST PREFORMED	FM no MDD N= 9	FM/ADE N= 32	FM/MDE N= 24
DST (n=46)			
# <= 5 ng/dl	6/6 (100%)	26/26 (100%)	10/14 (71%)
# > 5 ng/dl	0/6 (0%)	0/26 (0%)	4/14 (29%)
DEX/CRH (n=19)			
# <= 5 ng/dl	2/3 (67%)	6/6 (100%)	2/10 (20%)
# > 5 ng/dl	1/3 (33%)	0/6 (0%)	8/10 (80%)

Figure 4.3

Mean cortisol value for DST group across 6 time points

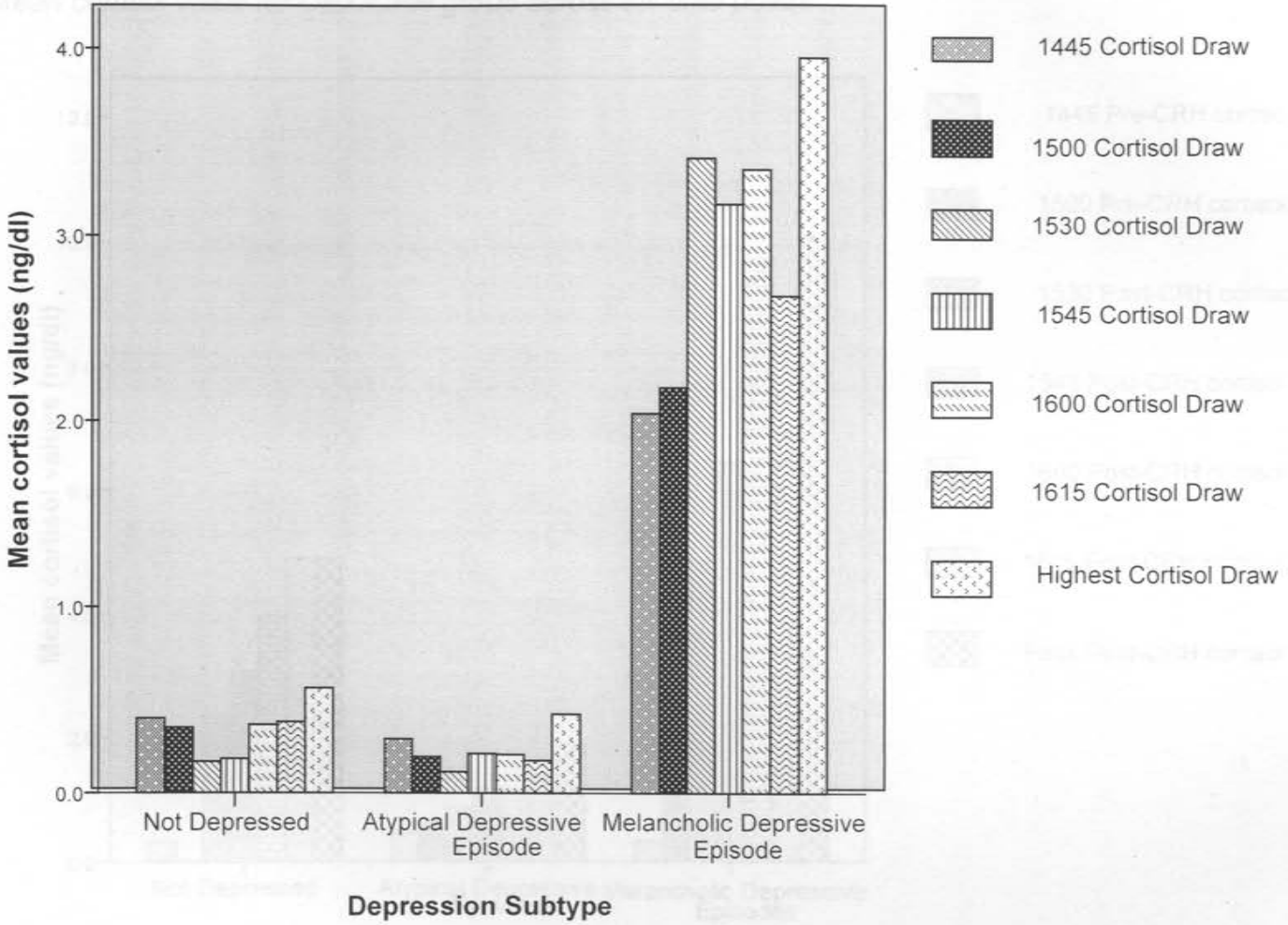
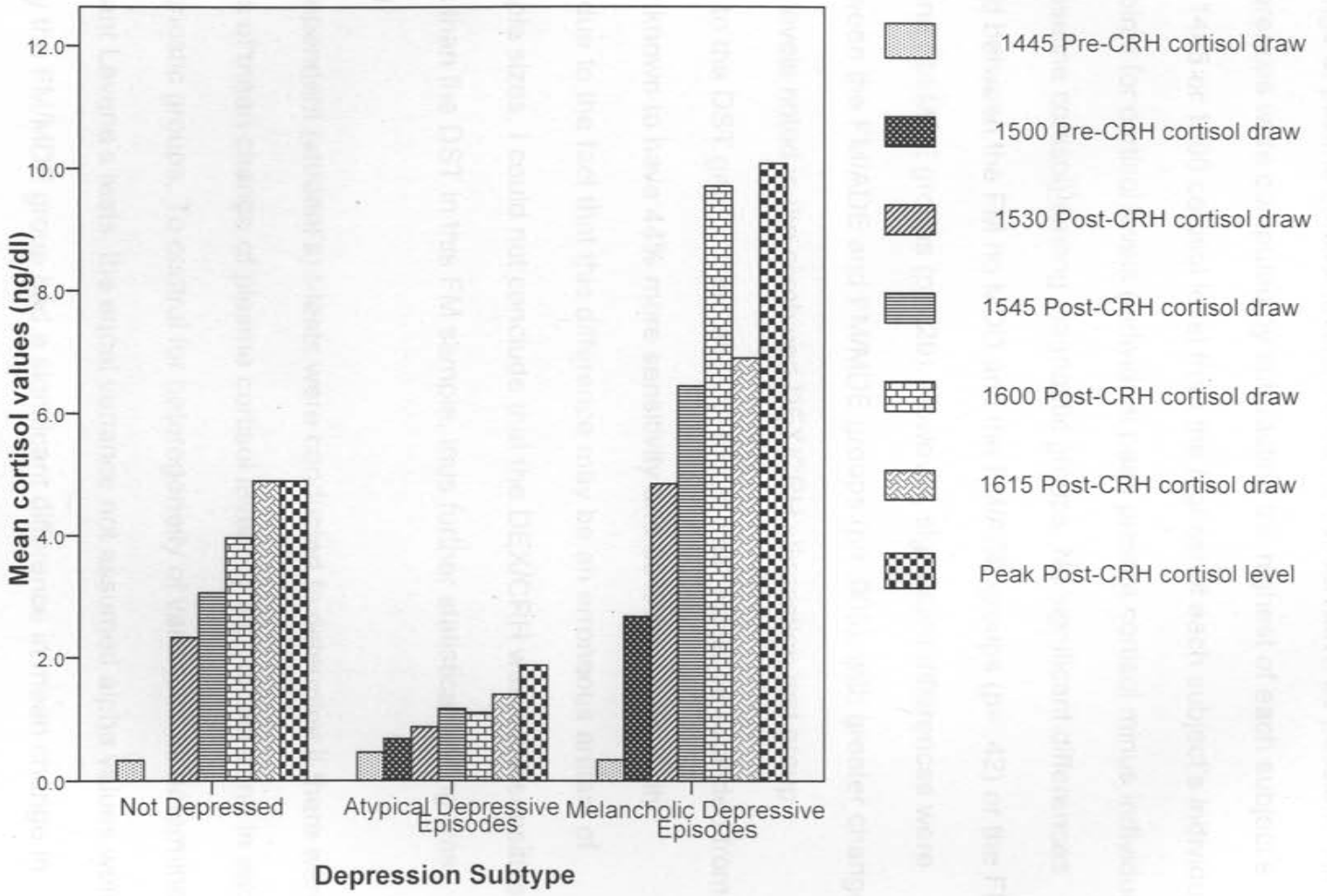


Figure 4.4

Mean cortisol value for DEX/CRH group across six time points



Analysis of variance with post hoc tests using either Bonferroni correction or the Welch's robust test of equality of means were conducted in the DST and DEX/CRH testing groups to determine if there were between-group differences of mean change of plasma cortisol levels. To be as conservative as possible, the mean differences were computed by subtracting the highest of each subject's individual 1445 or 1500 cortisol level from the highest of each subject's individual six time points for cortisol levels (individual peak plasma cortisol minus individual highest baseline cortisol) among diagnostic groups. No significant differences were found between the FM no MDD and the FM/ADE groups ($p = .42$) or the FM no MDD and FM/MDE groups ($p = .29$). However, significant differences were found between the FM/ADE and FM/MDE groups ($p = .005$), with greater changes of cortisol levels noted in the combined DEX/CRH stimulation test group compared to the DST group. Theoretically, this is what would be expected from a test that is known to have 44% more sensitivity and 80% more specificity. However, due to the fact that this difference may be an erroneous artifact of small sample sizes, I could not conclude that the DEX/CRH was more sensitive or specific than the DST in this FM sample, thus further statistical testing was preformed.

Independent (student's) t-tests were conducted to determine if there were differences of mean change of plasma cortisol levels by type of test done in each of the diagnostic groups. To control for heterogeneity of variances as determined by significant Levene's tests, the equal variance not assumed alpha values were used. Only the FM/MDE group had a significant difference in mean change in

cortisol levels between the DST and DEX/CRH tests (see Table 4.8). Although this might suggest the DEX/CRH was more sensitive and more specific than the DST in this FM sample, this may be an erroneous artifact of the small sample size and precludes me from making this conclusion.

Table 4.8

Post hoc analysis of mean cortisol difference (ng/dl) between highest baseline and peak cortisol (S.E.) by diagnostic group and test used

Diagnostic Group	FM no MDD A		FM/ADE B		FM/MDE C	
Type of Test Done	DST N=6	DEX/CRH N=3	DST N=26	DEX/CRH N=6	DST N=14	DEX/CRH N=10
Mean CORT Difference	.00	4.57	.06	1.00	1.61	6.43
Signif. Level Between Groups	p= .15		p= .15		p= .02	

* p <= 0.05

To further investigate the potential effect of the type of test done on plasma cortisol levels, a factorial ANOVA was used to examine mean dexamethasone-suppressed cortisol values (MDSCV) following DST testing and the mean peak plasma cortisol values following DEX suppression/CRH stimulation testing by diagnostic group and type of test done (DST vs. DEX/CRH). Although the DEX/CRH test made a difference in the mean peak plasma cortisol levels, it did not affect any group independently.

An analysis of covariance was conducted to examine the differences in mean 1500 and peak cortisol levels among the three diagnostic groups controlling for type of test done. There was a significant difference between

diagnostic groups on mean 1500 cortisol levels as a main effect (p= .01), but not by type of test done (p= .46) or as an interaction (p= .75). After taking out the effects of the type of test used, depression subtypes still demonstrated significant differences in peak cortisol. There was a significant difference between diagnostic group (p< .001) and type of test done (p< .001) on peak cortisol levels as main effects and also as an interaction (p= .04). Looking at post-test contrasts, there were no differences between FM no MDD and FM/ADE groups, but there were significant differences between FM/ADE and FM/MDE groups.

Aim 3

The final hypothesis of this study was to determine whether there were differences in the serum IGF-1 levels of FM subjects with MDE compared to FM subjects with ADE and no MDD. I hypothesized the FM subjects with MDE would have lower IGF-1 levels than FM subjects with ADE and no MDD.

As the groups did not significantly differ on age or BMI, it was not necessary to statistically control for these two potential confounders (Procopio & Maccario, 1998). Levene's test of homogeneity of variance found equal variance of IGF-1 means among the three diagnostic groups (p= .749). Therefore, a 2 X 3 ANOVA, with the dependent variable being MDD subtype and the independent variable being mean IGF-1 levels, was used to determine significant differences of IGF-1 among the three groups. Although there was a trend in the expected direction of mean IGF-1 levels, no significant differences were found (p= .31) (see Table 4.9).

Table 4.9

Mean IGF-1 levels adjusted for differences based on age range per diagnostic group

IGF-1 ng/ml	FM no MDD (n=9)	FM/ADE (n=32)	FM/MDE (n=23)
Mean (SD)	127.29 (39.05)	137.28 (41.20)	117.47 (49.17)
Range	79.0-207.0	51-201.0	50.3-256.0

In summary, Aim 1 was supported, Aim 2 was partially supported, and Aim 3 trended in the expected direction, but was not statistically significant.

CHAPTER 5: DISCUSSION AND CONCLUSIONS

This study yielded four novel findings: 1) biological subtypes of major depressive disorder (MDD) exist in fibromyalgia (FM) and exhibit similar characteristics as those found in depressed non-FM populations, 2) atypical depressive episodes (ADE) are more common than melancholic depressive episodes (MDE) in this FM sample, 3) peak plasma cortisol levels are reflective of MDD subtypes, and 4) the use of the combined dexamethasone (DEX)/ corticotropin-releasing hormone (CRH) stimulation test is feasible in an FM population and may demonstrate more sensitivity and specificity when testing hypothalamic pituitary adrenal (HPA) axis dysfunction. Although the present study was underpowered to detect a significant difference between groups on plasma IGF-1 levels, there was a trend in the expected direction.

Selye's General Adaptation Syndrome (GAS) model provides a helpful framework to understand these findings as they relate to HPA axis function. As discussed in Chapter 2, the HPA axis is the main mediator of the stress response system in humans. The GAS model defines three stages of the stress response: the stages of alarm/reaction, resistance, and exhaustion. The alarm/reaction stage is characterized by psychological and physiological responses including the activation of the sympathetic nervous system and the HPA axis. The resistance stage is characterized by adaptation by the body via the HPA axis negative feedback mechanisms, which attempt to return the multiple neuroendocrine systems involved in the stress response system to homeostasis. At times, the body is unable to cope with the stressor and the exhaustion stage is

entered. This stage is characterized by continued elevations of HPA axis hormones including CRH, ACTH, AVP, and cortisol, which can eventually lead to desensitization of the HPA axis negative feedback mechanisms. When long-term stressors occur, such as chronic pain and/or chronic depression, the HPA axis can become desensitized and blunted. Two manifestations of the exhaustion stage are decreased glucocorticoid receptor sensitivity and continued elevations of plasma CRH levels accompanied by blunted adrenal gland functioning and lowered plasma cortisol levels. These two opposite ends of the spectrum of HPA axis function are representative of HPA axis hypoactivity (demonstrated in this study to be associated with biochemical and clinical signs and symptoms of ADE) and hyperactivity (demonstrated in this study to be associated with biochemical and clinical signs and symptoms of MDE). The findings of the current study are reflective of the three stages of Selye's GAS model and support the hypothesis that FM is, at least in part, a dynamic process of HPA axis dysfunction.

Biological Subtypes of MDD Exist in FM

The present study provides evidence that two Major Depressive Disorder (MDD) subtypes, ADE and MDE, exist in FM and exhibit similar psychological and physiological characteristics as previously described in depressed non-FM populations.

Demographic Characteristics Similar to Other FM Populations

Age and gender of this sample compares to two large epidemiological studies that found 80-90% of persons with FM are female between the ages of 30 to 60 (Wolfe et al., 1995; Bennett et al., 2007). There were no significant

differences between diagnostic groups in this study (nor compared to the other two studies) in educational level, marital status, employment status, or disability status.

Body mass index was much higher in this study sample compared to the general population, but was similar to other FM samples. BMI figures for white females in the general public taken from the National Health Interview Survey of 2000 found 47% of women had a BMI greater than 25 and 21% had a BMI greater than 30 (U.S. Census Bureau, 2000). There are significant differences between the 2000 census bureau population and the FM total sample. Eighty-one percent of this study sample had a BMI greater than 25 and 47% had a BMI greater than 30. There were no significant differences in BMI among MDD groups for this FM sample. However, compared to the 2000 Census data, the total FM sample had 13% fewer women with BMI's less than 25, 13% fewer women with BMI's between 25 and 30, and 26% more women with BMI's greater than 30. These findings are similar to a recent large epidemiological study in FM (n=2,569), in which 70% of the sample had a BMI greater than 25 and 43% had a BMI greater than 30 (Bennett et al., 2007).

While statistically the FM groups did not differ from each other on BMI, clinically they are more obese than the general female population. The direct relationship between greater amounts of adipose tissue and higher estrogen levels, which can affect HPA axis interactions with other neuroendocrine systems, may warrant further examination of body composition and estrogen status. Therefore, future studies may wish to consider incorporating multiple

biochemical and biometric body composition measures including BMI, percentage of body fat, percentage of lean muscle mass and estrogen levels to further elucidate the relationship between BMI and the neuroendocrinology of FM with concurrent MDD.

Clinical Characteristics of FM More Severe in FM/MDD Groups

The data show the presence of depression is associated with more pain, poorer quality of sleep, poorer quality of life, and greater functional impairment in persons with FM. However, the specific subtype of MDD (ADE vs. MDE) did not affect the severity of the clinical characteristics of FM. Post hoc analyses found pain severity was higher in subjects with FM and concurrent MDD compared to the FM no MDD subjects. The visual analogue scale item for pain in the FIQ also showed subjects with FM and concurrent MDD reported more pain than the FM no MDD group. Non-depressed FM subjects slept the best while the FM/ADE and FM/MDE groups had the poorest quality of sleep. Quality of life was best in the FM no MDD group compared to the FM/ADE and FM/MDE groups and the impact of FM on ability to function was much worse in the depressed FM groups compared to the FM subjects with no depression.

While it is widely recognized that people with FM have sleep disturbances, poorer quality of life and increased functional impairment compared to the general population, these findings indicate there is even more significant negative impact of FM symptoms in those people with concurrent depression. This further reinforces the need to be vigilant in assessing for depression in clinical practice and to aggressively treat it. Especially as the symptoms of MDD

have repeatedly been proven to be amenable to medical and psychological interventions and that alleviation of MDD symptoms significantly improve pain, sleep quality, quality of life and ability to function (Kaplan & Sadock, 2005). In addition, research has shown certain antidepressants are effective in alleviating pain associated with depression and FM (Kaplan & Sadock, 2005; Arnold, Lu, Crofford, Wohlreich, Detke, et al, 2004). For these reasons, it is imperative to educate providers to institute appropriate interventions early on to decrease MDD symptoms as soon as possible as doing so may alleviate unnecessary suffering and possible disease progression.

ADE More Common than MDE

Although over-sampling of FM/MDE and FM no MDD was done in an attempt to achieve equal distribution of MDD subtypes across the three groups, equal sample sizes were not achieved due to the difficulty in finding non-depressed FM subjects and subjects with FM and MDE. The sample demonstrated a two-fold higher prevalence rate of ADE (52.6%) compared to depressed non-FM populations (ADE= 30% prevalence rate). Furthermore, this sample had a 1.5-fold higher prevalence rate of MDE (35.5%) compared to the non-FM depressed population (MDE= 20-30% prevalence rate). Theoretically, the preponderance of ADE in this FM sample is indicative of greater rates of HPA axis hypoactivity in FM subjects with concurrent ADE than is experienced in either FM or MDD alone. As this was the first study to identify biochemical markers of MDD subtypes in FM, further studies are needed to confirm these findings in a larger sample. Also, due to the degree of difficulty achieving equal

group sizes as an effect of the considerable prevalence of ADE over MDE, more time and monies will need to be allotted to assure equal groups are recruited and retained throughout the study.

It is to be noted that this preponderance may be a spurious finding due in part to the Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement (SIGH-ADS) inadvertently over-representing ADE subtypes as the criteria of leaden paralysis and fatigue are not exclusive to MDD, but are also part of the symptomology of FM. This was the first research study to use the SIGH-ADS or the Structured Interview Guide for the Hamilton Depression Rating Scale-Seasonal Affective Disorder-Self Report (SIGH-SAD-SR) in an FM population. Further investigation is needed to determine the relationships between the concepts measured by these instruments and concepts found in FM, MDD and FM with concurrent MDD.

One example is that this study found that 44.4% of the FM no MDD group, 100% of the FM/ADE group and 74.1% of the FM/MDE group endorsed leaden paralysis as a symptom they experienced. These rates are higher than those found in previous research conducted in depressed non-FM populations (Parker et al., 2002; Posternak & Zimmerman, 2002). In discussion with prominent researchers in the field of FM (K.D. Jones & R.M. Bennett, April 20, 2007), it was hypothesized there may be a conceptual link between the symptom of leaden paralysis reported by persons with ADE and the symptom of morning stiffness, which was reported by 2,569 persons with FM to be the most severe symptom of FM (Bennett et al, 2007). The principal investigator and the OHSU Fibromyalgia

Research and Treatment Team plan to further investigate the potential of conceptual overlap between these terms (leaden paralysis and morning stiffness) in future studies.

Another example of a conceptual overlap that needs further investigation is the concept of interpersonal rejection sensitivity, which is an exclusive symptom of ADE. As expected, interpersonal rejection sensitivity was reported by 0% (0/9) of the FM no MDD group, 71.1% (27/38) of the FM/ADE group but a surprising 48.1% (13/27) of the FM/MDE group. Non-FM people with MDE do not endorse having interpersonal rejection sensitivity and thus this finding is surprising. However, many people with FM report having experienced repeated invalidation from their families, friends, employers, and even health care providers regarding FM. They have been told that FM is not real and that it is "all in their head" implying they are lazy, not trying hard enough to be well, or that they are mentally ill. People with FM also report an increase in feelings of degradation and shame after visiting health care providers who either do not understand the etiology of FM or are not sensitive to the issues involved in having an "invisible" disease. Health care provider attitudes and behaviors can significantly affect interpersonal rejection sensitivity and the health seeking behaviors of persons with FM. It needs to be determined if interpersonal rejection sensitivity is a state versus a trait in those with FM and concurrent depression and to what extent attitudes and behaviors of health care providers affect this symptom of ADE.

An unexpected finding was that the data showed a trend toward significant

differences among MDD subtypes on the number of years FM symptoms had existed: the FM/ADE and FM no MDD groups had symptoms of FM for approximately six years longer than the FM/MDE group (20.36 years and 20.11 years respectively compared to 14.11 years). This novel finding raises several interesting questions. The first and foremost question is can this finding be indicative of the natural progression of FM? If so, does this imply there is a temporal association with FM disease progression and changes in HPA axis function (chronic hyperactivity with resulting glucocorticoid receptor blunting and desensitization followed by hypoactivity)? This theory would support the data showing persons with FM/MDE have more severe FM symptoms and seem to have an earlier awareness of problems as evidenced by the years from symptom awareness to diagnosis being approximately 13 years in the FM/ADE group and seven years in the FM/MDE group.

If one postulates that new onset FM is reflective of hyperactive HPA axis function characterized by elevated levels of CRH and cortisol (as found in MDE), which eventually can lead to glucocorticoid receptor desensitization and blunting of the negative feedback loop mechanisms, the differences in the number of years FM symptoms were experienced between the FM/MDE group and the FM/ADE and FM no MDD groups could be easily explained. The data from this study support there is a direct correlation between an improvement of symptom severity and length of time FM symptoms were experienced. The GAS model would support this theory and further suggest that HPA axis hyperactivity (which corresponds to MDE) is an alarm stage adaptation that if not intervened with,

may proceed to the exhaustion stage and lead to HPA axis hypoactivity (which corresponds to ADE). Theoretically, if this hypothesis is supported by future research, earlier pharmacological interventions targeted at new onset widespread pain using medications such as CRH antagonists and antidepressants that attenuate HPA axis hyperactivity may prove to be effective and might even slow the progression of FM and limit the extent of disability caused by FM as has been shown in MDD research.

While it is known that depressed individuals can experience alternating episodes of ADE and MDE over the course of their depressive illness (APA, 2001), this has not been investigated in a depressed FM population. Moreover, the literature regarding the natural progression of FM in relationship to the HPA axis is non-existent. Further investigation is needed to determine if the natural progression of FM is in part due to chronic HPA axis dysfunction with corresponding changes in neurochemical processes and/or glucocorticoid-receptor desensitization or if it is variable.

Cortisol Levels are Reflective of MDD Subtypes: Highest in MDE Group

As discussed in Chapters 2 and 3, previous research has demonstrated divergent findings of cortisol levels in FM studies (Adler, Manfredsdottir, & Rackow, 2002; Ataoglu et al, 2003; Crawford et al, 1998). Based on the theoretical framework presented in Chapter 2, one possible explanation for the different findings is that these studies failed to separate MDD subtypes prior to measuring cortisol levels and thus may have inadvertently combined high and low scores such that no differences were detected among groups. Therefore, this

study design separated FM subjects into MDD subtypes to determine if statistical differences existed. As hypothesized, the FM no MDD and FM/ADE groups were able to demonstrate HPA axis suppression (as evidenced by the mean group peak plasma cortisol levels being less than 5 ng/dl), and the FM/MDE group was not able to demonstrate HPA axis suppression, (as evidenced by the mean group peak plasma cortisol level being greater than 5 ng/dl). To further evaluate if the above hypothesis was indeed true, all three diagnostic groups' data were then collapsed back into one group and the mean peak plasma cortisol level was mathematically determined. The mean peak plasma cortisol level for the entire sample (n=65) was 2.06 ng/dl (SD=4.74), which is within normal limits and would erroneously indicate normal HPA axis function.

When considering the findings of leading FM researchers such as Dr.'s Crofford, Arnold, and Adler, it is conceivable that the separation of MDD subtypes would clarify the heretofore unexplained differences in cortisol levels in depressed and non-depressed FM samples. High peak plasma cortisol levels (>5 ng/dl) indicate a *hyperactive* HPA axis in the FM/MDE group and low peak plasma cortisol levels (< 5 ng/dl) indicate a *hypoactive* HPA axis in the FM/ADE group. As demonstrated in depressed non-FM populations, the FM/ADE and non-depressed FM groups did not differ significantly on mean peak plasma cortisol levels. The current findings are consistent with prior studies in depressed non-FM populations and support the hypothesis that there are higher peak plasma cortisol levels in FM subjects with MDE compared to those with ADE and no depression. This new knowledge points towards the necessity of future HPA

axis function studies in FM to separate biological MDD subtypes prior to analyzing cortisol data to eliminate this confounding variable.

The findings regarding different peak plasma cortisol levels among MDD subgroups are important as different antidepressants have different effects on HPA axis function. It is known that some antidepressants such as mirtazapine (Remeron) attenuate or decrease HPA axis hyperactivity while others such as buproprion (Wellbutrin) activate HPA axis function and normalize hypoactivity. Also, classic research has identified a stronger response of persons with ADE to monoamine oxidase inhibitor (MAOI) antidepressants than to tricyclic antidepressants. However, due to the potentially life threatening adverse side effects associated with drug-drug and drug-food interactions, less than 2% of psychiatrists currently prescribe MAOI's (Ross, Adams, & Jones, 2007). This research is timely as selegiline, a MAOI antidepressant in a transdermal delivery system was approved by the FDA in 2006. Selegiline (Emsam) eliminates first pass pharmacokinetics thus significantly reducing the potential for hypertensive crisis as a result of drug-drug interactions. It still remains to be seen if Selegiline (Emsam) will differentially benefit FM patients with concurrent ADE, but it is expected to do so in treatment resistant MDD. Further research is needed regarding its use in persons with FM and concurrent ADE.

DEX/CRH Test As Feasible as DST in FM Population

There were no significant differences in the level of difficulty nor the number of adverse events experienced between the dexamethasone suppression test (DST) compared to the combined DEX/CRH stimulation test. An

argument to support the use of the DEX/CRH over the DST is that significant differences were found between the FM/ADE and FM/MDE groups (p= .005) on amount of change of cortisol levels noted in the combined DEX/CRH stimulation test group versus the DST group. Prior research has shown the DEX/CRH to have 44% more sensitivity and 80% more specificity than the DST. A strong argument against using the DEX/CRH over the DST is the $402 cost of the corticotrophin-releasing hormone required for the combined DEX/CRH test.

IGF-1 Levels Did Not Differ Among Diagnostic Groups

Bennett and colleagues (1997) evaluated plasma IGF-1 levels of 500 patients with FM and found approximately 30% had significantly decreased levels for their age. Based on these findings and the rationale as presented in Chapter 2, I hypothesized the FM/MDE group would have lower plasma IGF-1 levels than the FM no MDD and FM/ADE groups. Although there was a trend in the expected direction of the mean IGF-1 levels among diagnostic groups, no statistical differences were found.

It is interesting to note, however, that the FM no MDD and the FM/ADE groups respectively had 11.1% and 12.5% of their subjects with below normal IGF-1 levels and the FM/MDE group had 25% of the subjects with below normal IGF-1 levels (see Table 5.1). This corresponds to a ratio of 1:2 between the normal (FM no MDD) and hypoactive HPA axis subtype (FM/ADE) compared to the hyperactive HPA axis subtype (FM/MDE).

Table 5.1

Number of subjects with abnormal IGF-1level for age by MDD subtype

IGF-1 Level for Age	FM no MDD (n=9)	FM/ADE (n=32)	FM/MDE (n=24)
Within normal range for age	8 (88.9%)	27 (84.4%)	17 (70.8%)
Below normal range for age	1 (11.1%)	4 (12.5%)	6 (25.0%)
Above normal range for age	0 (0%)	1 (3.1%)	1 (4.2%)

As the current study was not powered on IGF-1, it was postulated it might not have been adequately powered to detect statistical differences among groups on IGF-1. Therefore, a retrospective power analysis was performed to identify the power available in this study. It was determined the study had a power of 17% at an alpha of 0.05 and would require 245 subjects to detect a difference in IGF-1 levels among the three groups. Thus it cannot be concluded that the theoretical framework presented in Chapter 2 was flawed, but rather indicates that the current study needs to be replicated in a larger sample that is adequately powered to detect differences in IGF-1 levels in FM patients with concurrent depression. This finding also provides critical pilot data for future research study design.

Study Limitations

This study had the following limitations. While certain groups were excluded to decrease risk to subjects (severely depressed or suicidal patients or children with FM) and eliminate potential confounding variables, homogeneity of the sample may limit the generalizability of the results. Results may not generalize to men and minorities, as their representation was too low for gender or race specific subgroup analyses. Furthermore, the sample was recruited from

patients seen at a tertiary care facility for FM consultation and short-term management, thus their symptoms may have been more severe than patients managed in primary care clinics. In addition, this academic medical center is not able to accept reimbursement from the statewide Medicaid program, thus persons with lower socioeconomic status may have been underrepresented in the sample. As these findings are novel, they need to be confirmed in a larger sample from a more diverse patient population.

There is an inherent selection bias from a mailed invitation letter versus concurrent enrollment. Because the mailing had depression in the tile, this may have limited the number of FM patients without MDD who felt they were eligible for the study. While there were no statistical differences between the FM no MDD group and the FM/ADE group as hypothesized, the unequal group sizes affected the statistical power of the final findings.

Another limitation was the lack of funds to perform the combined DEX/CRH stimulation test on all eligible subjects. However, the data obtained from this pilot work supports the statement that the DST is less specific and sensitive than the DEX/CRH and that it is feasible to use the DEX/CRH in an FM population.

Also, antidepressant medications were not discontinued prior to HPA axis testing. In future studies, the control of potential HPA-attenuating medications may be necessary to eliminate confounding effects of medications on the HPA axis.

Lastly, findings may differ in persons newly diagnosed with FM compared

to persons with long-standing FM, as the HPA axis may change during the trajectory of FM. The six year difference in the mean number of years with FM symptoms between the FM/MDE and FM/ADE and FM/MDE and FM no MDD groups may indicate there is an initial period of HPA axis hyperactivity followed by a subsequent blunting of the negative feedback mechanisms resulting in eventual HPA axis hypoactivity. It would be interesting to evaluate this finding further in a large epidemiological study with a less labor-intensive measure of cortisol, such as salivary cortisol. In addition, baseline cortisol levels (prior to administration of dexamethasone and Acthrel) may lend greater understanding of the effects of these suppressing and activating medications on individual cortisol levels.

Clinical and Research Applicability

Clinical Applicability

The novel findings of biochemical subtypes of MDD in this FM sample may foretell a significant shift in the assessment of persons with FM and concurrent MDD. Traditionally, MDD subtype testing has not been routinely evaluated in psychiatry let alone primary care or Rheumatology practices. However, the use of the DSM-IV criteria to diagnose the presence of either of these MDD subtypes would require less than an hour and may provide significant insight into the HPA axis functioning without expensive or invasive testing. It is conceivable that initial assessment and ongoing evaluation would routinely include assessment of depression subtypes to identify if there is hyperactive versus hypoactive HPA axis functioning occurring. Individual interventions

targeted at attenuating or activating the HPA axis and rebalancing CRH, cortisol, serotonin, and norepinephrine may be helpful in reducing the impact of FM and MDD symptoms.

As discussed above, there is clinical data that supports the symptoms of ADE respond better to HPA activating antidepressants and the symptoms of MDE respond better to HPA attenuating antidepressants. Historical research has identified a significant differential response of patients with ADE to monoamine oxidase inhibitors, yet less than 2% of psychiatrists prescribe this class of antidepressant. With the recent approval of selegiline (Emsam), MAOI's may become more tolerable and clinically appropriate to use in FM patients non-responsive to SSRI or SNRI antidepressants. As more knowledge is discovered regarding polymorphisms of glucocorticoid receptors, the theory of altered glucocorticoid functioning in MDE and ADE is increasingly being considered for possible interventions. Case in point, investigations are currently ongoing for development of pharmaceutical interventions to target improving glucocorticoid receptor responsiveness.

Research Applicability

The novel findings from the current research study supports the theoretical framework of Chrousos and Gold that there are two distinct biological subtypes of MDD in an FM sample that demonstrate different cortisol suppression in response to DST and DEX/CRH testing. The findings also show the psychological characteristics of these two subtypes to be similar to those found in depressed non-FM populations. Identifying MDD subtypes may limit variability

when measuring the HPA and GH axes in future studies. Therefore, this finding supports the need for future research to identify subtypes of MDD prior to measuring cortisol and other HPA axis hormones.

Many interesting study design issues came to light during the conduct of this study. For instance, it was difficult to recruit non-depressed FM persons and persons with FM/MDE. Consultation with my dissertation committee members, who are respected clinicians and researchers, expressed the possibility that the presence of "depression" in the title of the research flyer may have contributed to the low response rate. When the Institutional Review Board approved the removal of this word from the invitation letter and recruitment flyers, and the letters were resent and the recruitment flyers were replaced, there was a significant increase in response rates. One implication for future recruitment in this population is to eliminate any pejorative wording from printed materials that may decrease the response rate, such as "depression".

Future Directions

The next logical step in furthering this line of investigation is to replicate the study in a larger population to ensure adequate power is obtained using the combined DEX/CRH stimulation testing in all subjects. Also, it will be essential to ensure a more uniform distribution of FM/MDD subtypes among the three groups is obtained for aim one and equal groups are maintained for aims 2 and 3.

The cost/benefit ratio of the combined DEX/CRH stimulation test needs to be examined in more detail to determine if the increased specificity and sensitivity outweigh the cost and time needed to conduct the test. Other forms of

cortisol evaluation, such as the salivary cortisol test, also need to be investigated to determine if they are as reliable as plasma testing.

Another issue that warrants investigation is whether or not non-pharmacological interventions targeted at reducing HPA axis hyperactivity such as decreasing heart rate variability through biofeedback (Del Pozo, Gevirtz, Scher & Guarneri, 2004) or if changing illness self-concept through psychotherapy (Morea, Friend, & Bennett, 2007) would alter disease progression and/or severity in FM patients with concurrent MDD. Further research is necessary to determine if these interventions are effective in a depressed FM population.

In conclusion, although much has been discovered concerning the pathophysiology of fibromyalgia and depression, there remain significant gaps in the literature and in our knowledge base regarding the psychological and physiological characteristics of depression subtypes in FM. These gaps need to be investigated further as more information regarding the biochemical markers of MDD subtypes in FM is needed to identify possible clinical tests to assist in the diagnosis of depression subtypes and also to discover targets amenable to psychological and pharmacological interventions. It is my intent to continue this research trajectory in the hope that it may provide novel information regarding HPA axis dysfunction and further elucidate the biochemical underpinnings of FM and MDD to assist in alleviating the negative impact of these diseases on the lives of persons with FM and/or MDD, their families and society as a whole.

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Appendixes

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   - H. Quality of Life Scale
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Appendix A

I. Appendix A: Assessment and Measurement Tools

A. Beck Depression Inventory- 1973 Revision
B. Current Medication List
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E. Tender Points / Cumulative Myalgia Score
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I. Structured Interview Guide for the Hamilton Depression Rating Scale: Seasonal Affective Disorder- Self-report Version
J. Jenkins Sleep Scale

Appendix A

A. Beck Depression Inventory- 1973 Revision

OHSU General Clinical Research Center

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Beck Depression Inventory - 1973 Revision

Today's Date:(MM/DD/YYYY) _____ / _____ / _____ Participant No: _____

Instructions: This is a questionnaire. On the questionnaire are groups of statements. Please read the entire group of statements in each category. Then pick out the one statement in that group which best describes the way you feel today, that is, right now! Check the box beside the statement you have chosen.

Be sure to read all the statements in each group before making your choice.

1.

- ☐ I do not feel sad
- ☐ I feel sad
- ☐ I am sad all the time and I can't snap out of it
- ☐ I am so sad or unhappy that I can't stand it

2.

- ☐ I am not particularly discouraged about the future
- ☐ I feel discouraged about the future
- ☐ I feel I have nothing to look forward to
- ☐ I feel that the future is hopeless and that things cannot improve

3.

- ☐ I do not feel like a failure
- ☐ I feel I have failed more than the average person
- ☐ As I look back on my life all I can see is a lot of failures
- ☐ I feel I am a complete failure as a person

4.

- ☐ I get as much satisfaction out of things as I used to
- ☐ I don't enjoy things the way I used to
- ☐ I don't get real satisfaction out of anything anymore
- ☐ I am dissatisfied or bored with everything

5.

- ☐ I don't feel particularly guilty
- ☐ I feel guilty a good part of the time
- ☐ I feel quite guilty most of the time
- ☐ I feel guilty all of the time

6.

- ☐ I don't feel I am being punished
- ☐ I feel I may be punished
- ☐ I expect to be punished
- ☐ I feel I am being punished

7.

- ☐ I don't feel disappointed in myself
- ☐ I am disappointed in myself
- ☐ I am disgusted with myself
- ☐ I hate myself

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Beck Depression Inventory - 1973 Revision

Be sure to read all the statements in each group before making your choice.

8.

- I don't feel I am any worse than anybody else
- I am critical of myself for my weaknesses or mistakes
- I blame myself all the time for my faults
- I blame myself for everything bad that happens

9.

- I don't have any thoughts of killing myself
- I have thoughts of killing myself but I would not carry them out
- I would like to kill myself
- I would kill myself if I had the chance

10.

- I don't cry any more than usual
- I cry more now than I used to
- I cry all the time now
- I used to be able to cry but now I can't cry even though I want to

11.

- I am no more irritated now than I ever am
- I get annoyed or irritated more easily than I used to
- I feel irritated all the time now
- I don't get irritated at all by the things that used to irritate me

12.

- I have not lost interest in other people
- I am less interested in other people than I used to be
- I have lost most of my interest in other people
- I have lost all of my interest in other people

13.

- I make decisions about as well as I ever could
- I put off making decisions more than I used to
- I have greater difficulty in making decisions than before
- I can't make decisions at all any more

14.

- I don't feel I look any worse than I used to
- I am worried that I am looking old or unattractive
- I feel that there are permanent changes in my appearance that make me look unattractive
- I believe that I look ugly

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Beck Depression Inventory - 1973 Revision

Be sure to read all the statements in each group before making your choice.

15.

- I can work about as well as before
- It takes extra effort to get started at doing something
- I have to push myself very hard to do anything
- I can't do any work at all

16.

- I can sleep as well as usual
- I don't sleep as well as I used to
- I wake up 1-2 hours earlier than usual and find it hard to get back to sleep
- I wake up several hours earlier than I used to and cannot get back to sleep

17.

- I don't get any more tired than usual
- I get tired more easily than I used to
- I get tired from doing almost anything
- I am too tired to do anything

18

- My appetite is not worse than usual
- My apetite is not as good as it used to be
- My appetite is much worse now
- I have no appetite at all any more

19.

- I haven't lost much weight, if any, lately
- I have lost more than 5 pounds
- I have lost more than 10 pounds
- I have lost more than 15 pounds

I am purposely trying to lose weight by eating less

- Yes
- No

20.

- I am no more worried about my health than usual
- I am worried about physical problems such as aches and pains; or upset stomach; or constipation
- I am very worried about physical problems and it's hard to think of much else
- I am so worried about my physical problems, I cannot think about anything else

21.

- I have not noticed any recent change in my interest in sex
- I am less interested in sex than I used to be
- I am much less interested in sex now
- I have lost interest in sex completely

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Appendix A

B. Current Medication List

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Current Medication List

Current Date: (MM/DD/YYYY) ____ / ____ / ____ Participant No: ____

Name	Dose (mg/day)	Frequency of Use (# of days a week)

Appendix A

C. Demographic Data Form

OHSU General Clinical Research Center

4018312469

Demographic Data Form

Today's Date: (MM/DD/YYYY) ____ / ____ / ____ Participant No: ____

Directions: Please answer all of the following questions accurately. The information you provide will only be used for purposes of this project. The information will not be seen by anyone else, including your health care provider or insurance company.

1. Age: ____ years

2. Education:

- ☐ No school
- ☐ 1-9 grade
- ☐ 10-12 grade
- ☐ High school graduate or GED
- ☐ Some college or trade school
- ☐ College degree
- ☐ Graduate degree or higher
- ☐ Other, explain ____

3. Employed outside the home:

- ☐ Full time
- ☐ Part time
- ☐ Not employed outside the home

4. Occupation:

- ☐ Skilled laborer
- ☐ Clerical/sales
- ☐ Technical/semi professional
- ☐ Executive/professional
- ☐ Homemaker
- ☐ Retired, previous occupation
- ☐ Other, explain

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2693312466

Demographic Data Form

Directions: Please answer all of the following questions accurately.

5. **Receiving Disability Payments:**
   - ☐ Yes
   - ☐ No

6. **Number of years you believe you have had fibromyalgia:** _____ years

7. **Number of years you have been diagnosed with fibromyalgia by a health care provider:** _____ years

8. **Marital status:**
   - ☐ Married
   - ☐ Separated
   - ☐ Single
   - ☐ Living together
   - ☐ Other

9. **Race**
   - ☐ Hispanic or Latino
   - ☐ Not Hispanic or Latino
   - ☐ Unknown or not reported

10. **Ethnicity: (check as many as applicable)**
    - ☐ Black or African-American
    - ☐ Asian
    - ☐ Native Hawaiian or Other Pacific Islander
    - ☐ American Indian/Alaska Native
    - ☐ White
    - ☐ Unknown or not reported

11. **Have you ever smoked?**
    - ☐ Yes
    - ☐ No

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Demographic Data Form

Directions: Please answer all of the following questions accurately.

12. Do you smoke now?

☐ Yes If yes, how many cigarettes per day? _____ # per day

☐ No

13. Over the past month, have you exercised regularly?

☐ Yes

☐ No

If you answered NO to question 13, SKIP to question 17

14. If you answered YES to question 13, what type of exercise do you usually do?

☐ Walking

☐ Cycling

☐ Aerobics/Dance classes

☐ Swimming or water exercise classes

☐ Stretching

☐ Yoga

☐ Weight lifting

☐ Other, please be as specific as possible _____

_____

15. On the average, how many days per week do you exercise? _____ days/week

16. On the average, how many minutes do you exercise at one time? _____ minutes

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Demographic Data Form

The research staff will contact you in the next few weeks to ask you some additional questions and answer any questions you have about the research study. They will also inform you about the group to which you have been assigned. Please write you address and phone number below. This will allow us to keep in contact with you during the study period and send you the results when the study has been completed.

Name

Street Address

City **State** **Zip Code**

Home Phone Number **Work Phone Number**

___ - ___ - ____ ___ - ___ - ____

Best time to call **E-Mail (optional)**

__ : __ ☐ AM ☐ PM

Although your participation in the study is only 6 months, the overall study will last 4 years. Please list someone NOT living in your home who can usually get in touch with you in the event that your contact information changes.

Name

Street Address

City **State** **Zip Code**

Home Phone Number **Work Phone Number**

___ - ___ - ____ ___ - ___ - ____

Relationship to you

Appendix A

D. Clinical Data Form

OHSU General Clinical Research Center

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Clinical Data

Today's Date: (MM/DD/YYYY) ___ / ___ / _____ Participant No: _____

Fibromyalgia Confirmation via ACR 1990 Criteria

Does participant have pain in 3 of 4 body quadrants? (See Symptom Survey) (Left of midline, right of midline, above the waist, below the waist)	☐ Yes	☐ No
Does participant have at least 13 of 18 tenderpoints on palpation? (See tender point/cumulative myalgic diagram)	☐ Yes	☐ No
Current or planned pregnancy or nursing in next 6 months?	☐ Yes	☐ No

Estrogen status:

Hysterectomy?	☐ Yes	☐ No	Birth control Pills?	☐ Yes	☐ No
Menopausal?	☐ Yes	☐ No	Hormone Replacement?	☐ Yes	☐ No

LMP: ___ / ___ / _____ PLMP: ___ / ___ / _____

Describe OB and GYN history:

Drug Allergies? ☐ Yes ☐ No

WHAT:

Past Medical History

Please check if you have ever had any of the following:

☐ Arthritis	☐ Unexplained Bleeding	☐ Vascular Disease
☐ Alcoholism	☐ AIDS/HIV Disease	☐ Depression
☐ Tuberculosis	☐ Emphysema	☐ Migraine
☐ Asthma	☐ Gallstones	☐ Lung Disease
☐ High Triglycerides	☐ Allergies	☐ Anemia
☐ High Cholesterol	☐ High Blood Pressure	☐ Endometriosis
☐ Anorexia	☐ Liver Disease	☐ Bulimia
☐ Pituitary disease or surgery	☐ Epilepsy	☐ Gout
☐ Diabetes	☐ Thyroid Disease	☐ Irritable Bowel or Bladder
☐ Ulcers	☐ Cancer	☐ Other
☐ Stroke	☐ High Blood Sugar	

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Clinical Data

Family medical history of:

Premature heart disease ☐ Yes ☐ No # of 1st degree relatives: ____

Chronic pain ☐ Yes ☐ No # of 1st degree relatives: ____

Review of Systems

Cardiac:

- ☐ Chest pain with exertion
- ☐ Edema
- ☐ Palpitations
- ☐ History of heart murmur
- ☐ Fainting
- ☐ Family history of sudden death
- ☐ Orthopnea

Respiratory:

- ☐ History of lung disease or asthma
- ☐ Wheezing
- ☐ Chronic cough
- ☐ Shortness of breath

Musculoskeletal:

Are you able to walk on a treadmill with an incline? ☐ Yes ☐ No

Physical Exam

Vital signs: BP ____ / ____ HR ____ R ____

Cardiac: RRR, no murmurs, ribs, gallops, no S3 or S4 ☐ Yes ☐ No

Note if otherwise: ____

Respiratory: Clear to auscultation, all lobes ☐ Yes ☐ No

Note if otherwise: ____

Musculoskeletal: WNL except for tender point exam ☐ Yes ☐ No

Deformities ____

Limitations ____

Primary Care Provider

First Name ____ Last Name ____

Number & Street Address ____

City ____ State ____ Zip Code ____

Phone Number ____ - ____ - ____

Appendix A

E. Tender Points / Cumulative Myalgia Score

OHSU General Clinical Research Center

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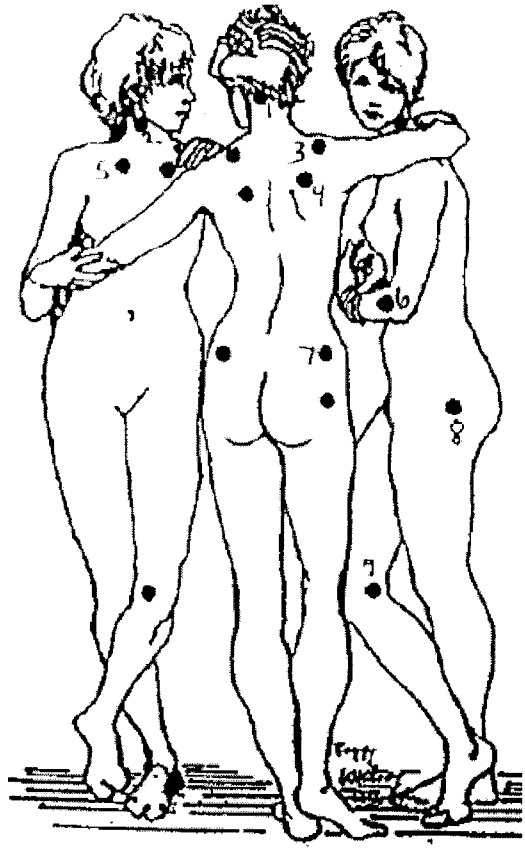
Tenderpoints/Cumulative Myalgic Score

	No pain	Some pain	Ouch	Moves Away
1. Occiput Left	☐ 0	☐ 1	☐ 2	☐ 3
Occiput Right	☐ 0	☐ 1	☐ 2	☐ 3
2. Low Cervical Left	☐ 0	☐ 1	☐ 2	☐ 3
Low Cervical Right	☐ 0	☐ 1	☐ 2	☐ 3
3. Trapozius Left	☐ 0	☐ 1	☐ 2	☐ 3
Trapozius Right	☐ 0	☐ 1	☐ 2	☐ 3
4. Supra spinatus Left	☐ 0	☐ 1	☐ 2	☐ 3
Supra spinatus Right	☐ 0	☐ 1	☐ 2	☐ 3
5. Second Rib Left	☐ 0	☐ 1	☐ 2	☐ 3
Second Rib Right	☐ 0	☐ 1	☐ 2	☐ 3
6. Lateral epicondyle Left	☐ 0	☐ 1	☐ 2	☐ 3
Lateral epicondyle Right	☐ 0	☐ 1	☐ 2	☐ 3
7. Gluteal Left	☐ 0	☐ 1	☐ 2	☐ 3
Gluteal Right	☐ 0	☐ 1	☐ 2	☐ 3
8. Greater Trochanter Left	☐ 0	☐ 1	☐ 2	☐ 3
Greater Trochanter Right	☐ 0	☐ 1	☐ 2	☐ 3
9. Knee Left	☐ 0	☐ 1	☐ 2	☐ 3
Knee Right	☐ 0	☐ 1	☐ 2	☐ 3



Total Myalgic Score: ____

# of Tender Points: ____

Appendix A

F. Fibromyalgia Impact Questionnaire

OHSU General Clinical Research Center

0767448590

Fibromyalgia Impact Questionnaire (FIQ)

Participant No: _____

Directions

For questions 1 through 11, please fill in the circle, **beside the number**, that best describes how you did overall for **the past week**. If you don't normally do something that is asked, do not fill in a circle for that question. For questions 12 and 13, please fill in the circle, **above the number**, that best answers the question.

Where you able to:	Always	Most	Occasionally	Never
1. Do shopping?	○ 0	○ 1	○ 2	○ 3
2. Do laundry with a washer and dryer?	○ 0	○ 1	○ 2	○ 3
3. Prepare meals?	○ 0	○ 1	○ 2	○ 3
4. Wash dishes/cooking utensils by hand?	○ 0	○ 1	○ 2	○ 3
5. Vacuum a rug?	○ 0	○ 1	○ 2	○ 3
6. Make beds?	○ 0	○ 1	○ 2	○ 3
7. Walk several blocks?	○ 0	○ 1	○ 2	○ 3
8. Visit friends or relatives?	○ 0	○ 1	○ 2	○ 3
9. Do yard work?	○ 0	○ 1	○ 2	○ 3
10. Drive a car?	○ 0	○ 1	○ 2	○ 3
11. Climb stairs?	○ 0	○ 1	○ 2	○ 3

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

○	○	○	○	○	○	○	○
0	1	2	3	4	5	6	7

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

○	○	○	○	○	○	○	○
0	1	2	3	4	5	6	7

OHSU General Clinical Research Center

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Fibromyalgia Impact Questionnaire (FIQ)

Participant No: _____

Directions

For the remaining items, fill in the circle, **within the range**, that best indicates how you felt overall for the **past week**.

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

○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○

No problem with work — **Great difficulty with work**

15. How bad has your pain been?

○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○

No pain — **Very severe pain**

16. How tired have you been?

○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○

No tiredness — **Very tired**

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

○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○

Awoke well rested — **Awoke very tired**

18. How bad has your stiffness been?

○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○

No stiffness — **Very stiff**

19. How nervous or anxious have you felt?

○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○

Not anxious — **Very anxious**

20. How depressed or blue have you felt?

○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○

Not depressed — **Very depressed**

Appendix A

G. Flannigan's Quality of Life Scale

OHSU General Clinical Research Center

0366446597

Fibromyalgia Impact Questionnaire (FIQ)

Participant No: _____

Directions

For the remaining items, fill in the circle, **within the range**, that best indicates how you felt overall for **the past week**.

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

○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○

No problem with work — **Great difficulty with work**

15. How bad has your pain been?

○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○

No pain — **Very severe pain**

16. How tired have you been?

○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○

No tiredness — **Very tired**

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

○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○

Awoke well rested — **Awoke very tired**

18. How bad has your stiffness been?

○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○

No stiffness — **Very stiff**

19. How nervous or anxious have you felt?

○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○

Not anxious — **Very anxious**

20. How depressed or blue have you felt?

○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○

Not depressed — **Very depressed**

Appendix A

H. Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement

STRUCTURED INTERVIEW GUIDE FOR THE HAMILTON DEPRESSION RATING SCALE with Atypical Depression Supplement

(SIGH-ADS 2003)

Janet B.W. Williams, D.S.W. and Michael Terman, Ph.D.

PATIENT'S NAME: _____ I.D. CODE: _____

INTERVIEWER: _____ DATE: ___/___/___

INTERVIEW SETTING: 1 – phone 2 – live DAY OF THE WEEK: ___

FOR PRE-MENOPAUSAL FEMALES, READ TO PATIENT:
When did your last period begin?

LAST MENSTRUAL PERIOD:

___/___/___

AS APPROPRIATE (FOR BLIND RATINGS), READ TO PATIENT: Please don't tell me if you have been on treatment this past week. I need to evaluate how you have been feeling, without knowing about your treatment. We can talk about everything else.

In general, how have you been feeling over the past seven days? (How long have you been feeling this way?)

OVERVIEW (note if patient mentions depressed mood or equivalent):

Over the last week, would you say that your mood and energy have been fairly consistent from day to day, or has there been any major change – either upward or downward -- from the beginning to the end of the week?

NOTE TO RATER: Try to use past 7 days. Exclude initial days of past week only if distinctly different from later in the week. Fewer than 4 days may result in unreliable judgments.

ESTABLISH EVALUATION WINDOW ENDING ON CURRENT DAY
(check one):

- ☐ 7 days
- ☐ 6 days
- ☐ 5 days
- ☐ 4 days
- ☐ 1-3 days

OK, then, for the next questions about your symptoms, please tell me how you've been feeling, on average, over the last (NUMBER) days, since last (DAY OF WEEK).

First day of evaluation window
(circle one):

Sun / Mon / Tue / Wed / Thu / Fri / Sat

In the last (NUMBER) days, have you been physically ill or taking any medications?

(I don't mean depression, low energy or trouble sleeping.)
(I don't mean antidepressants or sleeping pills.)

PHYSICAL ILLNESS AND DRUGS:

H1: What has your mood been like over the past (NUMBER) days compared to when you've felt well or OK?

Have you been feeling down or depressed?

Sad? Hopeless? Helpless? Worthless?

Over the last (NUMBER) days, how often have you felt (OWN EQUIVALENT)? Has it been every day or only some days? Has it lasted all day long or only parts of the day? About how much of the day?

Have you been crying at all?

DEPRESSED MOOD (sad, hopeless, helpless worthless):

0 – absent
1 – indicated only on questioning
2 – spontaneously reported verbally
3 – communicated non-verbally, i.e., facial expression, posture, voice, tendency to weep
4 – VIRTUALLY ONLY this in spontaneous verbal and non-verbal communication

NOTE TO RATER: All questions that ask for comparison with "well or OK" states refer to euthymic periods when the patient has felt "normal and calm," rather than somewhat depressed (as in dysthymia) or "speedy or high" (as in bipolar I or II disorder). If patient cannot identify a euthymic period (as in chronic depression), ask for a time that was "the best you have felt." If patient is not currently depressed, it may be necessary to adjust the time reference of certain stem questions. For example, in H1, the comparison would become "when you've usually felt well or OK."

H2: IF OUTPATIENT: Have you been working since last (DAY OF WEEK) (in or out of the home)?
IF NOT: Why not?

IF WORKING: Have you been able to get as much (work) done as you usually do (when you're feeling OK)?

How have you been spending your time since last (DAY OF WEEK), outside of work?

Have you felt interested in doing (THOSE THINGS), or have you had to push yourself to do them?

Have you stopped doing anything you would ordinarily do if you were feeling OK? IF YES: What? Why?

Is there anything you look forward to doing?

WORK AND ACTIVITIES:

0 – no difficulty
1 – thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies
2 – loss of interest in activities, hobbies or work – by direct report of the patient or indirect: listlessness, indecision and vacillation (feels it necessary to push self to work or activities)
3 – decrease in actual time spent in activities or decrease in productivity. In hospital, patient spends less than 3 h/day in activities (hospital job or hobbies) exclusive of ward chores
4 – stopped working because of present illness. In hospital, no activities except ward chores, or fails to perform ward chores unassisted

A1: **In the last (NUMBER) days, have you been spending less time with people, or talking to people less than when you feel well?**

IF YES: Have you just felt less interested in being social, or have you actually spent less time being with other people? Have you been interacting less with colleagues at work? How about with your family? How big a change is this for you?

IF NO: Have you felt less interested in being social with people even though you are still doing so? Would they notice that anything is different?

* SOCIAL WITHDRAWAL:

0 – interacting with people as usual
1 – less interested in socializing with others but continues to do so
2 – interacting less in social (i.e., optional) situations
3 – interacting less in work or family situations (i.e., where this is necessary)
4 – marked withdrawal from others in family or work situations

H3: Since last (DAY OF WEEK), how has your interest in sex been – relative to what's normal for you? (I'm not asking about your sexual activity, but about your interest in sex – how much you think about it.)

Has there been any change in your interest in sex (from when you were not depressed)?

Is it something you've thought much about? IF NO: Is that unusual for you compared to when you feel well?

Would you say your interest in sex is somewhat less or a lot less than is normal for you?

GENITAL SYMPTOMS (such as loss of libido, menstrual disturbances):

0 – absent
1 – mild
2 – severe

H4: **How has your appetite been since last (DAY OF WEEK), compared to your usual appetite when you're feeling well?**

Have you had to force yourself to eat?

Have other people had to urge you to eat? (Have you been skipping meals?)

Have you had any stomach or intestinal problems? (Have you needed to take anything for that?)

SOMATIC SYMPTOMS GASTROINTESTINAL:

0 – none
1 – loss of appetite but eating without encouragement
2 – difficulty eating without urging/ requests or requires laxatives or medication for gastrointestinal symptoms

H5: **Have you been losing weight** (while you've been depressed)?

IF YES: Have you lost any weight since last (DAY OF WEEK)? How much did you lose? Was it because of feeling depressed or down? (Have you been dieting or exercising a lot?)

IF NOT SURE: Do your clothes feel any looser on you?

LOSS OF WEIGHT (rate either A or B):

A. When rating by history:
0 – no weight loss in past week
1 – probable weight loss due to current depression
2 – definite (according to patient) weight loss due to depression
3 – not assessed

B. When actual weight changes are measured:
0 – less than 1 lb (~0.5 kg) loss in a week
1 – greater than 1 lb (~0.5 kg) loss in a week
2 – greater than 2 lb (~0.9 kg) loss in a week
3 – not assessed

A2: **ASK ONLY IF NO WEIGHT LOSS WAS REPORTED IN H5: Have you gained any weight since last (DAY OF WEEK)?**

IF YES: How much did you gain? Was it because of feeling depressed or down?

IF NOT SURE: Do your clothes feel any tighter?

*WEIGHT GAIN:

0 – no weight gain (or weight loss reported in H5)
1 – probable weight gain due to current depression
2 – definite (according to patient) weight gain due to depression

A3: Now we're going to talk about your appetite, rather than the amount you actually eat. Since last (DAY OF WEEK), has your appetite been greater than when you feel well or OK?

IF YES: Do you want to eat a little more, somewhat more, or much more than when you feel well?

*APPETITE INCREASE:

0 – no increase in appetite
1 – wants to eat a little more than usual
2 – wants to eat somewhat more than usual
3 – wants to eat much more than usual

A4: Over the past (NUMBER) days, have you actually been eating more than when you feel well or OK?

IF YES: A little more, somewhat more or much more?

*INCREASED EATING:

0 – is not eating more than usual
1 – is eating a little more than usual
2 – is eating somewhat more than usual
3 – is eating much more than usual

QUESTIONS FOR RATING A5:

Since last (DAY OF WEEK), have you been craving or eating more starches or sweets than when you feel well?

IF YES:
Has it been mainly starches or mainly sweets, or both?
Give me some examples.

CARBOHYDRATE CRAVING OR EATING (preliminary questions):

CIRCLE ONE OR BOTH: Mainly starches | Mainly sweets

EXAMPLES:

Have you actually been eating more (STARCHES AND/OR SWEETS), or just craving them?

Has this (CRAVING OR EATING) usually occurred at any particular time of day?
(____ a.m. / p.m.)

CIRCLE ONE OR BOTH: Craving | Eating

Usual time of craving and eating:
0 – it comes and goes at various times
1 – usually morning
2 – usually afternoon or evening
3 – virtually all the time

RATER: IF BOTH CRAVING AND EATING, RATE TIME OF EATING. DO NOT COUNT ABOVE SCORE IN SCALE TOTALS.

A5: RATER: IF NO CARBOHYDRATE CRAVING OR EATING, ENTER SCORE OF "0" AND SKIP THIS QUESTION.

Have you been (CRAVING OR EATING) (STARCHES AND/OR SWEETS) more than when you feel well, many more, or has it been irresistible?

*CARBOHYDRATE CRAVING OR EATING:

0 – no change in food preference or consumption
1 – craving or eating more carbohydrates (starches and sugars) than before
2 – craving or eating much more carbohydrates than before
3 – irresistible craving or eating of carbohydrates

QUESTIONS FOR RATING H6, H7, H8, A6 AND E1:

Now let's talk about your sleep. During times when you're feeling well or OK, when do you usually fall asleep at night? And what time do you usually wake up in the morning?

I'd like to ask you now about your sleeping over the past (NUMBER) days. On average, how long has it been taking you to fall asleep at the beginning of the night?

What time have you actually been falling asleep?

During the past (NUMBER) days, have you been waking up in the middle of the night? IF YES: How long does it take you to fall back asleep? On average, how much time have you been awake at night after falling asleep?

Over the last (NUMBER) days, what's been the average time you've woken up for the day (even if you were not yet fully alert)? (Was that with an alarm clock?)

Have you been napping at all during the day? How many days? About how long are these naps? So, on average, you've been napping about (HR:MIN) per day over the last (NUMBER) days. Is that correct? (CONFIRM AND ADJUST IF NECESSARY.)

Let's review this information now. You've been falling asleep at about (SLEEP ONSET TIME) and waking up at about (FINAL WAKE-UP TIME), which comes to a total of about (HR:MIN) of sleep per night.

IF PATIENT HAS HAD INTERRUPTED SLEEP: However, when we average across days, you've been awake for about (WASO VALUE) during the night, which reduces your total sleep to (HR:MIN).

IF PATIENT HAS BEEN NAPPING: You have also been napping for about (NAP TIME) per day (if we average across days), which adds to your total sleep time.

All in all, then, you have been sleeping a total of about (HR:MIN) per day over the last (NUMBER) days. Does that seem correct? (CONFIRM AND ADJUST IF NECESSARY.)

SLEEP DATA:

Euthymic sleep onset:
__ __ : __ __ p.m. / a.m.
Euthymic wake-up time:
__ __ : __ __ a.m. / p.m.
Euthymic sleep duration (calculate onset to wake-up):
__ __ : __ __ (hh:mm)

Current delay to sleep onset:
__ __ : __ __ (hh:mm)

Current sleep onset:
__ __ : __ __ p.m. / a.m.

Total duration of middle insomnia
(wake time after first sleep onset (WASO)):
__ __ : __ __ (hh:mm)

Current morning wake-up:
__ __ : __ __ a.m. / p.m.
Alarm clock? yes / no

Total nap time per day:
__ __ : __ __ (hh:mm)

Total nightly sleep (excluding WASO):
__ __ : __ __ (hh:mm)

Total nightly sleep (correcting for WASO):
__ __ : __ __ (hh:mm)

Total sleep duration:
__ __ : __ __ (hh:mm)

H6: ASK ONLY IF PATIENT REPORTED DELAYED SLEEP ONSET (otherwise, score "0"):

Have you had any trouble falling asleep at the beginning of the night? (Right after you go to bed, how long has it been taking you to fall asleep?)

Out of the last (NUMBER) nights, how many nights have you had trouble falling asleep?

INSOMNIA EARLY (SLEEP ONSET INSOMNIA):

0 – no difficulty falling asleep
1 – complains of occasional difficulty falling asleep, i.e., more than 30 min
2 – complains of nightly difficulty falling asleep

H7: ASK ONLY IF PATIENT REPORTED NIGHTTIME SLEEP INTERRUPTIONS (otherwise, score "0"):

You said you been waking up in the middle of the night. Do you get out of bed? What do you do? (Only to go to the bathroom?)

When you get back in bed, are you able to fall right back asleep? How long does it take?

Have you felt your sleeping has been restless or disturbed some nights? How often?

INSOMNIA MIDDLE (SLEEP MAINTENANCE INSOMNIA):

0 – no difficulty
1 – complains of being restless or disturbed during the night
2 – waking during the night – any getting out of bed (except to void)

H8: ASK ONLY IF WAKE-UP TIME APPEARS ABNORMALLY EARLY (otherwise, score "0"):

You said you've been waking up for the day at about (FINAL WAKE-UP TIME). Is that earlier than you intended to wake up? When you're feeling well, what's your usual wake-up time?

INSOMNIA LATE (EARLY AWAKENING):

0 – no difficulty
1 – waking in early hours of morning but goes back to sleep
2 – unable to fall asleep again if gets out of bed

E1: **Since last (DAY OF WEEK), how difficult has it been for you to wake up in the morning?** How long (after the alarm rings) has it taken you to feel wide-awake or fully alert? (__ __ hh:mm)

(Are you refreshed or sleepy after you wake up? How hard has it been to get out of bed? Have you been ignoring the alarm and going back to sleep? What about on weekends or days off?)

DIFFICULTY AWAKENING (including weekends or days off):

0 – no difficulty, wakes up alert
1 – wide awake within 30 min (with or without an alarm)
2 – feels sleepy for more than 30 min
3 – requires major effort to get out of bed, feels sleepy for at least 3 h
4 – feels sleepy for at least 5 h

RATER: DO NOT COUNT ABOVE SCORE IN SCALE TOTALS.

Time of alarm: __ __ : __ __ a.m. / p.m.

A6: RATING BASED ON COMPARISON OF TOTAL SLEEP DURATION TO TOTAL *EUTHYMIC* SLEEP DURATION.

HYPERSOMNIA (Compare sleep length to euthymic and NOT to hypomanic sleep length. If this cannot be established, use 8 hours.):

0 – no increase in sleep length
1 – at least 1 h increase in sleep length
2 – 2-3 h increase
3 – 3-4 h increase
4 – increase of 4 h or more

Sleep length used (circle one):

euthymic ___ ___ : ___ ___ (hh:mm) 8 hours

H9: How has your energy been since last (DAY OF WEEK)?

IF LOW: Have you felt tired? (How much of the time? How bad has it been?)

Have you had any aches or pains? Backaches, headaches or muscle aches? Do you think the (ACHES) are related to your depression, or is there some other reason?

Have you had any feelings of heaviness in your limbs, back or head? (DESCRIBE.)

SOMATIC SYMPTOMS GENERAL:

0 – none
1 – heaviness in limbs, back or head. Backaches, headaches, muscle aches. Loss of energy, fatigability.
2 – any clear-cut symptom

A7: RATER: IF NO SYMPTOMS REPORTED FOR H9, ENTER SCORE OF "0" AND SKIP THIS QUESTION. IF FATIGABILITY IS PRESENT, SCORE THIS ITEM. IF NECESSARY, ASK:

How much of the time have you felt tired? (Every day? How much of each day?)

Very tired, or just a little?

*FATIGABILITY (or low energy or feelings of being heavy, leaden, weighed down):

0 – does not feel more fatigued than usual
1 – feels more fatigued than usual but this has not impaired function
2 – more fatigued than usual at least 1 h per day, 3 days per week
3 – fatigued much of the time, most days
4 – fatigued almost all the time

H10: Have you been putting yourself down over the past (NUMBER) days, feeling you've done things wrong or let others down?

IF YES: What have your thoughts been?

Have you been feeling guilty about anything that you've done or not done? Are your thoughts focused on current problems, or also on things that happened a long time ago?

Have you been thinking that you are responsible in some way for bringing on (YOUR DEPRESSION)?

Do you feel that your being (DEPRESSED) is a punishment for anything you've done or not done?

FEELINGS OF GUILT:

0 – absent
1 – self-reproach, feelings of letting other people down
2 – ideas of guilt or rumination over past errors or sinful deeds
3 – present illness is a punishment; delusions of guilt
4 – hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

H11: **Since last (DAY OF WEEK), have you had any thoughts that life is not worth living?**

IF YES: What about thinking that you would be better off dead? Have you had any thoughts of hurting yourself? Of killing yourself? What have you been thinking about? Have you actually done anything to hurt yourself?

SUICIDE:

0 – absent
1 – feels life is not worth living
2 – wishes to be dead, or any thoughts of possible death to self
3 – suicidal ideation or gesture
4 – attempts at suicide

H12: **Have you been feeling especially tense or irritable since last (DAY OF WEEK)?**

IF YES: Is this more than when you are not depressed or down?

Have you been unusually argumentative or impatient with people?

Have you been worrying a lot about little things, minor matters that ordinarily wouldn't bother you and that you would usually ignore or put aside?
IF YES: Like what, for example?

ANXIETY PSYCHIC:

0 – no difficulty
1 – subjective tension and irritability
2 – worrying about minor matters
3 – apprehensive attitude apparent in face or speech
4 – fears expressed without questioning

H13: **People sometimes have physical symptoms that can go along with feeling anxious. I'm going to read you a list of symptoms. Stop me if you have had any of these since last (DAY OF WEEK).**

UNDERLINE POSITIVE SYMPTOMS AT RIGHT. SLOWLY READ LIST ALOUD: dry mouth, indigestion, gas, diarrhea, stomach cramps, belching, heart palpitations, headaches, hyperventilating, sighing out loud, urinating more frequently than usual, sweating.

Why do you think you are having these symptoms? (Do you think they might have to do with your being depressed or down?) How much have these things been bothering you since last (DAY OF WEEK)? (How much of the time or how often have you had them?)

Do you think these symptoms may have been caused by something else (like being sick or having a bad meal, or a side effect of a drug)? IF YES, NOTE CIRCUMSTANCES TO THE RIGHT, BUT RATE SYMPTOMS REGARDLESS OF CAUSE.

ANXIETY SOMATIC:
Physiologic concomitants of anxiety, e.g.:
Gastrointestinal—dry mouth, indigestion, gas, diarrhea, cramps, belching
Cardiovascular—heart palpitations, headaches
Respiratory—hyperventilating, sighing
Other—frequent urination, sweating

0 – absent
1 – mild
2 – moderate
3 – severe
4 – incapacitating

Note possible alternate causes of somatic symptoms:

F2: Over the past (NUMBER) days, have you felt either too warm or too cold, even when the temperature is comfortable for other people?

IF YES: Is it mostly during the day, mostly at night, or both?

Do you need to wear a sweater when other people don't? Do you find that a hot shower helps increase your energy? Do you continually try to change the thermostat (UP OR DOWN)? Have other people commented that you seem uncomfortably (COLD OR WARM?)

What about at night?

TEMPERATURE DISCOMFORT:

Cold:
0 – usually feels comfortable or too hot
1 – often feels too cool
2 – often feels too cold

Time of day feels cool or cold:
1 – daytime
2 – nighttime
3 – both day and night

Hot:
0 – usually feels comfortable or too cold
1 – often feels too warm
2 – often feels too hot

Time of day feels warm or hot:
1 – daytime
2 – nighttime
3 – both day and night

RATER: DO NOT COUNT ABOVE SCORES IN SCALE TOTALS.

H14: Over the last (NUMBER) days, how much have your thoughts been focused on your physical health or how your body works, compared to your normal thinking? (I'm not talking about just feeling tired or having problems sleeping.)

Have you worried a lot about being or becoming physically ill? Have you really been preoccupied with this? Have you spoken with your doctor about this? What does your doctor say?

Have you been complaining to other people about how you feel physically?

Have you found yourself asking for help with things you could really do on your own? IF YES: Like what, for example? How often has that been happening?

HYPOCHRONDRIASIS:

0 – not present
1 – self-absorption (bodily)
2 – preoccupation with health
3 – frequent complaints, requests for help, etc.
4 – hypochondriacal delusions

H15: RATING BASED ON OBSERVATION DURING INTERVIEW.

INSIGHT:

0 – acknowledges being depressed and ill, OR is not currently depressed
1 – acknowledges illness but attributes cause to bad food, overwork, virus, need for rest, etc.
2 – denies being ill at all

H16: RATING BASED ON OBSERVATION DURING INTERVIEW.

IF TELEPHONE INTERVIEW: Do you feel that your speech or physical movements are sluggish? Has anyone actually commented on it?

RETARDATION (slowness of thought and speech; impaired ability to concentrate; decreased motor activity):

0 = normal speech and thought
1 = slight retardation at interview
2 = obvious retardation at interview
3 = interview difficult
4 = complete stupor

H17: RATING BASED ON OBSERVATION DURING INTERVIEW.

IF TELEPHONE INTERVIEW: As we talk, are you fidgeting at all or having trouble sitting still? Are you doing anything like playing with your hands or your hair, or tapping your foot? Have other people been noticing that you're restless?

AGITATION:

0 = none
1 = fidgetiness
2 = playing with hands, hair, etc.
3 = moving about, can't sit still
4 = hand-wringing, nail biting, hair-pulling, biting of lips

TOTAL 17-ITEM HAMILTON DEPRESSION SCORE (without starred items): ____

QUESTIONS FOR RATING H18 (ASK ONLY IF PATIENT IS CURRENTLY DEPRESSED; OTHERWISE RATE "0"):

Think about your mood and energy in the morning and the evening over the past (NUMBER) days. In the first few hours after you wake up, have you been feeling generally better or worse or no different from the last few hours before you go to sleep?

IF VARIATION: Is it mostly your mood or mostly your energy that changes, or is it both?

DIURNAL VARIATION TYPE A:

Note whether symptoms are worse after awakening or before sleeping:

0 - no difference OR is not currently depressed
1 - worse after awakening
2 - worse before going to sleep

RATER: DO NOT COUNT ABOVE SCORE IN SCALE TOTALS.

CIRCLE ONE OR BOTH:	Mood variation	Energy variation

H18: IF VARIATION: How much worse do you feel in the (MORNING OR EVENING)? Is it a small difference or a big difference?

Rate the severity of diurnal variation:

0 - none, OR is not currently depressed
1 - mild
2 - severe

A8: Since last (DAY OF WEEK), have you regularly had a slump in your mood or energy in the afternoon or evening? (By "slump," I mean that your mood or energy decreases, but after awhile it returns and you get a second wind.)

IF YES: Is it mostly in your mood or energy, or is it both? Has it occurred every day? At what time does the slump usually begin? (__:__ p.m.) When does it generally end? (__:__ p.m.) (Does it end at least one hour before you go to sleep?)

How big is your slump – would you say it's generally mild, moderate or severe? (By "severe," I mean that you can't resist lying down to rest or nap.)

H19: Over the past (NUMBER) days, at any time have you had the feeling that everything is unreal, that you're in a dream, or cut off from other people in some strange way? Any spacey feelings?

IF YES: Tell me about it. How bad has it been? How often has it happened since last (DAY OF WEEK)? How long does it usually last?

H20: Over the past (NUMBER) days, have you had any thoughts that someone was trying to give you a hard time or hurt you?

What about talking about you behind your back?

IF YES: Tell me about that.

H21: Since last (DAY OF WEEK), have there been certain things you found yourself doing over and over, like checking the locks on the doors several times (or washing your hands)?

IF YES: Can you give me an example? (How long does it last? Is it hard to stop doing?)

CIRCLE (FOR COMPULSIONS): YES / NO

Have you had any thoughts that don't make sense to you but keep running over and over in your mind?

IF YES: Can you give me an example?

CIRCLE (FOR OBSESSIONS): YES / NO

* DIURNAL VARIATION TYPE B:

0 – no
1 – yes, of mild intensity
2 – yes, of moderate intensity
3 – yes, of severe intensity

CIRCLE ONE OR BOTH	Mood slump	Energy slump

RATER: CONSIDER ONLY SLUMPS THAT ARE FOLLOWED BY AT LEAST ONE HOUR OF RECOVERED MOOD OR ENERGY BEFORE SLEEP.

DEPERSONALIZATION AND DEREALIZATION (such as feelings of unreality and nihilistic ideas):

0 – absent
1 – mild
2 – moderate
3 – severe
4 – incapacitating

PARANOID SYMPTOMS:

0 – none
1 – suspicious
2 – ideas of reference
3 – delusions of reference and persecution

OBSESSIONAL AND COMPULSIVE SYMPTOMS:

0 – absent
1 – mild
2 – severe

SIGH-ADS SCORE SUMMARY

TOTAL 17-ITEM HAMILTON DEPRESSION SCORE
(without starred items): _____

TOTAL 8-ITEM ATYPICAL SYMPTOMS SCORE
(starred items only): _____

TOTAL 25-ITEM SIGH-ADS SCORE
(17-item Hamilton score + 8 item Atypical Symptoms score): _____

SIGH-ADS ATYPICAL BALANCE SCORE
(total 8-item Atypical Symptoms score divided by total 25-item SIGH-ADS score, multiplied by 100): _____ %

SCORE CORRESPONDENCES WITH EARLIER INSTRUMENT VERSIONS:

TOTAL 21-ITEM HAMILTON DEPRESSION SCORE
(without starred items): _____

TOTAL 29-ITEM SIGH-*SAD* SCORE
(21-item Hamilton score + 8 item Atypical Symptoms score, as used in Seasonal Affective Disorder versions between 1988-2002): _____

SIGH-*SAD* ATYPICAL BALANCE SCORE
(total 8-item Atypical Symptoms score divided by total 29-item SIGH-ADS score, multiplied by 100, as used in Seasonal Affective Disorder Versions between 1988-2002): _____

NOTE 1 (hypomania): If patient is not depressed, and the SIGH-ADS total score is derived primarily from symptoms consistent with hypomania (e.g., items H4, H5, H6, H7, H8, H12, H17), administer the *Hypomania Interview Guide (with Hyperthymia – Current Assessment Version* (HIGH-C) and report both scores. (The HIGH-C is part of the *Clinical Assessment Tools Packet*, Center for Environmental Therapeutics, www.cet.org, email, info@cet.org.)

NOTE 2 (scoring accuracy): Having the patient complete the self-report version of the SIGH-ADS on the same visit as the interview enhances the accuracy of ratings. Ideally, a staff member other than the rater should immediately compare item scores for interview and self-report versions. The rater is informed of any item score discrepancy of 2 points or more, and asked to further probe with the patient before determining the final score. The rater's decision should be final. (The self-report instrument is part of the *Clinical Assessment Tools Packet*, Center for Environmental Therapeutics, www.cet.org, email, info@cet.org.)

NOTE 3 (translations): Valid administration of the SIGH-ADS (or its predecessor SIGH-SAD) in other languages requires an author-approved back-translation protocol. A translator in the target language writes a first draft, using a word-processor template, which is back-translated into English by a second translator who has not seen the original English version. The authors then review the back-translation with the principal investigator, on which basis the draft is revised. The process ordinarily requires several iterations prior to author approval. Publications that report SIGH-ADS (or SIGH-SAD) scores based on foreign language administration should note use of the endorsed translation. In the authors' experience, ad hoc translations are likely to introduce inadvertent changes in meaning or emphasis that compromise score validity and comparability to the English version. To arrange for back-translation and review, contact the authors.

Appendix A

I. Structured Interview Guide for the Hamilton Depression Rating Scale: Seasonal Affective Disorder- Self-report Version

Self-Report Summary

Have you been physically ill in the past week? ☐ Yes

☐ No

If yes, please explain: _____

Have you take any medications in the past week? ☐ Yes

☐ No

If yes which ones: _____

Have you had treatment(s) of any other kind in the past week? ☐ Yes

☐ No

If yes, please describe:

_____

Females (pre-menopausal): About when did your last period begin?

__|__/__|__/__|__|__|__|__

In the questions that follow, ***please circle the number*** *of* *one* *alternative in each set that* ***best*** *describes how you have been during the* *past week.* ***If you have changed during the last few days,*** *circle the alternative* ***that best describes how you are today.*** *Before you select an alternative in each set, read all of the choices to make sure you pick the most accurate one. Each new set of alternatives that you should consider begins with a pointer sign* ⇛

During the past week . . .

⇛ ***Question 1***

0 - I have **not** been feeling down or depressed at all.
1 - I have been feeling somewhat down or depressed.
2 - I have been feeling quite down or depressed.
3 - I have been feeling and looking very depressed (or others have said so).
4 - I haven't been able to think about anything else except how bad or depressed I feel.

⇛ ***Question 2***

0 - I have been keeping busy and have been interested in the things I've been doing.

1 - I haven't been quite as interested in doing things as I used to be.

2 - I have definitely not been as interested in things as I used to be, and I have had to push myself to do them.

3 - I have not been doing much because I feel so bad.

4 - I have stopped doing nearly everything – I just sit or sleep most of the day.

Note: When an item refers to how you "normally" are, it means when you are feeling OK, or as close to OK as you can get.

⇛ ***Question 3***

0 - I have been interested in socializing with others as much as normal.

1 - I have still been interacting with others but am less interested in doing so.

2 - I have been interacting less with other people in social situations.

3 - I have been interacting less with others at home or at work.

4 - I have been become quite withdrawn at home or at work.

⇛ ***Question 4 (This question is about your interest in sex, not you actual sexual activity.)***

0 - My interest in sex has been about the same as it was before I became depressed, or greater than normal.

1 - I have not been quite as interested in sex as I was before I became depressed.

2 - I have been much less interested in sex than I was before I became depressed.

Remember, "normal" means how you're feeling when you are OK.

⇛ ***Question 5***

0 - My appetite has been normal or greater than normal.

1 - I have had less appetite than normal, but I eat without anyone having to urge me.

2 - I have had so little appetite that I have not been eating regularly unless someone urges me to.

(Circle "0" for this question if you have lost weight due to dieting, or have lost weight that you had previous gained when you were depressed.

⇛ ***Question 6***

0 - I don't think I have lost any weight since I became depressed, or if I have lost weight, I have started to gain it back.

1 - I have probably lost some weight (that I haven't gained back at all) because I haven't felt like eating.

2 - I have definitely lost weight (that I haven't gained back at all) because I haven't felt like eating.

⇛ ***Question 7***

0 - I have **not** gained weight above my normal level in the past week.
1 - I have probably gained weight (two or more pounds) in the last week, and my current weight is above normal for me.
2 - I have definitely gained weight (two or more pounds) in the last week, and my current weight is above normal for me.

⇛ ***Question 8*** **(This question is about your appetite, not what you have actually been eating.)**

0 - My appetite has been normal or less than normal.
1 - I have wanted to eat just a little more than normal.
2 - I have wanted to eat somewhat more than normal.
3 - I have wanted to eat much more than normal.

⇛ ***Question 9*** **(This question is about what you have actually been eating.)**

0 - I have **not** been eating more than normal.
1 - I have been eating a little more than normal.
2 - I have been eating somewhat more than normal.
3 - I have been eating much more than normal.

⇛ ***Question 10***

0 - I have **not** been craving or eating sweets or starches any more than when I feel normal.
1 - I have been craving or eating sweets or starches somewhat more than when I feel normal.
2 - I have been craving or eating sweets or starches much more than when I feel normal.
3 - I have an irresistible craving for sweets or starches.

If you circled "1", "2" or "3" for the question above, please also answer the following:

⇛ ***Question 11*** **The craving or eating has focused mainly on:**

1 – sweets
2 – starches
3 – both sweets and starches

I. List any specific foods you have been craving:

_____

Question 12 **Which of the following describes you best?**

1 – I have been craving sweets or starches, but have been able to control eating them.
2 – I have actually been eating sweets or starches excessively.

Question 13 **At what time of the day has the craving or eating usually occurred?**

0 - It can occur at any time – it comes and goes.
1 - It usually occurs in the morning.
2 - It usually occurs in the afternoon or evening.
3 - It has been nearly all the time.

⇛ ***Question 14***
0 - I have **not** had any difficulty falling asleep at night.
1 - Some nights it has taken me longer than half an hour to fall asleep.
2 - I have had trouble falling asleep every night.

⇛ ***Question 15***
0 - I have **not** been waking up in the middle of the night, or if I have gotten up to go to the bathroom, I have fallen right back asleep.
1 - My sleep has been restless and disturbed during the night.
2 - I have been waking during the night without being able to get right back to sleep, or I've been getting out of bed in the middle of the night (not just to go to the bathroom).

⇛ ***Question 16***
0 - I have been oversleeping **or** waking up at a reasonable hour in the morning.
1 - I have been waking up very early in the morning, but I have been able to go back to sleep.
2 - I have been waking up very early in the morning without being able to go back to sleep, especially if I've gotten out of bed.

Remember, "normal" means how you're feeling when you're OK.

When I am feeling normal, I usually sleep about ___ hours each day, including naps.

⇛ ***Question 17***
0 - I have been sleeping no more than I usually do when I feel normal.
1 - I have been sleeping at least one hour more than I usually do when I feel normal.

2 - I have been sleeping at least two hours more than I usually do when I feel normal.
3 - I have been sleeping at least three hours more than I usually do when I feel normal
4 - I have been sleeping at least four hours more than I usually do when I feel normal.

The following question asks about how difficult it has been waking up in the morning:

⇒ ***Question 18***

0 - Usually I have been waking up on time and quickly feeling wide awake.
1 - Although I've had had to depend on an alarm clock to wake up on time, I've usually felt wide awake with 30 minutes.
2 - I've been feeling sleepy for more 30 minutes or longer after I wake up.
3 - It's been a major effort to get out of bed, and I've continued to feel sleepy for at least three hours after I wake up.
4 - I've been falling back asleep after the alarm, or feeling sleepy for at least five hours after I first wake up.

If you have been using an alarm, what time is it set for? _____ : _____ AM/PM (circle)

⇒ ***Question 19***

0 - I have **not** had a heavy feeling in my limbs, back or head.
1 - I have had a heavy feeling in my limbs, back or head, some of the time.
2 - I have had a heavy feeling in my limbs, back or head, a lot of the time.

⇒ ***Question 20***

0 - I have **not** been bothered by backaches, headache or muscle aches.
1 - I have been bothered some of the time by backaches, headache or muscle aches.
2 - I have been bothered a lot of the time by backaches, headache or muscle aches.

Remember, "normal" means how you're feeling when you're OK.

⇒ ***Question 21***

0 - I have **not** been feeling more tired than normal.
1 - I have felt slightly more tired than normal.
2 - I have been more tired than normal for at least a few hours per day.
3 - I have felt tired much of the time most days.
4 - I have felt an overwhelming fatigue all of the time.

⇛ ***Question 22***

0 - I have **not** been putting myself down, or feeling like a failure or that I have let other people down, or feeling guilty about things I have done.

1 - I have been feeling like a failure or that I have let other people down.

2 - I have been feeling very guilty or thinking a lot about bad things I have done, or bad mistakes I have made.

3 - I believe that my being depressed is a punishment for something bad that I've done.

4 - I have been able hearing voices accusing me of bad things or seeing things that are scary, that others said were not really there.

⇛ ***Question 23***

0 - I have **not** had any thoughts about dying or about hurting or killing myself, or that life is not worth living.

1 - I have had thoughts that life is not worth living, or that I'd be better off dead.

2 - I have had thought about dying, or wish I were dead.

3 - I have thought about killing myself, or I have done something to hurt myself.

4 - I have tried to kill myself.

⇛ ***Question 24***

0 - I have **not** been feeling especially tense or irritable, or worrying a lot.

1 - I have been feeling somewhat tense or irritable.

2 - I have been worrying about little unimportant things – that I wouldn't ordinarily worry about – or I have been excessively tense or irritable.

3 - Other people notice that I look or sound tense, anxious or fearful.

4 - I feel tense, anxious, or fearful all of the time.

⇛ ***Question 25***

Check off all the following physical symptoms that have <u>bothered</u> you in the past week:

___ dry mouth
___ gas
___ indigestion
___ diarrhea
___ cramps
___ belching
___ heart palpitations
___ headaches
___ hyperventilating
___ sighing
___ having to urinate frequently
___ sweating

If you have checked off any of the symptoms listed above, please also the answer the following:

⇛ ***Question 26***

1 - Altogether, the symptom(s) have only been bothering me a little bit.
2 - Altogether, the symptom(s) have been bothering me somewhat.
3 - Altogether, the symptom(s) have been bothering me a lot.
4 - Altogether, the symptom(s) have been making it difficult for me to function.

⇛ ***Question 27***

0a - These symptoms bother me only when I am depressed.
0b - These symptoms bother me from time to time, but they get worse when I'm depressed.
2 - In my experience, these symptoms occur whether or not I am depressed.
3 - I think these symptoms are due to physical illness or a medication that I am taking.

II. If you circled "3" above, what illness or medication?

_____

⇛ ***Question 28***

0 - I have **not** been thinking much about my physical health.
1 - I have been worrying about being or becoming physically ill.
2 - I have been spending most of my time worrying about my physical health.
3 - I have been complaining frequently about how I feel physically, or asking for help a lot.
4 - I am sure that I have a physical disease, even though the doctors tell me that I don't.

Have you had a specific medical problem this week? If yes, please describe?

_____

⇛ ***Question 29***

0a - Although previously I was depressed, this past week I have felt distinctly better.
0b - I have become depressed, or have continued feeling depressed, in the past week.

If neither 0a nor 0b is true, circle 1 or 2 below:

1 - I haven't been feeling very good, but it's not because of depression – rather I ate something bad, or overworked, or had a virus, or just have been needing a rest.
2 - Depression has not been a problem of mine, now or before.

Remember, "normal" means how you're feeling when you're OK.

⇒ ***Question 30***

0 - My rate of speech and thought are normal.
1 - My speech and physical movements are slightly slowed down, or my thoughts are slightly slower, which has made it difficult for me to concentrate.
2 - My physical movements, speech or thoughts are somewhat slow compared to normal, and other people have noticed this.
3 - My physical movements are markedly slower, or my speech or thoughts are so slow that it has been hard to have a conversation with me.
4 - My physical movements are greatly slowed down, or my speech and thoughts are so slow that it has been difficult for me to think or talk at all.

⇒ ***Question 31***

0 - I have **not** been restless or fidgety.
1 - I have been somewhat restless, or sometimes have been playing with my hands, hair or other things.
2 - I have been very restless, or often have been playing with my hands, hair or other things.
3 - I have been had trouble sitting still, and need to keep moving about a lot of the time.
4 - I am unable to sit still, or have been wringing my hands, biting my nails, pulling my hair, or biting my lips, nearly all of the time.

⇒ ***Question 32***

0 - Overall, the problems I have been asked about in this questionnaire have bothered me equally in the morning and the late evening.
1 - Overall, the problems have bothered me more in the morning.
2 - Overall, the problems have bothered me more in the late evening.

If you circled "1" or "2" for the question above, please also circle one of the following:

1 - I have been feeling only a little worse in the mornings (**or** evenings).
2 - I have been feeling much worse in the mornings (**or** evenings).

⇒ ***Question 33*** **In the following question, a "slump" means a temporary reduction in mood or energy from which you recover, at least partially, later in the day.**

0 - I have **not** regularly had a slump in my mood or energy in the afternoon or evening.
1 - I have regularly had a slump in my mood or energy in the afternoon or

evening.

Question 34 **If you circled "1" for the question above, please also answer the following:**

The slumps usually begin about ___ p.m. and end about ____ p.m.

Please specify:

0 - Once these slumps occur, they usually last till bedtime.
1 - I have usually come out of these slumps at least an hour before bedtime.

If you usually come out of these slumps at least an hour before bedtime, please also circle one of the following:

1 - Usually, the slumps have been only mild in intensity.
2 - Usually, the slumps have been moderate in intensity.
3 - Usually, the slumps have been severe in intensity.

How would you characterize the slumps?

0 - They are mostly in my mood.
1 - They are mostly in my energy.
2 - They are in both mood and energy.

⇒ ***Question 35***

0 - I have **not** been having any sensation that things around me are unreal, or that I'm in a dream.
1 - I have been only very mild sensations of unreality.
2 - I have been some definite sensations of unreality or of being in a dream.
3 - I have been having sensations of unreality a lot of the time.
4 - I have been so bothered by sensations of unreality that it has been hard for me to function.

⇒ ***Question 36***

0 - I have **not** thought that anyone was trying to give me a hard time or hurt me.
1 - I have been suspicious of people.
2 - I have noticed certain things that probably mean that someone is trying to harm me.
3 - I have am sure someone is trying to get me or hurt me.

⇒ ***Question 37***

0 - I have **not** had things that I've had to do over and over again, like checking the locks on the doors several times, or repeatedly washing my hands.
1 - I have been compelled to check certain things repeatedly – more than should be necessary.
2 - I have been spending excessive amounts of time checking certain things repeatedly.

⇒ ***Question 38***

0 - I have **not** been bothered by thoughts that run over and over in my mind but don't make any sense to me.

1 - I have been feeling a little bothered by thoughts that keep running through my mind but don't make any sense to me.

2 - I have been very bothered by thoughts that keep running though my mind but don't make any sense to me.

Appendix A

J. Jenkins Sleep Scale

The Jenkins Scale

Check (√) one response on each line.

How often in the past month did you:	**Not at all**	**1-3 nights**	**4-7 nights**	**8-14 nights**	**14-21 nights**	**22-31 nights**
1. Have trouble falling asleep?						
2. Wake up several times during the night?						
3. Have trouble staying asleep (including waking up too early)?						
4. Wake up after you usual amount of sleep feeling tired and worn out?						

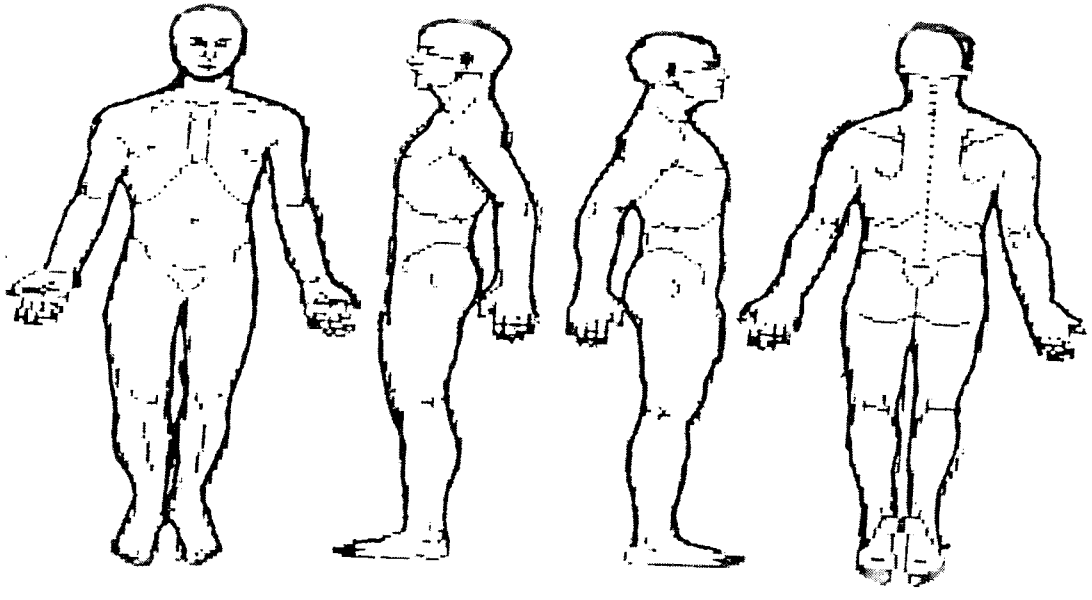
Appendix A

K. Pain Laterality

What hand do you usually use to write with?

Right Left Both/No preference

Can you identify a specific area of your body that is generally the most painful or that signals that a flare is coming? Please specify the location on the diagram below.



How many times (episodes) in your life have you been depresses for at least a two week period? (An episode is defined by having significant depression symptoms daily nearly all the time for two weeks at a time followed by a normal mood state for at least two weeks.)

II. Appendix B: Study Forms

A. Consent Form
B. Lay Language Protocol Summary
C. Recruitment Letter to Potential Subjects
D. Combined DEX/CRH Stimulation Test
    1. Patient Information Sheet
    2. Laboratory Protocol Sheet

Appendix B

A. Consent Form

OHSU Oregon Health & Science University
Consent and Authorization Form

IRB#: 8613

Protocol Approval Date: 7/28/05

NAME_____

OREGON HEALTH & SCIENCE UNIVERSITY
Consent and Authorization Form

TITLE: Biochemical Markers of Depression Subtypes in Fibromyalgia

PRINCIPAL INVESTIGATOR: Kim Jones RN, PhD, FNP
503-494-8963

CO-INVESTIGATORS: Rebecca Ross RN, PhD-C, PMHNP
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Robert Bennett MD, FRCP
503-494-5307
Deborah Eldredge RN, PhD
503-494-1131
Dianne Adams MPH
503-494-0399

SPONSOR: National Institutes of Health

PURPOSE:

You have been invited to be in this research study because 1) you have been diagnosed with Fibromyalgia and you are aged 18 or older. The purpose of this study is to see if the same types of depression found in depressed people without fibromyalgia (FM) are also found in depressed people with FM. We also want to measure certain hormones that are common to fibromyalgia and depression. This study requires two visits to OHSU. The study will be finished in about 4 weeks. 180 people with fibromyalgia will be enrolled in this study at OHSU and we will need 120 people to complete the study.

PROCEDURES:

At the **first** visit, you will be asked to fill out four questionnaires 1) a standard depression questionnaire, 2) a medical health questionnaire, 3) a personal

information questionnaire, and 4) a medication sheet asking you to list your current medications.
In addition, you will be asked questions about your depression, if any. If you are still having periods, you will also give a urine sample to check for pregnancy. This visit will last about 3 hours.

At the end of the first visit, you will get two tablets of an approved FDA steroid medication, dexamethasone (DEX). You will take the tablets the night before the second visit. The study investigator will call you at 10:55 PM the night before the second visit. This call will remind you to take the dexamethasone tablets. These tablets must be taken exactly 16 hours before the hormone test blood draws.

The **second** visit will take up to 4 hours. This visit will be about seven to twenty-one days from the first visit, depending on your period, if any. It is very important that you arrive at the clinic no later than 12:00 P.M. (noon) for your visit. The results of the blood test will depend on the amount of time since you took the dexamethasone tablets. At the beginning of the visit, you will have a physical exam to check for fibromyalgia symptoms. Then the investigator will ask you questions about depression symptoms, if any, to confirm the type of depression you have and to see how bad your depression is. A small group of 15 people will be selected (based on medical history and current symptoms) to receive a second study drug, corticotropin-releasing hormone (CRH), to test the stress hormone system more directly. You will then be walked to the lab and you will be introduced to the registered nurse who will do the hormone test for you. The nurse will put an intravenous catheter in your vein on your forearm or the back of your hand. You will then be allowed to rest in a comfortable reclining hospital chair and asked to complete another depression questionnaire during a 30-minute rest period so you can relax and get use to the setting. The catheter will be used to give you the CRH. This catheter will also be used to draw blood five times over the course of the next hour. In total, 3 1/3 tablespoons of blood will be taken (2 tablespoons for the study tests and an additional 1 1/3 tablespoons for additional tests that may be needed). The nurse will measure and record your height, weight, and vital signs. You will also be asked if you had any side effects from the dexamethasone or corticotropin-releasing hormone.

Between the hormone tests, you will be asked to fill out three final questionnaires. These questionnaires will ask you about your fibromyalgia and depression symptoms including 1) pain, 2) depression, 3) impact of fibromyalgia on your daily living, 4) quality of life and 5) quality of your sleep.

The order of procedures is listed below. If you have any questions regarding this study now or in the future, contact Rebecca Ross RN, MSN, PhD-C at (503) 494-0399.

Order of Study Tests	Day 1	Day 2-30
Informed Consent	X	
Eligibility Checklist	X	
Demographic Data Form	X	
Beck Depression Inventory	X	
Medication Sheet	X	
Clinical Data Form- Page 1	X	
REFRESHMENT BREAK (Staff will confirm eligibility at this time)	X	
Clinical Data Form- Page 2	X	
DSM-IV Depression Subtype Screening (Clinical interview)	X	
Urine HCG (Sexually active females of childbearing ages)	X	
Urine HCG (Sexually active females of childbearing ages)		X
Tenderpoint/Cumulative Myalgic Scale (Physical exam)		X
SIGH-ADS		X
SIGH-SAD-SR		X
DST **OR** Combined DEX/CRH Stimulation Test		X
Quality of Life Scale		X
Fibromyalgia Impact Questionnaire		X
Jenkins Sleep Scale		X
Total time	3 hours	4 hours

RISKS AND DISCOMFORTS:

Taking the test medications involves some possible side effects. The known side effects of the dexamethasone are difficulty sleeping (you may not sleep well after taking the dexamethasone the night before the test) and for corticotropin-releasing hormone are mild flushing (getting red in the face), anxiety, a metallic taste in your mouth, and mild nausea. These side effects may last a day.

We will draw blood from a vein in your forearm or the back of your hand. You may feel some pain when your blood is drawn. There is a small chance the needle will cause bleeding, a bruise, or an infection.

If you are nursing an infant or you are pregnant now, you must not be in the study because we do not know how these drugs could affect a nursing infant or fetus. If you are sexually active and are at risk of getting pregnant, you and your male partner(s) must use a method of birth control that works well, like birth control pills, Depo-Provera, Norplant, an IUD, a diaphragm or condom with spermicide, or abstinence. You will have to do this the whole time you are in this study. If you become pregnant during the research study, please tell the investigator and your doctor immediately.

There are several drugs (prescription and non-prescription) that may cause problems when taken with the test medications. The investigator will carefully review all of the drugs you are taking before giving you the test medications. If any other health care provider prescribes any new drug(s) for you while you are in this study, please tell the investigator before you take the new drug. You could also have that provider talk to the investigator before prescribing the new drug. Do not take any new over-the-counter drugs while you are in this study unless you first check with the investigator.

Some of the questionnaires may seem very personal or embarrassing. They may upset you. You may refuse to answer any of the questions that you do not wish to answer. If the questions make you very upset, we will help you to find a counselor.

BENEFITS:

You may or may not personally benefit from being in this study. However, by serving as a subject, you may help us learn how to benefit patients with fibromyalgia in the future.

ALTERNATIVES:

You may choose not to be in this study. You do not need to participate in the research study to receive usual treatment for fibromyalgia and/or depression.

CONFIDENTIALITY AND PRIVACY OF YOUR PROTECTED HEALTH INFORMATION:

We will not use your name or your identity for publication or publicity purposes.

If you sign this form, you are agreeing that OHSU may use and disclose protected health information collected and created in this research study. The specific health information and purpose of each use and disclosure are described in the table below:

Health Information *(Check as applicable)*	Purpose(s) *(Enter corresponding letter(s) from Purpose Categories)*
☐ Your complete existing health record **	_____
☒ Limited information from your existing health record** (specify): Name, address, Emotional Problems Checklist (from intake paperwork), and dictated letter to your primary care physician.	a,c,e

** If we are requesting existing health records that are located outside of OHSU, you will need to complete an additional authorization to release these records to OHSU.

THE FOLLOWING CHECKED ITEM(S) WILL BE GENERATED/COLLECTED DURING THE COURSE OF THIS STUDY:

☒ History and physical examinations	a,c,e
Reports: ☒ Laboratory ☐ Operative ☐ Discharge ☐ Progress	a,c,e
☐ Photographs, videotapes, or digital or other images	_____
☐ Diagnostic Images/X-ray/MRI/CT	_____
☐ Bioelectric Output (e.g., EEG, EKG)	_____
☒ Questionnaires, interview results, focus group survey, psychology survey, behavioral performance tests (e.g., memory & attention)	a,c,e
☒ Tissue and/or blood specimens	a,c,e
☐ Other:	_____

Purpose Categories

a. To learn more about the condition/disease being studied
b. To facilitate treatment, payment, and operations related to the study
c. To comply with federal or other governmental agency regulations
d. For teaching purposes
e. Other-To complete research obligations in this study and to perform quality assessments related to research at OHSU.

The persons who are authorized to use and disclose this information are all the investigators listed on page one of this Consent and Authorization form; other OHSU staff who are participating in the conduct of this study, the General Clinical Research Clinic and the OHSU Institutional Review Board. The persons who are authorized to receive this information are the study sponsors as listed on page one, the Food and Drug Administration, the Office

for Human Research Protections (OHRP) and the National Center for Research Resources (NCRR).

We may continue to use and disclose protected health information that we collect from you in this study up to five years. Blood samples will also be kept up to five years.

While this study is still in progress, you may not be given access to medical information about you that is related to the study. After the study is completed and the results have been analyzed, you will be permitted access to medical information collected about you in the study.

You have the right to revoke this authorization and can withdraw your permission for us to use your information for this research by sending a written request to the Principal Investigator listed on page one of the research consent form. If you do send a letter to the Principal Investigator, the use and disclosure of your protected health information will stop as of the date she receives your request. However, the Principal Investigator is allowed to use and disclose information collected before the date of the letter or collected in good faith before your letter arrives. If you withdraw any tissue or blood samples that were collected from you, they either will be destroyed or stored without any information that identifies you. Revoking this authorization will not affect your health care or your relationship with OHSU.

The information about you that is used or disclosed in this study may be re-disclosed and no longer protected under federal law.

If the information to be used or disclosed contains any of the types of records or information listed just below, additional laws relating to use and disclosures of the information may apply. You understand and agree that this information will be used and disclosed only if you place your **INITIALS** in the applicable space next to the type of information.

_____ Mental or behavioral health or psychiatric care

Under Oregon Law, suspected child or elder abuse must be reported to appropriate authorities.

COSTS:

You will not be charged for taking part in this study. The sponsor will pay for all laboratory tests and the testing drugs. You will need to provide transportation for study participation. You will not be paid for participating in this study. You and/or your health plan are responsible for all costs related to your clinical treatment that are not associated with this research study.

LIABILITY:

If you believe you have been injured or harmed while participating in this research and require immediate treatment, contact Rebecca Ross RN, PhD-C, PMHNP at (503) 494-0399.

It is not the policy of the U.S. Department of Health and Human Services, or any federal agency funding the research project in which you are participating, to compensate or provide medical treatment for human subjects in the event the research results in physical injury.

The Oregon Health & Science University is subject to the Oregon Tort Claims Act (ORS 30.260 through 30.300). If you suffer any injury and damage from this research project through the fault of the University, its officers or employees, you have the right to bring legal action against the University to recover the damage done to you subject to the limitations and conditions of the Oregon Tort Claims Act. You have not waived your legal rights by signing this form. For clarification on this subject, or if you have further questions, please call the OHSU Research Integrity Office at (503) 494-7887.

PARTICIPATION:

If you have any questions regarding your rights as a research subject, you may contact the OHSU Research Integrity Office at (503) 494-7887.

You do not have to join this or any research study. If you do join, and later change your mind, you may quit at any time. If you refuse to join or withdraw early from the study, there will be no penalty or loss of any benefits to which you are otherwise entitled.

Your health care provider may be one of the investigators of this research study, and as an investigator is interested in both your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may ask for a second opinion about your care from another doctor who is in no way involved in this project. You do not have to be in any research study offered by your physician.

You may be removed from the study even if you would like to continue. This may happen if the investigator or sponsor stops the study, if you become pregnant, if you develop a serious side effect, if your disease gets worse, or if you do not follow instructions. If you choose to withdraw, we will contact you to discuss the reasons for your withdrawal.

We will give you a copy of this consent form.

SIGNATURES:

Your signature below indicates that you have read this entire form and that you agree to be in this study.

_____
Printed Name of Subject

_____ _____
Signature of Subject Date

_____
Printed Name of Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date

Appendix B

B. Lay Language Protocol Summary

LAY LANGUAGE PROTOCOL SUMMARY

Principal Investigator: **Kim Jones RN, PhD** IRB#:
Doctoral Student: **Rebecca Ross RN, PhD-C** **8613**
Study/Protocol Title: **Biochemical Markers of Depression Subtypes in Fibromyalgia**

Please answer all of the following questions using lay language, similar to the language used in a consent form. Please number your responses.

1. Briefly describe the purpose of this protocol.
2. Briefly summarize how participants are recruited.
3. Briefly describe the procedures subjects will undergo.
4. If applicable, briefly describe survey/interview instruments used.
5. If this is a clinical trial using an experimental drug and/or device, or an approved drug and/or device used for an unapproved purpose, briefly describe the drug and/or device.
6. Briefly describe how the data will be analyzed to address the purpose of the protocol.

1. The purpose of this study is to see if two kinds of depression that are found in the general population are found in fibromyalgia (FM). We will also see if we can tell the difference between the two types of depression by their symptoms and/or hormone levels.

FM is a chronic condition. People with FM have long-term full-body pain, sleep problems, fatigue, trouble thinking, pain after exercising and sometimes even after normal movement. They also have a greater number of other chronic pain conditions, such as headaches, irritable bowel and irritable bladder. In addition, many FM patients also have depression and hormone imbalances including cortisol (a hormone released during stress) and growth hormone (a hormone that builds and repairs muscles). We think there will be more of one kind of depression (atypical) than the other (melancholic) in FM. We think atypical depression will have lower cortisol and lower growth hormone levels. If this information about the two different depression types is true, then doctors and nurses can pick better treatments for people with fibromyalgia with depression.

2. People will be chosen from the OHSU Rheumatology Clinic's charts of FM patients seen in the past five years. Patient charts will be searched by hand for answers to a depression questionnaire that may suggest they have depression. 1000 charts will be chosen at random and an invitation letter will be mailed to these 1000 subjects.

3. The initial mailing will include a recruitment letter with information about the study and the telephone number for the principal investigator. All interested persons that qualify for

the study will be asked to come to an orientation session that will tell them about the reason for the study, what will be asked of them while they are in the study, and how research differs from clinical care. The session will also include a group question and answer period. The reasons for the hormone test will be explained to subjects and they will be told about the study medication (two 0.75 mg dexamethasone tablets) they have to take the night before the hormone test. Dexamethasone is a steroid medication that is commonly used in diagnostic testing of adrenocortical system over function. An initial eligibility screening checklist will be reviewed with subjects and eligibility will be confirmed. An informed consent, a standard depression questionnaire, a medical health questionnaire, clinical data questionnaire and a medication sheet asking what medications people are currently taking will also be completed at this time.

A **second** appointment for 120-minutes will be made to confirm diagnosis of FM and to see what types of depression the person has, if any. A physical examination will be done to see how many tenderpoints each person has and how severe their pain is. For depression sub-typing, a questionnaire made for this purpose will be given to the subject to fill out and then the investigator will ask the subject the same types of questions using a similar depression scale. Subjects will be separated into one of three groups based on the type of depression they have or if they have no depression.

A **third** two-hour laboratory appointment will be made in approximately seven days of the second appointment to draw blood for the hormone tests and to complete more questionnaires. The principal investigator will call the subject the night before the testing at 10:55 P.M. to remind them to take the steroid test drug. The subjects will be scheduled to arrive at the clinic at 1:00 P.M. the next day for the hormone testing. Subjects will have vital signs recorded, fill out questionnaires, note hormone test drug side effects, and have blood drawn. In total, participants will come to the clinic three times over a two-week period.

4. Subjects will fill out a variety of surveys designed to measure their fibromyalgia and depression symptoms including pain, depression, impact of fibromyalgia on their daily living, quality of life and sleep quality. The time allotted for filling out the questionnaires has been specifically set to make sure the subject can complete the questionnaires without having to hurry.

5. N/A

6. Data from all subjects will be evaluated for differences between the three groups on their characteristics and hormone levels.

Aim 1: To describe the traits of FM subjects with depression and no depression, descriptive statistics will be used to describe the demographics (age, gender, education level, ethnicity, and how much money they make) and the clinical variables (how bad the FM symptoms are, how bad the depression symptoms are, sleep quality, quality of life and body mass index). We will test for group differences using analysis of variance.

Aim 2 and 3: To determine if there are significant differences in hormone levels, analysis of variance will be used. However, if there are significant differences in demographic traits or in variables, then analysis of co-variance will be used. It will control for specific traits or variables such as drug class, age or body mass index.

Appendix B

C. Recruitment Flyer Placed in Clinics

Fibromyalgia Study

- OHSU's School of Nursing is looking for 120 women and men **ages 18 or above** with fibromyalgia, to participate in a two-day study. Each day will last about three to four hours.

- The purpose of the study is to see if the same symptoms are found in people without fibromyalgia (FM) are also found in people with FM. We also want to measure certain hormones that are common to fibromyalgia.

- You will come to OHSU on the first day to see if you are eligible for the study.

- If you are eligible, you will fill out some questionnaires and make an appointment for your second visit.

- You will take two pills of a mild steroid medication called Decadron the night before the second visit. The study investigator will call you at 10:55 P.M. the night before to remind you to take the Decadron pills.

- At your second visit, you will come to OHSU to fill out some more questionnaires about your FM and mood. Then you will have an interview to see if you have sad or blue moods. You will have an IV placed in your arm that will be used to draw blood for hormones. A total of 3 1/3 tablespoons of blood will be taken.

- Additionally, a subset of people will be invited to take a second medication called Acthrel to further test the stress hormone system.

- You can take your regular medications while on this study.

For more information please leave a message for **Rebecca Ross or Dianne Adams at (503) 494-0399.**

Study investigators are Dr. Robert Bennett, Dr. Kim D. Jones, and Rebecca Ross, RN, PMHNP, PhD-C.

Appendix B

C. Recruitment Letter to Potential Subjects

Arthritis and Rheumatic Diseases

James T. Rosenbaum MD
Professor and Chair
A. Barkhuizen MD, FRCPSA
R. M. Bennett
S. M. Campbell MD, FACR
M. P. Davey PhD, MD, FACR
A. Deodhar MD, MRCP
D. Smith MD
R. Wernick MD, FACR

OHSU OREGON HEALTH & SCIENCE UNIVERSITY

S.R. Clark PhD,FNP
C.S Burckhardt PhD, RN
S.H. Hefeneider PhD
A.C.Bakke PhD
S. Planck PhD
J.R.Walczyk MS,ANP
C. Hryciw, FNP
K. Jones, PhD FNP

May 23, 2006

Dear Fibromyalgia Sufferer,

You are receiving this letter because Dr. Robert Bennett, Dr. Atul Deodhar, Dr. Kim Dupree Jones, or Cheryl Hryciw, FNP, has treated you for fibromyalgia at Oregon Health & Science University (OHSU) and/or you have indicated interest in being contacted for research opportunities. We would like to invite you to a session to learn more about participating in this study (IRB #8613; GCRC #924). There will be a meeting **Saturday, June 17, 2006 at 10am to 12pm (noon), in the School of Nursing Auditorium, 1st floor, Room 144** (see enclosed map). Light refreshments will be served.

The purpose of the orientation session is to provide you with details of the study and invite your questions. The purpose of the study is to see if there are different types of depression in fibromyalgia. This study involves 2 visits to OHSU over a 4-week period. We are looking for people with and without depression. If you volunteer for the study, you will be asked to fill out some questionnaires, allow us to interview you, take a one time dose of a steroid pill, and allow us to draw some blood from you to measure two hormones we think are imbalanced in fibromyalgia and depression.

If you would like directions to the orientation or want to be notified of future study orientations, please call Rebecca Ross RN, MSN, PMHNP, PhD Candidate, or Dianne Adams MPH, at (503) 494-0399 or (503) 494-3864 and leave a message with your telephone number and the best time to reach you. Thank you for sharing your valuable time with us so that we can learn more about the causes and potential treatments for fibromyalgia and depression.

Please RSVP to Dianne to assist us in planning for your presence (paper work and refreshments).

Sincerely,

Dr. Kim Jones RN, PhD, FNP

Appendix C

III. Appendix C: Diagnostic Criteria

A. 1990American College of Rheumatology Diagnostic Criteria for Fibromyalgia

B. DSM-IV-TR Diagnostic Criteria for Major Depressive Disorder

C. DSM-IV Depression Subtype Screening

Appendix C

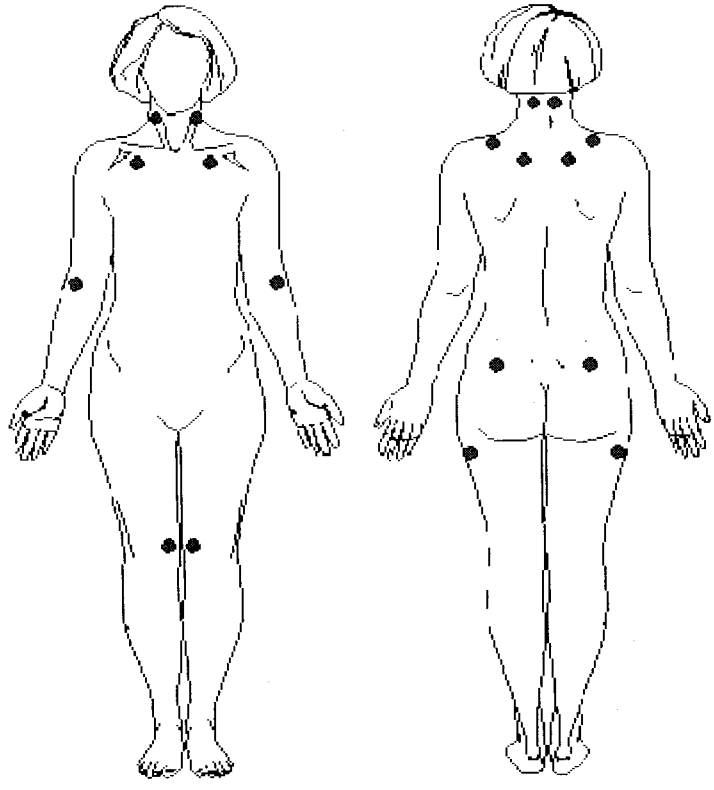
A. 1990 American College of Rheumatology Diagnostic Criteria for Fibromyalgia

1. Pain in 11 of 18 tender point sites on digital palpation using 4 kg of pressure.

2. History of widespread* pain present for at least 3 months in 3 out of 4 body quadrants. (*Pain is considered widespread when present in both sides of the body and above and below the waist. In addition, axial skeletal pain (cervical spine, anterior chest, thoracic spine or low back pain) may be present. Low back pain is considered lower segment pain.)

3. Pain can not be explained by other mechanisms or diseases.

Illustration of Tender Points



1-Occiput (2) - at the suboccipital muscle insertions.
2-Low cervical (2) - at the anterior aspects of the intertransverse spaces at C5-C7.
3-Trapezius (2) - at the midpoint of the upper border.
4-Supraspinatus (2) - at origins, above the scapula spine near the medial border.
5-Second rib (2) - upper lateral to the second costochondral junction.
6-Lateral epicondyle (2) - 2 cm distal to the epicondyles.
7-Gluteal (2) - in upper outer quadrants of buttocks in anterior fold of muscle.
8-Greater trochanter (2) - posterior to the trochanteric prominence.
9-Knee (2) - at the medial fat pad proximal to the joint line.
(Adapted and reprinted with permission from the National Fibromyalgia Research Association)

Appendix C

B. DSM-IV Diagnostic Criteria for Major Depressive Disorder

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly due to a general medical condition, or mood incongruent delusions or hallucinations.

(1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observations made by others (e.g., appears tearful)
(2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
(3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
(4) insomnia or hypersomnia nearly every day
(5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down
(6) fatigue or loss of energy nearly every day
(7) feelings of worthlessness or excessive guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
(8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
(9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for a Mixed Episode.

C. The symptoms cause a clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

E. The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation psychotic symptoms, or psychomotor retardation.

Appendix C

C. DSM-IV Depression Subtype Screening

With Melancholic Features (can be applied to the current or most recent Major Depressive Episode in Major Depressive Disorder and to a Major Depressive Episode in Bipolar I or Bipolar II Disorder only if it is the most recent type of mood)

CRITERIA	YES/NO/PARTIAL	COMMENTS
A. Either loss of pleasure in all, or almost all, activities		
A. Lack of reactivity to usually pleasurable stimuli (does not feel much better, even temporarily, when something good happens.		
B. distinct quality of depressed mood (i.e., the depressed mood is experienced as distinctly different from the kind of felling experienced after the death of a loved one)		
B. depression regularly worse in the morning		
B. early morning awakening (at least two hours before usual time of awakening)		
B. marked psychomotor retardation or agitation		
B. significant anorexia or weight loss		
B. excessive or inappropriate guilt		
III. MELANCHOLIC DIAGNOSIS		

Appendix C

C. DSM-IV DEPRESSION SUBTYPE SCREENING (continued)

With Atypical Features (can be applied when these features predominate during the most recent 2 weeks of a current Major Depressive Episode in Major Depressive Disorder or in Bipolar I or Bipolar II Disorder when a current major Depressive Episode is the most recent type of mood episode, or when these feature predominate during the 2 years of Dysthymic Disorder; if the Major Depressive Episode is not current it applies if the feature predominates during any 2 week period)

CRITERIA	YES/NO/PARTIAL	COMMENTS
A. Mood reactivity)i.e., mood brightens in response to actual or potential positive events)		
B. Significant weight gain or increase in appetite		
B. hypersomnia		
B. leaden paralysis (i.e., heavy leaden feelings in arms or legs)		
B. long-standing pattern of interpersonal rejection sensitivity (not limited to episodes of mood disturbance) that results in significant social or occupational impairment		
C. Criteria are not met for With Melancholic Features or With Catatonic Features during the same episode.		
IV. ATYPICAL DIAGNOSIS		

IV: Appendix D: Human Subjects Research: Protection of Human Subjects

A. Human Subjects Research: Protection of Human Subjects

Appendix D

A. Human Subjects Research: Protection of Human Subjects

1. RISKS TO THE SUBJECTS

a. Human Subjects Involvement and Characteristics:

1. The proposed study will describe the psychological and physiological characteristics of individuals with Major Depressive Disorder (MDD) in Fibromyalgia (FM). It will focus on evaluating the differences between three groups: subjects with FM without MDD and FM with two subtypes of MDD (melancholic and atypical).
2. The human subjects as outlined in the Research Design and Methods section will include adult men and women ages 18 and older diagnosed with FM. Some will also have one of two depression subtypes. A minimum sample of 120 will complete the study. Up to 180 individuals will be consented to control for attrition.

   Inclusion of children and adolescents: Persons less than 18 years old will be excluded because of the significant difference in the manifestation, HPA function, and treatment of depression in this age group. However, children 18 to 21 will be included.

   Inclusion of women: Pregnant women and fetuses will be excluded due to the potential risk from dexamethasone and corticotropin-releasing hormone to harm the fetus. Nursing mothers will also be excluded. Pregnancy status will be determined via self-report of potentially being pregnant at the time of the study. For women who are capable of reproduction, pregnancy status will be confirmed using a standard urine pregnancy test. Non-pregnant women will be included as they constitute the majority of the adult population that is depressed with FM.

   Inclusion of minorities: English speaking men and women of all ethnic groups will be recruited to participate in this research study. Efforts will be made to approach communities in areas of Portland, Oregon with a diverse population to increase the potential recruitment of ethnic minorities. As Portland is predominantly white (82.6%), the Hispanic/Latino (3.2%), African American (5.3%), Asian American (5.3%), and Native American or Alaskan Native (1.2%) populations will be over-sampled to obtain as close to a representative sample as possible.

   Inclusion of prisoners and other institutionalized individuals: This population is exceptionally vulnerable, thus these individuals will not be included in the study as this would constitute an unnecessary burden.

3. The inclusion of vulnerable subjects with FM and possibly depression is necessary as the purpose of the study is to evaluate depression subtypes

in FM. The benefit that may come of this research far outweighs the minimal risk of the study.

b. Sources of Materials:
Existing clinical charts for patients in the Rheumatology Clinic will be manually searched for screening purposes. Data to be gathered are name, address, and responses to an abbreviated DSM-IV depression criteria checklist taken from the PRIME-MD mood module. In the event this procedure does not produce enough subjects, convenience sampling will be used and differences between groups will be evaluated. Recruitment strategies for convenience sampling will include handing out recruitment flyers to local FM support groups, placing recruitment flyers in the waiting area of the OHSU Rheumatology Clinic, a mental health clinic in Salem, Oregon, and a link on the www.myalgia.com site with contact information for the study coordinator. The outcome measures will be obtained via voluntary completion of self-report pencil and paper testing, including a Beck Depression Inventory, Demographic Data Form, Clinical Data Form, Medication Sheet, Fibromyalgia Impact Questionnaire, Quality of Life Scale, and the Jenson Sleep Problems Scale. Further evaluation of disease state will involve physical examination of tenderpoints (palpitations of tendon-muscle junctions) and verbal interview for assessment of depression symptoms using the standardized criteria from the DSM-IV-TR. Biochemical markers will be obtained via plasma samples taken from an indwelling venous catheter placed in the forearm or the back of the hand.

c. Potential Risk:
The potential risks to the subjects involved are minimal. There are no identifiable social, legal or other risks of harm involved in the study. Although there have been no reports of psychological harm with use of the above measures in prior studies by the research team, subjects will be offered mental health support with a licensed counselor in the event of distress or anxiety resulting from the study. There is a small risk of physiological discomfort and potential injury from the venous catheter insertion. To minimize this risk, trained RN's from the GCRC with extensive experience will insert all catheters and monitor the subject during the hormone test.

2. ADEQUACY OF PROTECTION AGAINST RISKS
a. Recruitment and Informed Consent:
Recruitment strategies and informed consent procedures will be approved by the IRB at OHSU. Subjects will be recruited from the Rheumatology Clinic at OHSU. Recruitment is expected to begin in October 2005 and continue until September 2006. Recruitment and enrollment will continue until 120 subjects have completed the study. It is anticipated, based on discussions with the providers at the Rheumatology clinic, that 15 subjects will be recruited and complete the study each month. The recruitment strategies have been designed to maximize protection of subjects. The invitation letters will be sent via United States Postal Service in unmarked envelopes. The voice mail potential subjects will call is a confidential line with a password only the principal investigator knows. Initially, the potential subjects will read the Informed Consent Form and be asked to sign

the form prior to the evaluation of eligibility for study inclusion or completing any study forms. The consent form will be validated prior to scheduling the second appointment. All data and information will be obtained specifically for research purposes.

b. Protection against Risk:

The only risks involved in this study are 1) the small potential of injury during venous catheter insertion and 2) possible minor adverse side effects from the medications used for the DST and DEX/CRH test. Nursing attention will be offered to the subject via the GCRC clinic staff if physical injury occurs. The study medical director will review all adverse event reports and make recommendations as appropriate. Dr.'s Jones and Bennett will also provide medical treatment if injuries occur in direct relationship to the study as necessary. For psychological injury, Ross RN, PhD-C, who is a trained therapist and Psychiatric Mental Health Nurse Practitioner, will observe for signs of distress in the subjects and address these issues. The experience of distress will be addressed in the orientation session and at each visit.

Coercion is minimized by using a mailing as the initial contact for the study and allowing for self selection via a flyer or a website. There is no overt pressure to participate in the study. Using a unique identifier on the questionnaires and having no individual identifying information on any data gathered will further protect confidentiality. Clinic personnel and primary care providers will not be informed of individuals participating in the study. The potential for breech of confidentiality is limited to seeing a fellow patient in the general clinical research center and/or in an orientation session. Both depressed as well as non-depressed individuals will participate, but the study group assignment will only be discussed in private. Participants will be warned of the potential for individual information to be repeated by other participants and encouraged not to discuss or share private information in any way. As an added safeguard, all completed questionnaires will be placed in a locked case and transported to the researchers work area where it will be placed in a locked file cabinet. The cabinet will remain locked at all times except when the researcher is within direct line of sight of the data and the file cabinet. The data will be kept until deemed no longer usable or until five years, which ever occurs first. It will then be destroyed via cross-hatched shredding procedures. Additional details of safety monitoring are included in the Data and Safety Monitoring Plan form.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

It is hypothesized that the proposed study will contribute unique and meaningful information to the field of FM research. The subjects, primary care providers, and other health care professionals stand to benefit from this information by gaining a fuller understanding of the causes and treatments of depression in FM. If this hypothesis is supported, researchers may be able to determine new differential prescribing practices that will enhance the effectiveness of current psychopharmacological interventions in this population.

4. IMPORTANCE OF KNOWLEDGE TO BE GAINED

Depression is second only to ischemic heart disease in the level of disability experienced. The cost of depression is estimated to be over $43 billion per year in the United States. Fibromyalgia is a debilitating disease in its own right and is the number one reason for visits to Rheumatologists. Therefore, this study will provide knowledge regarding HPA axis function in this population that may enhance current practices to significantly increase effectiveness of interventions. The benefit to individuals of potentially decreasing suffering is highly significant. In addition, the benefit to society of increased productivity and decreased loss of revenue has the potential to increase the financial well being of individuals as well as government, corporations, and businesses of all sizes. The small potential of physiological and psychological distress is outweighed by the benefit to individuals and society as a whole.

5. Data and Safety Monitoring Plan- See DSMP Form Also

1. Study Performance Review Process

The principal investigator will produce administrative reports after each 30 subjects enrolled that describe study progress including: accrual, demographics, study subject status, outstanding study forms, error rate pertaining to adherence to inclusion/exclusion criteria and the study protocol. These reports will be reviewed internally by the principal investigator, and the dissertation committee chair Dr. Kim Jones, and the medical director for the project, Dr. Robert Bennett.

2. Safety Reports

The principal investigator will produce safety reports that list any adverse effects, serious adverse events and deaths after each event, if any occur during the course of the study. All reports will be submitted to the OHSU IRB and GCRC as required.

3. Interim Data Review

The principal investigator will have regular contact with the subjects and will ask if they are experiencing any adverse events from the dexamethasone, corticotrophin-releasing hormone, or any other study measures. If this occurs, the subject will be asked to stop participation and will be referred to the clinic staff, Dr. Kim Jones, Dr. Robert Bennett, or Rebecca Ross RN, PMHNP, PhD-C. If any unusual or concerning symptoms are noted that are not adverse side effects of the above, the subjects will be referred to their primary care provider.

Vertbrate Animals

None will be used in the proposed study.

Appendix E

V. Appendix E: Inclusion/ Exclusion Criteria
    A. Inclusion/Exclusion Table
    B. Initial Eligibility Screening Checklist

Appendix E

A. Inclusion and Exclusion Criteria with Rationale

Inclusion Criteria	Rationale
12. Female or male aged 18 and above.	12. It was appropriate to include women and children over 18 in the study as FM occurs in these groups. It also occurs in children under 18, but IGF-1 is age dependent and their inclusion in this study would have potentially confounded results for the third aim.
13. Diagnosis of FM as per the 1990 ACR criteria for 3 or more years.	13. Necessary criteria for group characteristics. A 3 year limit was chosen based on previous research experience by the team as they note that patient soften alter their medications extensively during the first 3 years of diagnosis. Such medication changes could potentially alter the HPA and GH Axis, confounding aims 2 and 3.
14. Willing to maintain a steady treatment regime during the 4 weeks of the study.	14. Changes in treatment regime may introduce confounding variables.
15. Able to speak and read English at a sixth grade level.	15. The interviews and forms are in English thus requiring this skill.
Exclusion Criteria	**Rationale**
16. A BDI score greater than 31.	16. A score of 31 and above indicates potentially severe depression. It was unethical and unsafe to enroll severely depressed people into a study and ask them to maintain their treatment regime without changes for 4 weeks when there are antidepressant treatments that have been proven efficacious in FM.
17. Any medical disorder that alters the HPA axis or puts the person at increased risk related to DEX/CRH testing.	17. Contraindications of DEX use are current untreated infections such as viral, fungal, or tuberculosis diseases of the eyes. Dr. Bennett, the study's medical director, screen for medical contraindications to study inclusion.
18. Suicidal ideation.	18. Suicidal ideation is a psychiatric emergency and may require changes in medication regimes or hospitalization.
19. Pregnant or nursing mothers.	19. Dexamethasone is a pregnancy category C drug and it is not known if it crosses into breast milk therefore represents a risk to the child.
20. Abnormal thyroid stimulating hormone (less than 0.28uIU/ml or greater than 5.00uIU/ml).	20. Abnormal thyroid function potentially alters GH/IGF-1 levels and symptoms of hyper and hypothyroidism may mimic depression.
21. Planned elective surgery during the 4 weeks of the study period.	21. Prior studies by the FM Research Team at OHSU have lost subjects to attrition due to elective surgery.
22. Weight change of 15 pounds or more during the 3 months prior to the study or active weight loss as a result of a weight loss regime.	22. Significant weight loss or gain prior to and during the 4-week trial could influence IGF-1 levels.

Appendix E

B. Initial Eligibility Screening Checklist

You have been selected to participate in a study looking at depression in Fibromyalgia. If you are 18 years old or older, we would like to invite you to join our study. Please complete the following yes/no questions so we can see if you are eligible to participate.

Have you been:

☐ Diagnosed with Fibromyalgia by a medical provider more than one year ago?

☐ Diagnosed with depression before and/or are currently depressed?

☐ Losing or gaining weight (more than 15 pounds) in the last 2 months?

Do you:

☐ Currently have: Rheumatoid Arthritis, Osteoarthritis, Lupus, Cushing's Disease,
Diabetes, Active Asthma, Pituitary Tumors, uncontrolled Thyroid Disease?

☐ Currently take: Insulin, Steroids, Asthma Inhalers, Antidepressants, or pain medications?

☐ Have surgery planned in the next three months?

Are you:

☐ Currently pregnant or plan on getting pregnant in the next six months?

☐ Able to leave your home to come to appointments (total of 2)?

Thank you for your time and we look forward to talking with you soon. Please feel free to call if you have any further questions.

Rebecca Ross, RN, PMHNP
(OHSU School of Nursing PhD student)
503-494-0399