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CHRONIC OPIOID USE IN FIBROMYALGIA SYNDROME: CHARACTERISTICS AND OUTCOMES

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CHRONIC OPIOID USE IN FIBROMYALGIA SYNDROME: CHARACTERISTICS AND OUTCOMES

DISSERTATION

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy in the
College of Pharmacy at the
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By
Jacob T. Painter, Pharm.D., M.B.A.

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ABSTRACT OF DISSERTATION

CHRONIC OPIOID USE IN FIBROMYALGIA SYNDROME: CHARACTERISTICS AND OUTCOMES

Fibromyalgia syndrome (FMS) is a chronic pain condition with significant societal and personal burdens of illness. Chronic opioid therapy in the treatment of chronic nonmalignant pain has increased drastically over the past decade. This is a worrisome trend in general, but specifically, given the pathophysiologic characteristics seen in fibromyalgia syndrome patients, the use of this class of medication deserves special scrutiny. Although the theoretical case against this therapy choice is strong, little empirical evidence exists. In order to supplement this literature, retrospective analysis methods are utilized to examine the association of state-, provider-, and patient level characteristics with the prevalence of chronic opioid use in this disease state. Data gathered through this analysis is then used to develop a propensity index for the identification of an appropriate control group for fibromyalgia patients, a task that has proven difficult in the literature to date. Using propensity stratification and matching techniques analysis of the impact of fibromyalgia, chronic opioid use, and the interaction of these two variables are undertaken.

Several key findings and updates to the understanding of chronic opioid use and fibromyalgia syndrome are reported. Wide geographic variation in chronic opioid utilization between states is seen. The role of diagnosing provider type in the rate of chronic opioid prescribing is significant and can be aggregated at various levels. Demographic characteristics, comorbid conditions, and concurrent medication use are all important associates of chronic opioid use in fibromyalgia syndrome. Additionally, chronic opioid use in fibromyalgia patients, independent of propensity to receive that therapy choice is a significant correlate with healthcare costs. A diagnosis of fibromyalgia is a statistically significant source of healthcare costs, though the clinical significance of its impact when compared to a closely matched control group is minimized. Despite the minimization of the role of this diagnosis the impact of the interaction of chronic opioid use with fibromyalgia, despite control for myriad regressors, is significant both statistically and clinically.

KEYWORDS: Cost of illness (COI), Evidence-based medicine (EBM), Fibromyalgia syndrome (FMS), Geographic variation, Opioid

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Student’s signature

May 4, 2012

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To Mom and Dad, you always supported my decisions to pursue my passions. To Granny, your candle-lightings lifted my spirits countless times. To my family, your love and prayers were constant. To my friends, you kept me sane.

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A: Introduction

According to Relieving Pain in America, a recent report published by the Institute of Medicine, pain is the leading affliction affecting Americans and costs the nation over 635 billion dollars annually in medical costs and lost production.[1] The Institute stresses the importance of increased research into the translation of effective treatments into practice and into the occurrence and cost of pain.[1] Chronic pain research is a difficult endeavor because of the subjective and heterogeneous nature of the disorder. One approach to pursuing answers to some of these difficult research questions is to look at individual chronic pain ailments. Fibromyalgia syndrome, due to the nature of the disorder, the recent development of medication with proven safety and efficacy, the significant burden of illness it inflicts on sufferers, and the wide range of treatment alternatives currently in use without efficacy evidence, is an ideal disease state for this goal.

Fibromyalgia syndrome, also labeled FMS or simply fibromyalgia, is an idiopathic, functional disorder characterized by chronic widespread pain and diffuse tenderness.[2] This disorder affects over 6 million patients in the United States and is associated with significant clinical and economic burden to patients, the healthcare system, and society as a whole. Over the past decade a troubling trend has manifested, the increased

prescribing and utilization of opioids for the treatment of chronic nonmalignant pain.

In his book *Powerful Medicines*, Dr. Jerry Avorn describes medication use according to a triad of characteristics: benefits, risks, and costs. By applying this theoretical framework to chronic opioid use in fibromyalgia syndrome, a clear case against their use can be formulated. The benefits of use of these medications in this disorder are not clear. There is no evidence supporting the efficacy of opioid use in this disorder. The risks associated with use of these medications are severe and varied; both personal and societal risks are described in detail below. Finally the costs of opioid use in this population are negligible when only the prescription cost is considered. However, when considering treatment failure, adverse effects, and indirect costs, both to the individual and to society the cost becomes a serious concern.

There are several characteristics, physiological and clinical, that separate fibromyalgia patients from those with general chronic nonmalignant pain. Though the theoretical case, which is presented in detail in the following pages, is strong, there is a lack of evidence specifically comparing utilization and cost characteristics of patients using opioids chronically in this disease state and those receiving evidence-based therapy.

Although the hallmark symptom of fibromyalgia is dispersed pain, the syndrome is also characterized by fatigue, non-restorative sleep, and cognitive difficulties.[2] There are many

unanswered questions regarding both etiology and treatment of fibromyalgia. Although the literature has increased due to the recent introduction of medications approved for the indication of fibromyalgia, research addressing issues such as cost of care, off-label treatment patterns, or healthcare utilization for patients receiving medications other than those currently under patent is less than rigorous, outdated, or nonexistent. The purpose of this review is to describe fibromyalgia syndrome and highlight the consequences of use of chronic opioid therapy for the symptomatic control of patients with fibromyalgia. Use of opioids in this disease state is of particular interest due to the lack of evidence supporting utilization and the growing concern over the clinical and societal consequences of utilization of these drugs. Many of these consequences are unique to or elevated in patients with fibromyalgia when compared to those suffering from other nonmalignant pain syndromes.

In this literature review we first describe the complicated etiology and pathophysiology of fibromyalgia. Then, we discuss diagnosis, burden of illness, and treatment options for the disorder. Next, we highlight the various consequences of opioid use and their application to fibromyalgia patients. Finally, we analyze the outcomes of chronic opioid use, specifically in patients suffering from fibromyalgia.

The conclusion of this literature review outlines a plan for addressing the identified gap in the literature regarding use of opioids chronically in fibromyalgia patients. Briefly, this

plan examines contributing factors associated with chronic opioid use in fibromyalgia syndrome including geographic variation, physician characteristics, and patient characteristics. These characteristics will provide information regarding the inputs that are present when the clinical decision is made to use opioids chronically in a patient. We then will examine the outputs of this clinical decision; comparing fibromyalgia patients using opioids chronically to those receiving evidence-based therapy. We will also make pairwise comparison with each of these groups to similar control patients using opioid chronically for nonmalignant pain and those similar controls not using opioids chronically.

B: Fibromyalgia and its relation to other disorders

The understanding of fibromyalgia has developed greatly since the early 20th century when Sir William Gowers assigned the term fibrositis to muscular pain seen in clinic. Fibromyalgia did not develop in the nomenclature of this presentation until the mid-1970s.[3] This shift represented the growing notion that the presentation represented pain but not inflammation of the fibrous tissue. Although the etiology of fibromyalgia remains unclear, it is becoming increasingly evident that disordered central pain processing is the primary source of the syndrome.[4] Research has shown that fibromyalgia patients have shifted pain response profiles when exposed to either pressure[5] or thermal[6] stimuli. Fibromyalgia is not an organic disorder characterized by a structural or functional abnormality; rather it is considered a

functional somatic syndrome. These disorders are identified by symptoms, suffering, and disability.[7] Other examples of somatic pain syndromes include irritable bowel syndrome, temporomandibular disorder, and vulvodynia. Each of these syndromes is characterized by nondescript, regional pain without an underlying mechanistic cause.[4]

Idiopathic chronic generalized musculoskeletal pain is present in 10% to 12% of the general population.[8] Most patients suffering from this type of chronic pain also meet the clinical criteria often used to identify patients suffering from fibromyalgia syndrome. Despite the similarities in description however fibromyalgia is only diagnosed in approximately 5% of women[9] and 1.6% of men[10] in the general population. The difference in diagnosis rates seen between chronic nonmalignant pain and fibromyalgia syndrome can partially be attributed to the nature of fibromyalgia, which is not a homogeneous pain condition. Rather, the disorder can be observed along a spectrum where at one end pain and tenderness are the exclusive symptoms, and at the other, pain is accompanied by significant psychological and cognitive detriment.[11] This spectrum is multidimensional and is not a definite indicator of severity. Patients may exhibit severe pain symptoms exclusively or have moderate pain but suffer from mental clouding, irritable bowel symptoms, or numerous other symptoms.

Fibromyalgia is generally considered a disorder that occurs in women between 20 and 50 years of age. Although this is the

typical presentation, fibromyalgia occurs in males, children, adolescents and the elderly. Fibromyalgia is increasingly prevalent until age 80, after which prevalence declines.[12] Higher prevalence rates are seen in relatives of patients suffering from fibromyalgia suggesting both environmental and genetic factors leading to the disorder.[9]

C: Difficulties in diagnosing fibromyalgia patients

The diagnosis of fibromyalgia is generally a difficult and tenuous endeavor, which involves ruling out differential diagnoses such as rheumatoid arthritis, systemic lupus erythematosus, and other conditions that present with nondescript pain as a major complaint. In 1990, the American College of Rheumatology developed diagnostic criteria for fibromyalgia syndrome.[13] These criteria focus on the pain and tenderness associated with the disease. They were initially developed for use as inclusion criteria for fibromyalgia research, but have been adopted as the *de facto* diagnosis criteria in practice. Practitioners palpate 18 pressure points throughout the body; patients exhibiting abnormal tenderness in 11 of the 18 points, in addition to a three-month history of bilateral, widespread pain in multiple segments of the body, are said to have fibromyalgia.[13] These criteria are difficult to implement in practice, and are inadequate for use by clinicians for several reasons. First, the exclusive focus on pain and tenderness ignores the varied presentation of fibromyalgia patients seen in practice. Second, the tender point exam is rarely performed in

primary care, where many potential fibromyalgia patients are seen initially, and when performed is often incorrect.[14] Finally, because the diagnosis is symptomatic in nature, when patients improve and are not afflicted in as many areas of the body, they no longer meet the diagnostic criteria.[15]

Although patients suffering from fibromyalgia are generally diagnosed based on symptomatic reports, over the past decade the further development of observation techniques has allowed the medical community to better understand the pathophysiology of fibromyalgia syndrome. Functional magnetic resonance imaging (fMRI) has been utilized to show that cerebral blood flow patterns differ between patients with fibromyalgia and control subjects when exposed to low-pressure stimuli. Increased flow in the secondary somatosensory cortex in patients suggests an augmented pain response to these stimuli.[16] More recent work using fMRI shows fibromyalgia patients have augmented pain processing as well as impaired mechanisms for descending pain inhibition.[17] Further, when compared to age-matched controls, fibromyalgia patients have been shown to have disruptions in intrinsic connectivity within multiple brain networks, suggesting central nervous system hyperexcitability.[18] These advances in brain imaging support the hypothesis that fibromyalgia patients have brain chemistry that differs from controls; many of these differences affect the way treatment should be approached for this disorder.

D: Burden of illness

Patients suffering from fibromyalgia have been shown to be burdened with increased healthcare utilization and costs compared to similar controls. The London Fibromyalgia Epidemiology Study compared four groups: fibromyalgia patients, patients with widespread pain but no fibromyalgia diagnosis, patients accessing healthcare without widespread pain, and a group of controls. This study showed fibromyalgia patients accessing pain-related medication more often and having significantly greater average healthcare cost than those with general widespread pain.[10] Another study, utilizing a US-based health-insurance database, found that total annual healthcare costs for fibromyalgia sufferers averaged $9573 versus $3291 for age and sex matched controls.[19] Statistically significant differences were seen across all cost types including: inpatient care, outpatient care, pain-related medications, other medications, and other medical care.[19] These totals ignore the increased personal and societal burden due to pain and interference of the illness on the patients' daily lives.

This may be a large omission considering one cost of illness study showed that up to four-fifths of the illness cost for fibromyalgia are from indirect sources, such as employment losses.[19,20] Moreover, a review examining quality of life considered 37 studies of fibromyalgia patients and showed that patients had mental health summary scores one standard deviation below the general population, and physical health summary scores two standard deviations below the general population. The

literature shows that fibromyalgia is a significantly impairing disorder with increased direct and indirect healthcare costs compared both to controls and other pain conditions.

E: Pharmaceutical treatment alternatives

Treatment of fibromyalgia syndrome typically focuses on the two most troublesome aspects of the disorder: pain and lack of restorative sleep. Treatment is generally multimodal, consisting of pharmacologic agents and non-pharmacologic therapies such as massage or acupuncture. According to a 2004 review published in the *Journal of the American Medical Association* pharmacologic therapies for fibromyalgia can be divided according to the level of existing efficacy evidence: strong, modest, weak, or none.[21]

Only a very limited number of medications are considered to have strong evidence for efficacy in fibromyalgia. These include amitriptyline, a tri-cyclic antidepressant, and cyclobenzaprine, a muscle relaxant. Amitriptyline has been shown to be effective at reducing pain, fatigue and sleep disturbances, each of these results having large effect sizes in fibromyalgia patients.[22] A meta-analysis of cyclobenzaprine use in patients with fibromyalgia showed significant short-term benefit, though a troublesome adverse effect profile hampers increased use of this medication.[23]

Many medications have shown modest evidence of efficacy in fibromyalgia. Among these are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and tramadol. Selective serotonin reuptake

inhibitors, particularly fluoxetine and paroxetine, have been shown to be effective in reducing pain associated with fibromyalgia; however, no significant effect on mood or fatigue has been demonstrated.[24] Although pure analgesics in general have not proven efficacious in the treatment of fibromyalgia, tramadol has shown efficacy in several randomized controlled trials.[25,26] This is due to its complicated mechanistic action combining mu-receptor agonistic activity with serotonin and norepinephrine reuptake inhibition. Despite the efficacy evidence supporting the use of tramadol for treatment of fibromyalgia, recent warnings from the Food and Drug Administration (FDA) concerning suicide risk associated with the use of this medication suggest that other treatment alternatives may be preferable.[27]

Since publication of this review, three medications have been approved for use in the US for treatment of fibromyalgia syndrome. In 2007, the FDA approved pregabalin, an alpha-2 delta ligand, which reduces calcium influx at nerve terminals and therefore reduces the release of several relevant neurochemicals.[28] Pregabalin has been shown to be superior to placebo in reducing pain and fatigue, improving sleep index scores, improving both patient and clinician global impression of change, and improving four of eight SF-36 domains.[29] One year following the approval of pregabalin, the FDA approved duloxetine. Duloxetine, a balanced nor-epinephrine, serotonin reuptake inhibitor, has been shown in two randomized placebo controlled trials to improve fibromyalgia symptoms across many domains in

women with and without major depressive disorder.[30] In 2009, the FDA approved a third drug for use in fibromyalgia known as milnacipran. Milnacipran is another balanced norepinephrine, serotonin reuptake inhibitor, which was shown to be superior to placebo in pain response, patient global impression of change, fatigue, cognition, and several SF-36 domains.[31] Although the 2004 clinical review of fibromyalgia was published before these medications were approved, all three were classified at the time as having moderate evidence to support efficacy. Based on the criteria used in the review and considering the increased body of literature surrounding their use, they would now be classified as medications with strong evidence.

In addition to classifying medications with moderate and strong evidence for efficacy, the authors of the 2004 clinical review on fibromyalgia treatment also described a class of medications with no evidence for efficacy. Included in this class were corticosteroids, non-steroidal anti-inflammatory drugs, benzodiazepines, and other hypnotics. Opioid analgesics are also included in this category. However, despite the lack of evidence supporting the use of opioids for the treatment of fibromyalgia, evidence suggests widespread and increasing clinical utilization.[4] For a summary of efficacy evidence for medications commonly used in fibromyalgia syndrome see Table 1.

F: Various consequences of opioid use

The use of chronic opioid therapy for the control of chronic nonmalignant pain has increased tremendously over the

past decade.[32] Between 2005 and 2009, the rate of emergency department visits due to misuse or abuse of oxycodone products increased by 242.2%, the leading agent in a problem that spans the entire opioid class; morphine, hydrocodone, and fentanyl products all more than doubled in their rates of emergency department visits over the same period.[33] In 2007, misuse of abuse of pharmaceuticals surpassed illicit drugs becoming the second leading cause of drug related emergency department visit.[33] Concurrent with this trend, the US has seen a steep rise in opioid abuse, misuse, and diversion.[34] With the increased availability of opioids, the consequences of their use have led to increases in many negative outcomes associated with utilization. Increased utilization is especially concerning because it leads to an increased propensity for opioid addiction.[35]

Beyond the obvious risks presented to those using opioid medications, there is also an increased risk to those within their households. Poison control data gathered between 2003 and 2006 show nearly 10,000 children with inadvertent exposure to opioid medications, nearly all of these exposures occurred within the child's home.[36] Increased crime such as theft from pharmacies and individuals is also a concern, as is diversion between household members.[37]

In addition to the immense societal concerns posed by increased opioid utilization, there are the individual adverse effects seen in patients treated with these medications. Common

complications due to opioid administration include constipation, pruritus, respiratory depression, nausea, vomiting, delayed gastric emptying, sexual dysfunction, muscle rigidity and myoclonus, sleep disturbance, pyrexia, diminished psychomotor performance, cognitive impairment, dizziness, and sedation.[38] Beyond the effects seen with short-term administration, another set of adverse effects is seen with administration of opioids for the treatment of chronic pain. Long-term utilization of opioids is associated with hormonal and immune effects, abuse and addiction, tolerance, and hyperalgesia.[38]

Both tolerance and opioid-induced hyperalgesia are concerns with any chronic pain condition. Opioid treatment generally is characterized by the need for increased dosing over time. The need for this increase is typically attributed clinically to tolerance due to cellular adaptation resulting in the reduction of either opioid receptors or turnover rate, or the desensitization of receptors.[39] An alternative, or possibly additional, explanation for the apparent decreased response to these medications, however, is opioid-induced hyperalgesia.

G: Increasing concern around opioid-induced hyperalgesia

The idea of opioid-induced hyperalgesia has been present in the literature for over a century, labeled as hyperesthesia, opioid abstinence syndrome or other terms that failed to fully grasp the etiology of the disorder.[40] Clinical research into opioid-induced hyperalgesia today is due, in large part, to a number of studies performed in the 1970’s showing that in animal

models administration of opioids may paradoxically result in increased sensitivity to, and aggravation of, preexisting pain.[40] Opioid-induced hyperalgesia manifests as reduced nociceptive threshold, and is primarily thought to be the result of central sensitization of pronociceptive pathways.[41] Opioid-induced hyperalgesia presents as heightened atypical pain sensations distinct from the original pain stimulus, with a separate location and altered distribution from the original complaint.[42]

The presentation of opioid-induced hyperalgesia has many complicating factors. First, the extent of presentation may differ depending on an individual opioid's mu- or kappa- receptor activity. Another consideration is the varying evidence available for opioid-induced hyperalgesia based on type of stimulus. There is literature supporting the presence of opioid-induced hyperalgesia to different extents for cold,[43] electrical,[43] mechanical,[44] and thermal[45] stimuli. In addition, there is conflicting evidence regarding the reversibility of the condition once opioid exposure is removed.[46,47]

The defining difference between tolerance and opioid-induced hyperalgesia is the increased baseline pain sensitivity seen in opioid-induced hyperalgesia. Unfortunately, clinically this requires removing the opioid exposure to clearly demonstrate which phenomenon is occurring. Clinical manifestation of opioid-induced hyperalgesia is typically seen within one month of therapy initiation, and may present as reports of new unexplained pain or diffuse allodynia. This presentation is very similar to

the classic pain and tenderness seen in fibromyalgia. In fact, the possibility of opioid-induced hyperalgesia is of particular concern in patients suffering from fibromyalgia. Studies suggest that patients with fibromyalgia have dysregulated opioiergic pathways.[34] The low mu-opioid receptor binding activity seen in these patients suggests decreased central mu-opioid receptor availability.[48] The concern regarding development of this complication in fibromyalgia patients is also increased due to the complicated neuropathic nature of the pain seen in these patients. The current understanding of fibromyalgia pain implicates both efferent and afferent modulation systems. Possible altered functioning in descending cortical structures of fibromyalgia patients may decrease efficacy of strong opioids that ignore the noradrenergic aspect of pain seen in fibromyalgia.[42]

H: Specific concerns regarding opioid use in fibromyalgia

Opioid use in chronic nonmalignant pain is a divisive subject in the current literature. Current guidelines suggest guarded use of opioids chronically in nonmalignant pain and these recommendations are based on moderate quality evidence at best.[32] The use of opioids chronically in fibromyalgia patients deserves extra scrutiny for several reasons. First, the use of opioids in fibromyalgia patients ignores the complicated presentation of the disorder discussed above. Although opioids may temporarily control the pain experienced in the disorder, their use ignores

the other aspects of the disorder including non-restorative sleep, fatigue, and irritable bowel.

Patients suffering from fibromyalgia may also have altered endogenous opioid activity. A study utilizing positron emission tomography found that patients suffering from fibromyalgia syndrome exhibit decreased mu-opioid receptor availability in areas of the brain key to pain and nociception processing.[48] There are two possible explanations for the demonstrated reduced availability. First, endogenous enkephalins levels are elevated in patients with fibromyalgia, even when compared to patients suffering from chronic low back pain.[49] Elevated endogenous ligands in these patients may explain the reduced availability of receptors to opioids, decreasing their effectiveness in fibromyalgia patients. Another possible explanation is the increased presence of endogenous ligands may lead to down regulation of opioid receptors.

Not only is the failure rate of opioid use a greater concern in patients with fibromyalgia, there is also an increased concern of misuse or abuse among this population due to characteristics commonly seen in these patients. Risk factors commonly associated with nonmedical use of opioids include anxiety and mood disorders, each a common comorbidity seen in patients with fibromyalgia.[50] In addition low self-rated health status, commonly seen in fibromyalgia, increases the propensity toward misuse or abuse of opioids.[50]

Beyond these reasons there is also increased concern of adverse effect presentation in patients with fibromyalgia for several reasons. Fibromyalgia patients report adverse effects and intolerance to treatment at elevated rates.[51] In addition to the increased reporting of adverse effects in general there are also concerns with the way certain specific adverse effects seen with opioid use may affect fibromyalgia patients. Constipation is a hallmark effect seen with opioid use and may be of increased concern in patients suffering from the irritable bowel symptoms commonly associated with fibromyalgia. Other adverse effects such as sedation and mental clouding are also of particular concern in patients with fibromyalgia due to the possible pre-existing presence of these problems due to the disorder.

I: Time for an evidence-based approach

Given the profound lack of controlled or anecdotal efficacy evidence supporting the use of opioids in fibromyalgia, their prevalence as a treatment option is mysterious. Couple this lack of efficacy with the increasing armamentarium that does have evidence of safety and efficacy supporting use, and with the clear societal and personal adverse effects of chronic use of opioids, and the prevalence of their use in fibromyalgia becomes very troubling. Beyond all of these concerns, which are common to the treatment of most chronic non-malignant pain conditions, the pathophysiology of fibromyalgia and the increased risk of opioid-induced hyperalgesia that results from this

pathophysiology, make the use of opioids in this condition ill advised.

J: Future research directions

Although the body of literature focusing on fibromyalgia continues to increase, much of the most recent literature is funded through pharmaceutical companies and focuses on recently approved medications. Unfortunately this focus ignores a large portion of fibromyalgia patients who are receiving therapy that does not meet current treatment guidelines. Recent evidence suggests that nearly one-third of fibromyalgia patients are receiving opioid therapy as at least part of their therapy.[52] This includes both acute and chronic opioid therapy, which does not address the fact that opioids are appropriate for short-term use to alleviate acute pain conditions. There is no evidence currently available to answer questions specifically comparing healthcare utilization and costs associated with fibromyalgia patients receiving chronic opioid therapy versus fibromyalgia patients receiving evidence-based therapy.

To address this gap in evidence there are multiple research questions that must be addressed. The following are specific aims associated with each of these research questions.

<u>Specific Aim 1: Identify factors contributing to the utilization of chronic opioid therapy for the treatment of fibromyalgia syndrome</u>

Factors contributing to the prescribing and utilization of chronic opioid therapy for the treatment of fibromyalgia syndrome

can be divided into three categories. Each of these categories will be addressed in this research plan.

1.A. Geographic variation of contextual variables

Geographic trends will allow us to examine if chronic opioid use in fibromyalgia is a national phenomenon or if the use is localized by state. Differing rates of use among states may signal overuse in certain populations. A nationally representative cross-section allows us to examine a large number of patients at a certain point in time to examine opioid utilization. Various factors such as average sex, age, and fibromyalgia prevalence within a state can be examined to determine what macro level factors are associated with the use of opioids chronically in fibromyalgia patients.

A more advanced approach to geographic variation includes the examination of an annual panel of the same characteristics mentioned above for states. This will allow us to control for state and time effects to see if characteristics significant within the cross-section are statistically significant independent of state identity and year. State fixed effects allow comparison between those states with large levels of chronic opioid use and those with lower levels. In addition examination of fixed effects and the between estimator allows within the regression of panel data allows for estimates of effects of changes in independent variables overtime and the means of variables during the period.

1.B. Prescriber characteristics

Geographic variation is a small part of the concern for opioid use in fibromyalgia. Macro trends are important, but analysis of individual level prescriber characteristics will provide information regarding who is prescribing these medications despite strong caution against it in the literature and treatment guidelines. Characteristics such as gender, age, years in practice, practice specialty, urbanicity, state of practice, and practice site all help to form a more detailed picture how patients are receiving these medications.

1.C. Patient characteristics

Perhaps more important that who is prescribing the medication is who is receiving them. Patient characteristics of interest include gender, age, comorbidities, concurrent medications, severity, urbanicity, and state of residence. All of these individual-level factors allow for a more robust picture of both who is prescribing opioids for chronic use in fibromyalgia and who is using this medication for treatment.

Specific Aim 2: Analyze the effect of chronic opioid use in fibromyalgia syndrome on healthcare costs and utilization

Identification of who is prescribing and receiving opioids is an intermediary step on the way to addressing the questions that may provide the most clinically significant answers. These questions deal with the outcomes associated with chronic opioid use in patients suffering from fibromyalgia syndrome. Ultimately these questions are best answered through the identification of

four groups of patients. Patients with fibromyalgia receiving chronic opioid therapy, patients with fibromyalgia treated without chronic opioids, similar patients without fibromyalgia treated with opioids chronically, and similar patients without fibromyalgia not receiving chronic opioid therapy. Identification of these groups allows two-way comparisons analyzing various outcomes of interest. These outcomes include cost and utilization measures typical in this area of research: hospital admissions, outpatient visits, prescription costs, medical costs, etc.

Completion of this research track will provide answers to key outstanding questions in the current fibromyalgia research. Research addressing geographic variation, patient and prescriber characteristics, and utilization and cost outcomes associated with chronic opioid use in fibromyalgia patients would provide much needed evidence. This evidence could be used to further inform evidence-based guidelines influencing the future treatment of patients suffering from fibromyalgia syndrome.

Table 1.1: Pharmaceutical treatment options for fibromyalgia syndrome

Strong Evidence for Efficacy: Amitriptyline Cyclobenzaprine *Pregabalin *Duloxetine (SNRI) *Milnacipran (SNRI)
Modest Evidence for Efficacy: Tramadol Serotonin reuptake inhibitors (SSRIs): Fluoxetine Dual-reuptake inhibitors (SNRIs): Venlafaxine
No Evidence for Efficacy: Opioids, corticosteroids, nonsteroidal anti-inflammatory drugs, benzodiazepines, hypnotics, melatonin, calcitonin, thyroid hormone, guiafenesin, dehydroepiandrosterone, magnesium
Table adapted from Goldenberg et al., 2004 **Denotes difference from Goldenberg due to evidence sufficient for FDA approval since 2004*

Chapter 2: Cross-sectional analysis of geographic variation of chronic opioid use in fibromyalgia syndrome

Given the gaps in literature identified in Chapter 1, Chapter 2 begins an analysis of the factors determined at the lowest level of granularity considered. These factors are state-specific, and this chapter specifically considers these factors in a time-invariant approach.

A: Background

Fibromyalgia syndrome, also labeled FMS or simply fibromyalgia, is an idiopathic, functional disorder characterized by chronic widespread pain and diffuse tenderness.[2] Although the etiology of fibromyalgia remains unclear, it is becoming increasingly evident that disordered central pain processing is the primary source of the syndrome. Fibromyalgia is diagnosed in approximately 5% of women in the US[9] and 1.6% of men.[53] In the US this translates to more than 6 million patients. Patients suffering from fibromyalgia are burdened with significantly increased healthcare utilization and costs compared to similar controls.[19]

Treatment of fibromyalgia syndrome typically focuses on the two most troublesome aspects of the disorder: pain and lack of restorative sleep. Treatment is generally multimodal, consisting of pharmacologic agents and non-pharmacologic therapies such as massage or acupuncture. Unfortunately, one of the increasingly common therapeutic classes of choice for the treatment of pain associated with fibromyalgia syndrome is the opioid analgesic

class. According to a 2004 review published in the *Journal of the American Medical Association*, opioids have no evidence of efficacy for use in fibromyalgia patients.[21] Chronic opioid therapy, for the control of chronic nonmalignant pain of many types, has increased tremendously over the past decade.[32] Despite the lack of evidence of efficacy for their use in fibromyalgia syndrome, the pattern of use in fibromyalgia has mirrored that of use in chronic non-malignant pain.[4]

This elevated use is troublesome not only due to lack of efficacy presented by utilization but also because of the myriad societal and individual adverse effects associated with opioid use.[34] These effects include the common adverse effects seen with acute (constipation, pruritus, respiratory depression, nausea, vomiting, delayed gastric emptying, sexual dysfunction, muscle rigidity and myoclonus, sleep disturbance, pyrexia, diminished psychomotor performance, cognitive impairment, dizziness, and sedation) as well as chronic (hormonal and immune effects, abuse and addiction, tolerance, and hyperalgesia) use of these medications. Opioid-induced hyperalgesia is of particular concern in fibromyalgia patients because treatment with these medications may not only be inefficacious, but also may result in the manifestation of a separate pain condition. Although opioid treatment may result in hyperalgesia in any patient, the dysregulated opioidergic pathways seen in fibromyalgia patients is cause for increased concern.[32] Possible altered functioning in descending cortical structures of fibromyalgia patients may

decrease efficacy of strong opioids that ignore the noradrenergic aspect of pain seen in fibromyalgia.[42]

Geographic variation in care patterns is well documented for some disease states and medication classes. Notably, colorectal cancer[54], cardiac care procedures[55], antihypertensive medications[56], and stimulant medications[57] all have been examined and shown to have significant differences in utilization with respect to geography. Several studies have recently shown that geographic variation exists in opioid prescribing for various disease states. Curtis *et al.* examined schedule II opioid analgesics and found significant variation at the county level, with the presence of a statewide prescription monitoring program being a factor significantly associated with less opioid utilization.[58] Webster *et al.* examined opioid prescribing for acute lower back pain and found that geographic variation exists and that nearly four-fifths of the between-state variation can be explained by state level factors.[59]

Many leading researchers in this literature have stated that geographic variation of an intervention is a sign of inappropriate use.[60] In general, the interpretation of whether this inappropriate use is under- or overutilization is indeterminable using standard methods. However, the chronic use of opioids for the treatment of fibromyalgia provides a unique situation due to the current treatment guideline's statement that "strong opioids are not recommended".[61]

To date, no studies have been found that report on geographic variation in chronic opioid prescribing for patients with fibromyalgia. Providing detailed information regarding geographic treatment variation in opioid use for fibromyalgia patients is an important intermediate goal on the way to ultimately improving the quality of care for these patients. The current study aims to assess the extent of geographic variation at the state level for opioid utilization in patients suffering from fibromyalgia syndrome across the nation. First, we will examine the prevalence and geographic variation of chronic opioid use in fibromyalgia syndrome patients. We hypothesize that significant geographic variation exists at the state level for opioid prescribing in this population. Second, we will examine the effect of prescription monitoring programs and various other factors on the rate of chronic opioid use at the state level. Based on previous work[58], we hypothesize that prescription monitoring programs and the percent of patients between 45 and 64 will be negatively associated, whereas female gender and prior illicit opioid use rate will be positively associated with chronic opioid use at the state level.

B: Materials and methods

Data Source

The University of Kentucky Institute for Pharmaceutical Outcomes and Policy has a licensing agreement for the i3 Invision Data Mart (IVDM) for the years 2007-2009. We obtained de-identified patient information from January 1, 2007 to December

31, 2009 from the IVDM. The IVDM is a nationally representative de-identified sample of 15 million patients from a commercial health plan across the United States and includes commercially insured patients as well as patients in Medicaid managed care plans. The data are collected at the patient level, and consist of eligibility and enrollment information (eligibility date, eligibility span, health plan type), demographic information (gender, age, state), medical (inpatient, outpatient, professional services, including ICD-9-CM, DRG, CPT-4, revenue code and links to participating providers), pharmacy (prescriber, NDC, day supply, quantity), and laboratory (type of test and results) for approximately 15 million patients each year.

Study Cohort Definitions

The dataset was searched for patients with fibromyalgia syndrome as identified by *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-CM-9) code 729.1 (myalgia and myositis unspecified). Patients with at least one claim in between January 1, 2007 and December 31, 2009 were included in the sample. Only patients between ages 18-64 were considered for this study. The reasons for this restriction are utilization patterns may differ for children, and missing data problems are more common for those eligible for Medicare. Patients with malignancies were excluded from analysis because medical care patterns may differ for these patients. The University of Kentucky Institutional Review Board provided approval for this study via a blanket data use agreement for IVDM.

Outcome Variable

Chronic opioid therapy was the primary outcome of interest for this study. Chronic opioid therapy is defined as receiving a day supply in excess of one-half the total eligibility span for an individual patient. Similar outcome measures have been used in the past to describe chronic opioid use.[62] This individual level outcome variable is aggregated at the state level to provide a rate of chronic opioid use over the three-year cross-section for each state. Receipt of opioids was based on paid prescription claims with National Drug Codes (NDC) for opioid medications. Each claim is associated with a day supply calculated at the pharmacy based on directions for use from the prescriber. Using American Hospital Formulary Service Codes[63] and verifying with Pharmaprojects Therapeutics Class Codes[64], drugs were divided into two classes, opioids and non-opioids (including tramadol). A secondary outcome presented in the findings is monthly opioid prescriptions per patient.

Independent variables

Individual-level variables

Collected patient characteristics include demographic variables age, gender, eligibility span, and insurance type (private vs. Medicaid). Means of individual level variables were calculated for each state for the entire cross-section and used as state level characteristics.

State level variables

State level variables were adapted from two previous studies measuring geographic variation in opioid use. Curtis *et al*[58] included proportion of females, rate of illicit drug use, state prevalence of surgeons, presence of a statewide prescription monitoring program, and proportion of population in younger and older age groups. We adapted these variables for our data and outcome resulting in the following variables: proportion of female at the state level and within our patient sample, rate of illicit drug use and rate of illicit opioid use, state rate of physicians and surgeons, presence of statewide prescription monitoring program, and proportion of state population between 45 and 64 years of age.

Beyond these variables, economic and healthcare quality variables were added based on the work of Webster *et al*.[59] State unemployment rate and median income were included from July 2008, the middle of the cross-section. Physician discipline sanction rates were taken from Public Citizen.[65] Healthcare quality state rankings were taken from The Commonwealth Fund[66] as an average of the 2007 and 2009 biannual rankings. Level of evidence based medicine was calculated based on an average of three quality indicators used by The Dartmouth Atlas.[67]

Data Analysis

Individual level factors were aggregated and a descriptive analysis was performed. State level geographic variation was measured using the weighted coefficient of variation (wCOV), the

ratio of the standard deviation of the prevalence rates to the mean rate among states, weighted by the IVDM population in each state. To analyze potential contributing factors to chronic opioid use among fibromyalgia patients, we performed a robust multivariate linear regression. All calculations and analyses, including geographic variation analysis, were performed using Stata v11.2. Map generation was performed using ‘spmap’ and ‘uscoord’ within Stata. For all analyses the entire three-year period is treated as a single cross-section.

C: Results

State level analysis included 245758 patients with a diagnosis of fibromyalgia in the IVDM. Patients were selected from the 48 contiguous states and the District of Columbia. Of these patients, 11.3% received chronic opioid therapy during the study period (Table 1). Most patients were female (69.89%) and the average age was 44.7 years. Overall, patients received nearly 70 prescriptions per year and about 10% of these were for opioids. The average eligibility span for patients in the sample was about two of the total three-year study period.

Figure 1 illustrates the geographic distribution at the state level of the IVDM patient population. It is from this general population that we pulled our fibromyalgia syndrome patients. Figure 2 highlights the geographic variation seen in the distribution of fibromyalgia patients in the sample. Correlation IVDM population in a state and the distribution of FMS patients is 98%.

The overall prevalence of fibromyalgia for this sample is 1.6% (Table 1). The minimum is 0.7% (Vermont) and a maximum is 3.0% (North Dakota). It should be noted that each of these extrema are found in states with small samples. The geographic variation in the prevalence of fibromyalgia syndrome can be seen in Table 2 and Figure 3.

Figure 4 illustrates the large variation seen in monthly opioid prescriptions per patient. The values for opioids per patient per year eligibility vary between 1.47 in New York and 9.84 in Minnesota (Table 2). In this case it should be noted that the extrema each occur in states with large sample sizes. Also of note, Minnesota is one of three states (Rhode Island and New Mexico being the others) with a significant number of Medicaid patients included in the sample. Both Rhode Island and New Mexico fall within a standard deviation unit of the mean in this measure.

Figure 5 shows the geographic variation in the primary outcome of interest, patients receiving chronic opioid therapy. The wCOV for chronic opioid therapy was 36.2%. The states with the lowest proportion of chronic opioid use were South Dakota, North Dakota, and New York, each under 5%. The states with the highest proportion of chronic opioid use in fibromyalgia patients were Utah, Nevada, and West Virginia, each around 20%.

The results of the multivariate regression (Table 3) examining factors associated with chronic opioid use in patients suffering from fibromyalgia syndrome were generally as predicted. The proportion of the state population between ages 45 and 64 was

negatively associated with chronic opioid use and both percent of fibromyalgia patients that are female and past illicit opioid use rates were positively associated. However, the prediction that the presence of a statewide prescription-monitoring program would be negatively associated with chronic opioid use in this condition was not correct; this variable was not statistically significant.

In addition to the independent variables that were predicted to be related to chronic opioid use in fibromyalgia, there were also three variables with significant associations that were unpredicted. The prevalence of fibromyalgia diagnosis within a state, the population of a state, and physician prevalence within a state are all significantly (alpha=0.05) negative predictors of chronic opioid use in this population.

D: Discussion

Geographic Variation: Existence in Fibromyalgia

The primary aim of this study was to assess the level of the geographic variation in chronic opioid use for patients with fibromyalgia syndrome. In order to do this, we examined data within the i3 Invision Data Mart, extracting a sub-population with a diagnosis for fibromyalgia syndrome. Using this data we found that nearly 1 in 8 patients with fibromyalgia were receiving chronic opioid therapy. This rate is similar to that seen in other studies.[68] Between states there was an over 5-fold difference between the most conservative (South Dakota, 4.0%) and

liberal (Utah, 20.2%) opioid prescribers. The wCOV seen for chronic opioid therapy in this population was 36.2%.

These rates of variation are similar to that seen in previous literature examining geographic variation of opioid use at the state level. Curtis *et al.* examined use of opioids for any condition across states using a similar data set and found wCOV of 45%.[58] Zerzan *et al.* examined opioid prescribing in Medicaid population and found variation with a wCOV of 50%.[69] Webster *et al*. examined variation in opioid prescribing for acute, work related low back pain and found a wCOV of 53%.[59] Variation was found to be slightly higher in each of these studies, which may be a result of the outcome measures that were used. Each of these studies was looking at acute and chronic use of opioids, where variation among patients is expected to be greater.

Geographic Variation: Explanatory Variables

The robust multivariate linear regression showed many state level variables are significantly associated with chronic opioid use. These state level variables explain three-quarters of the variability in the data set. The remaining quarter is likely made up of within state variation that is not observable using cross-sectional analysis. As seen in Webster *et al*[59] the large proportion of between state variation explained with state level factors stresses the importance of characteristics not associated with patient, provider, or third party characteristics.

Statewide prescription monitoring program (PMP)

The presence of a statewide PMP was not significantly associated with chronic opioid use in fibromyalgia patients. This factor was significant in Curtis *et al*[58] but not in Webster *et al*.[59] One possible explanation for this is the simplicity of the variable. A state was considered positive for a PMP if it had an operational PMP for the study period, regardless of the details of the program. Much variation exists in characteristics of PMPs and the effectiveness of PMPs across states is currently debated in the literature.[70]

Physicians per capita

The number of surgeons per capita was not found to be a significantly associated factor in this study as it was in Curtis *et al.*[58], where it was explained as increased use in postoperative pain. The present study model is more closely related to Webster *et al*.[59] due to the lack of importance of surgery as a treatment alternative for fibromyalgia. In agreement with the findings of Webster *et al*[59] we found that although surgeons per capita was not a significantly associated factor, the number of physicians per capita was significantly and negatively associated. This could be explained by greater peer-to-peer interaction resulting in more information diffusion, or by reduced work burden resulting in better knowledge of or adherence to evidence based medicine.

Fibromyalgia prevalence

An unexpected significantly negative associated variable is the level of fibromyalgia prevalence within a state. A similar

explanation to that proposed for the relationship of physicians per capita may apply here. As the level or fibromyalgia patients in a given geographic area increases, information regarding the proper treatment of the disorder may disseminate more fully. An alternate but related explanation is that geographic areas able to diagnose fibromyalgia better are able to treat fibromyalgia better, so as the diagnosis of a disease becomes more common so does evidence based treatment. There is no evidence of this effect either related to fibromyalgia syndrome or the rate of opioid use in the current literature.

Other explanatory variables

The only other significantly associated variable was state population. States with large population were less likely to prescribe opioid chronically for patients. Quality variables such as evidence based medicine use in states and healthcare quality rankings were not found to be significantly associated with chronic opioid use. Also state economic indicators such as median income and unemployment rate were not significantly related to use within fibromyalgia patients.

Theoretical Implications

The findings of this study back up those seen in previous studies looking at geographic variation of opioid use. These studies support the theory proposed by Westert and Groenewegen that social context and structural factors affect prescribing behavior.[71] This study extends that theoretical framework by demonstrating the contribution of factors such as physician

prevalence, disease prevalence, and state population to the way a chronic disease is treated.

E: Limitations

There are limitations to this study. First, although the data are aggregated from individual patient level data the analysis is done by state. State levels of comorbid conditions are not considered as a confounding variable. As with fibromyalgia, treatment of chronic nonmalignant pain using opioid analgesics is strongly cautioned in current guidelines.[32] Also the level of opioid use in the general population was not considered as an explanatory variable. Opioid use for nonmalignant pain is a controversial topic, in need of further study in various conditions. The present study is limited in scope to fibromyalgia patients due to unique physiological characteristics and literature stating the lack of efficacy evidence of opioids for treatment. The rate of chronic opioid therapy among fibromyalgia patients is an outcome of interest independent of opioid use among others within the state.

The calculation of the chronic opioid use variable is also a concern. Because the measure only considers day supply and span of eligibility there is a possibility that patients receive several opioid medications concurrently, bolstering their observed day supply. The main concern with this limitation is that ‘chronic’ may not be an adequate descriptive term to use for this measure, as patients may be receiving several medications over a short period of time. However, for the majority of

patients this still results in having a day supply of greater than 183 days during a single year or 537 days over the entire period. This measure has been used in similar studies in the past[62], and although the labeling of this variable may not be completely satisfactory the clinical significance of what it measures is evident.

Another possible limitation is seen in the various levels of Medicaid participation from state to state. The concern is minimal, however. The majority of states had no Medicaid participation in the study and only three states (Minnesota, New Mexico, and Rhode Island) had greater than 5% of their sample from Medicaid. Analysis of the findings accounting for the inclusion of a Medicaid variable was also completed and no significant differences were found in the results.

Finally, the cross-sectional design of this study did not allow for the analysis of changes in contextual factors within states over time. Analysis of a longitudinal sample would be useful in determining the role of state fixed effects on chronic opioid use for the treatment of fibromyalgia syndrome.

F: Conclusion

Chronic opioid therapy for the treatment of fibromyalgia syndrome is a practice based, not on evidence, but on other factors that have been heretofore unreported in the literature. The current study reports on one set of such characteristics that result in wide geographic variation similar to that previously reported in other pain conditions. This large level of geographic

variation suggests that the prescribing decision is not based solely on physician-patient interaction, but also on contextual and structural factors at the state level. The level of physician and disease prevalence suggest that information dissemination and peer-to-peer interaction may play a key role in adopting evidence based medicine for the treatment of patients suffering from fibromyalgia syndrome. Level of disease prevalence as a predictor of evidence-based practice has not been reported in the literature previously and is an important contribution to not only the fibromyalgia literature, but also possibly other literatures where significant geographic variation in practice exists.

Given the cross-sectional approach to this study the interpretation of the findings is limited. In order to better clarify the role of state-level factors and to ascertain the role of state identity in the rate of chronic opioid use in fibromyalgia patients the next chapter analyzes similar data using a longitudinal approach generally seen in the social sciences.

Table 2.1: State summary characteristics for fibromyalgia patients

n=245758	Mean	SD	Median	Min	Max
FMS prevalence (%)	1.56	0.39	1.57	0.72	2.98
Annual prescriptions per patient	66.8	22.0	67.0	45.8	193.8
Annual opioids per patient	6.9	2.6	6.5	2.8	18.7
Female (%)	69.89	3.46	70.33	59.38	78.18
Age (years)	44.7	1.3	44.8	41.9	47.5
Eligibility span (months)	24.1	1.3	24.3	22.0	26.4
Chronic opioid therapy (%)	11.65	4.16	11.60	3.95	20.18

Table 2.2: State characteristics for fibromyalgia patients

State	n	Female (%)	Age (years)	FMS Prevalence (%)	Annual opioids per patient	Eligibility Span (month)	Chronic Opioid Therapy (%)[1]
AL	1759	72.1	44.7	1.48	8.92	22.4	16.71
AR	2565	74.7	45.2	1.81	7.92	24.3	13.06
AZ	8376	73.1	45.4	1.62	9.23	24.1	16.95
CA	12053	64.9	43.7	1.58	4.33	25.4	7.35
CO	7478	68.7	44.6	1.62	8.53	25.7	12.58
CT	1667	69.2	44.4	1.57	5.38	25.2	8.76
DC	269	70.6	42.5	0.76	3.95	22.3	5.58
DE	175	66.3	45.5	0.90	6.03	22.4	14.86
FL	27658	70.3	45.7	1.57	7.92	24.7	14.88
GA	16962	72.8	46.4	1.70	6.45	24.7	9.81
IA	2048	69.9	46.9	1.82	5.46	25.6	8.74
ID	575	73.4	43.9	1.42	9.14	25.9	14.26
IL	6480	67.6	44.3	1.25	4.86	24.2	7.81
IN	4057	71.7	45.5	1.53	7.36	23.1	14.52
KS	2443	68.0	44.3	1.84	5.96	23.6	9.01
KY	2242	71.5	44.1	1.66	7.46	22.8	17.08
LA	4099	69.0	44.7	1.52	6.95	25.1	11.34
MA	2377	67.3	45.2	1.36	4.28	25.1	7.07
MD	4971	68.4	44.1	1.47	5.57	22.1	10.28
ME	238	73.1	46.3	1.62	4.28	24.5	7.56
MI	1770	67.7	43.3	1.21	6.24	23.2	11.69
MN	18219	72.7	43.6	2.29	18.73	22.8	9.49
MO	8469	71.6	45.1	1.65	5.82	25.0	8.93
MS	1969	71.6	44.8	1.57	8.03	22.6	14.07
MT	165	78.2	46.8	1.38	6.11	22.6	15.76
NC	8857	70.3	45.6	1.61	7.74	24.5	14.11
ND	607	62.8	42.3	2.98	4.11	24.0	4.94
NE	2325	69.8	45.0	1.92	5.89	25.9	7.35
NH	411	74.9	46.2	1.38	5.31	24.3	8.03
NJ	4287	63.2	42.9	1.40	3.96	25.8	6.04
NM	2257	73.6	46.4	2.03	5.45	25.9	9.26
NV	1152	67.1	43.5	1.18	8.62	21.9	19.79
NY	8154	62.8	42.0	1.69	3.12	26.4	4.99
OH	15101	72.8	45.5	1.75	7.01	25.2	12.85
OK	1975	68.7	43.4	1.34	8.26	22.5	13.82
OR	1553	72.9	45.5	1.51	9.01	23.5	17.84
PA	3355	69.8	44.2	1.23	5.30	22.2	11.60
RI	3911	71.9	45.8	2.18	10.52	25.9	13.63
SC	2716	70.8	45.2	1.60	7.13	22.8	13.66
SD	506	68.6	45.2	2.29	2.75	23.2	3.95
TN	5021	70.9	44.3	1.71	8.60	24.5	7.31
TX	24775	70.2	44.3	1.28	7.29	24.8	11.60
UT	1670	71.2	41.9	1.17	12.30	23.9	20.18
VA	5836	67.4	43.6	1.69	5.20	22.4	8.69

Table 2.2: State characteristics for fibromyalgia patients (continued)

VT	32	59.4	47.5	0.72	5.28	25.1	9.38
WA	2262	71.0	45.4	1.20	8.17	24.0	13.84
WI	9215	68.8	45.6	1.79	6.63	25.9	9.38
WV	545	73.6	45.5	1.38	8.54	22.4	19.63
WY	151	68.2	43.8	1.01	5.44	23.1	10.60

1: Opioid day supply is the sum of the day supplies of all opioid prescriptions for an individual patient.

2: Chronic opioid therapy is defined as having a day supply greater than one-half of an individual patients eligibility span.

Table 2.3: Multivariate linear regression: state level chronic opioid analgesic use

	Coef. (SE)	P
FMS prevalence (%)	**-5.300(0.797)**	0.001
FMS female (%)	**0.300(0.123)**	0.021
Evidence based medicine (%)	0.197(0.136)	0.157
Illicit drug use (%)	-0.122(0.514)	0.815
Surgeon prevalence (per 100k)	-0.129(0.295)	0.665
Prescription monitoring program	1.266(1.044)	0.234
Healthcare quality rank	0.045(0.037)	0.230
State population (1000000)	**-0.220(0.063)**	0.001
State female (%)	0.239(0.579)	0.682
Age 45-64 (year)	**-0.684(0.328)**	0.045
Unemployment rate (%)	0.749(0.507)	0.149
Median income ($1000)	-0.012(0.082)	0.888
Illicit opioid use (%)	**0.992(0.442)**	0.032
Physician prevalence (per 100k)	**-0.022(0.007)**	0.002
Physician sanctions (per 100k)	0.002(0.030)	0.946
Constant	-5.856(26.658)	0.827
[Observations=49] [R^2=0.749]	[Root MSE=2.512]	

Figure 2.1: General patient distribution of i3 Invision Data Mart

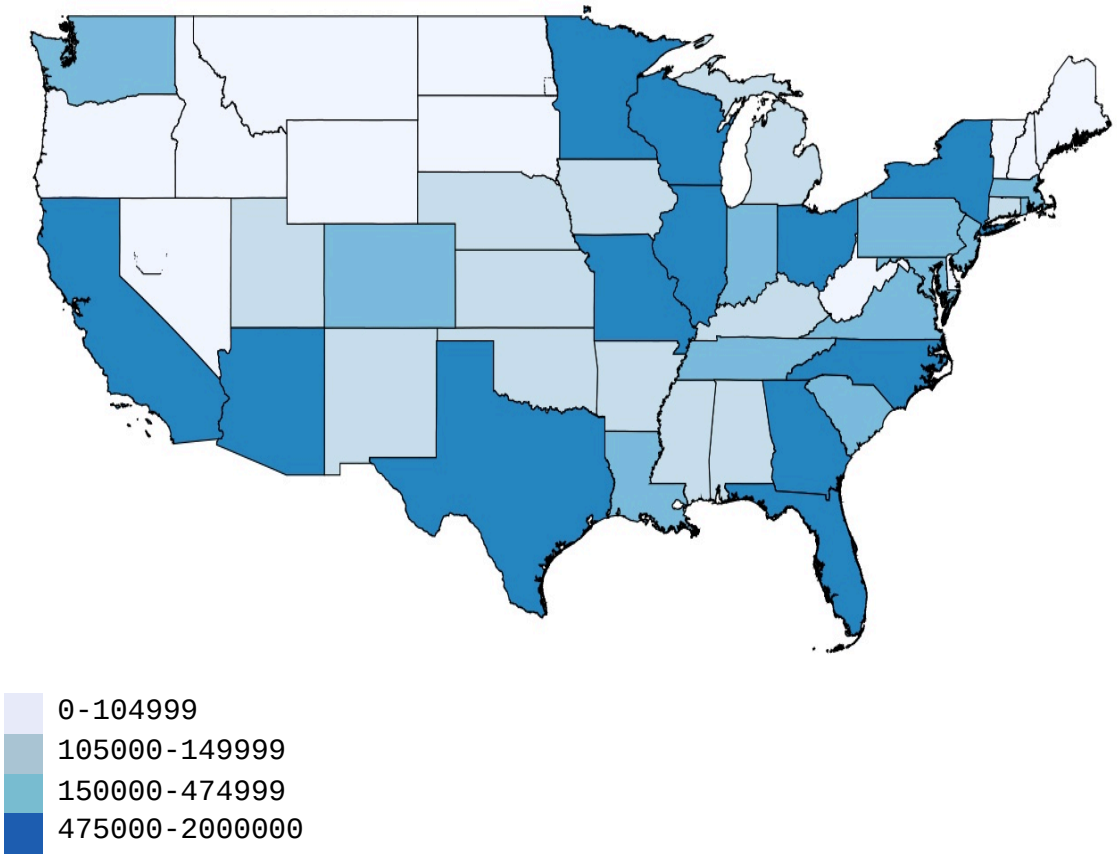


Figure 2.2: Distribution of fibromyalgia patients in sample

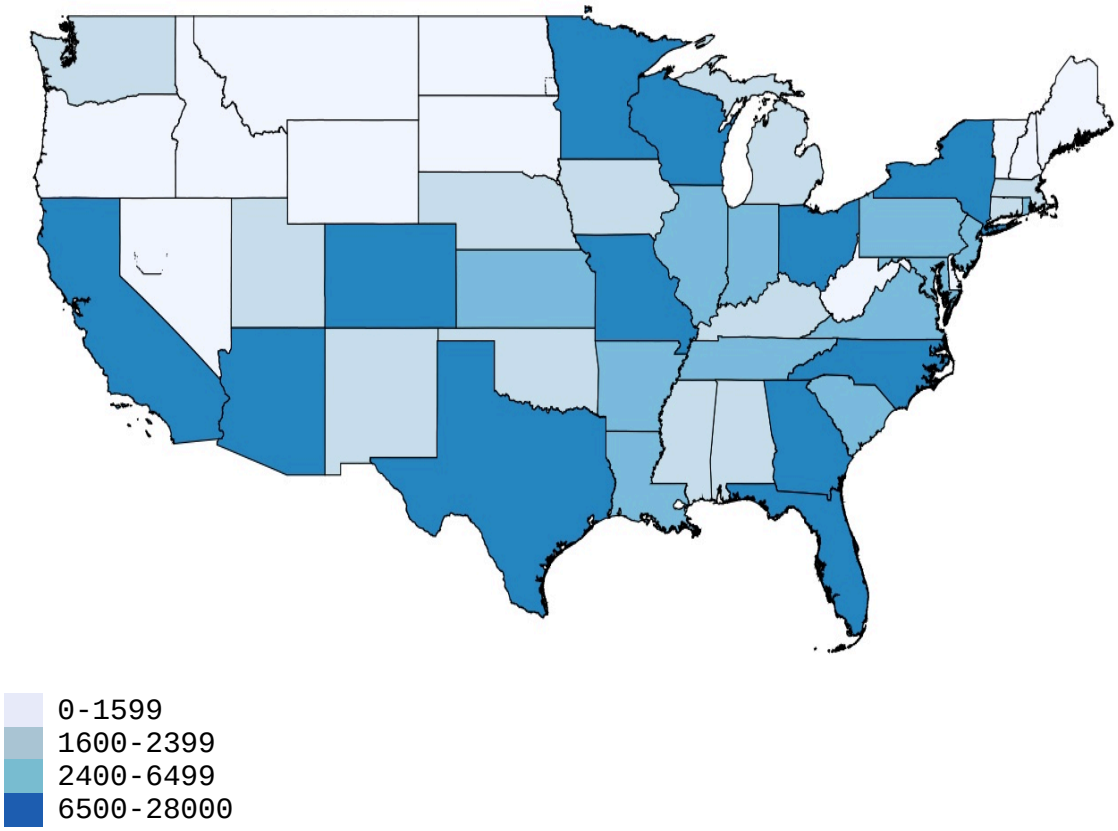


Figure 2.3: Fibromyalgia prevalence by state

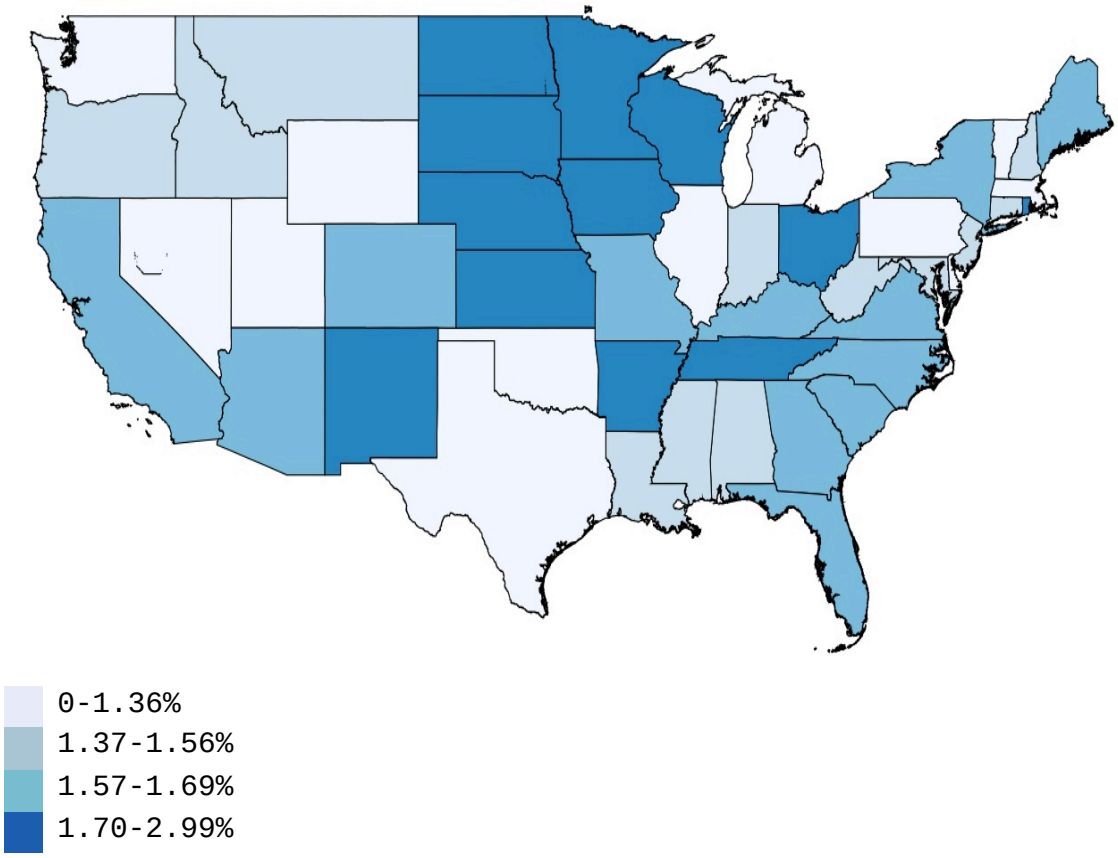


Figure 2.4: Monthly opioid prescriptions per fibromyalgia patient

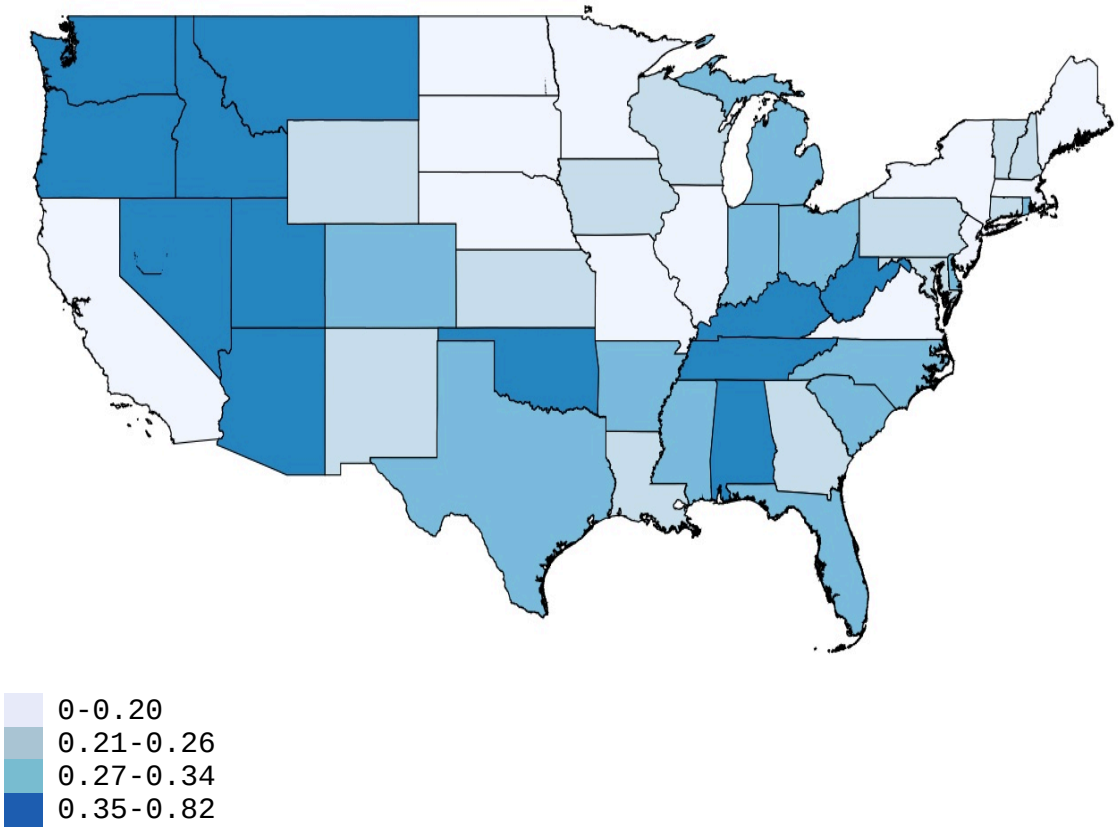
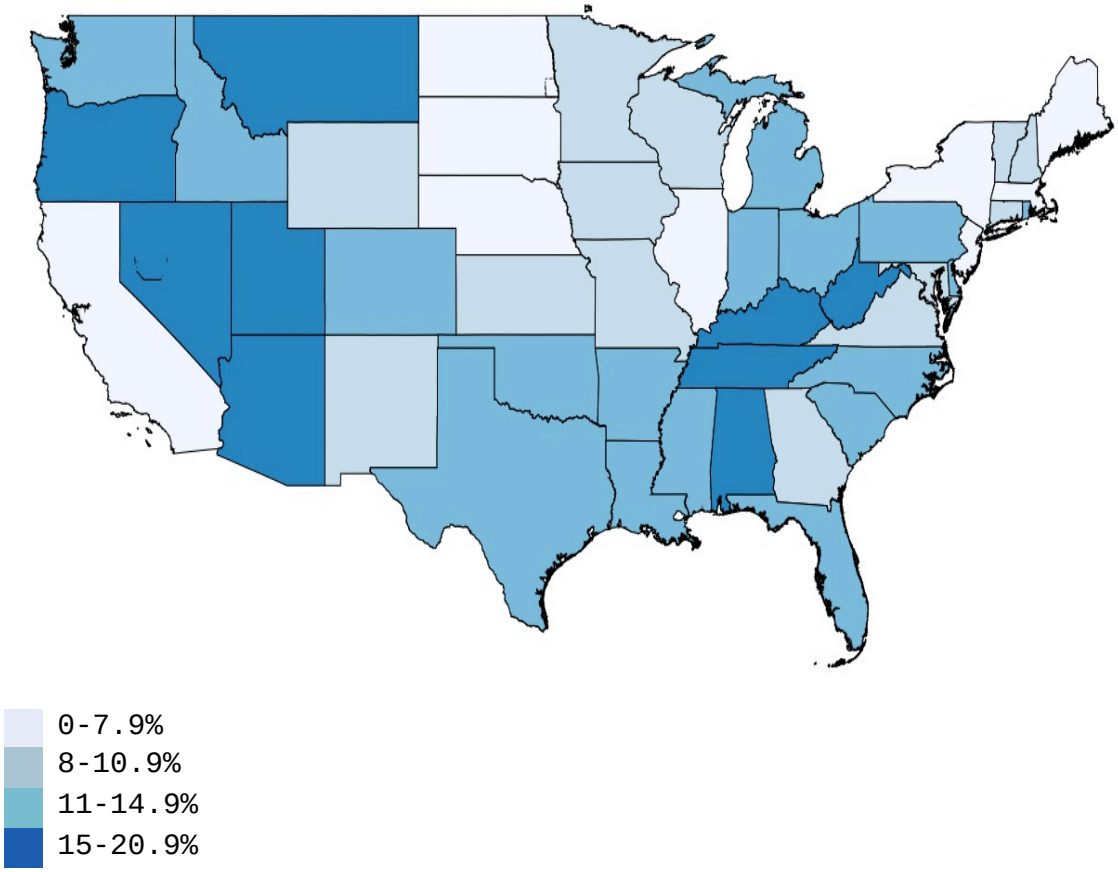


Figure 2.5: Distribution of fibromyalgia patients receiving chronic opioid therapy



Chapter 3: Longitudinal analysis of geographic variation of chronic opioid use in fibromyalgia syndrome

Given the interesting findings reported in Chapter 2, and considering the limitations imposed by the use of a cross-sectional design, Chapter 3 utilizes a longitudinal analysis approach to answer a similar research question. Longitudinal data analysis, commonly seen in the social sciences such as public policy research, allows for separation of within group variation from between group variation. In Chapter 3 we use this methods approach to control within state variation over the three-year observation period seen in Chapter 2.

A: Background

Geographic variation in care patterns is well documented for some disease states and medication classes. Notably, colorectal cancer[54], cardiac care procedures[55], antihypertensive medications[56], and stimulant medications[57] all have been examined and shown to have significant differences in utilization with respect to geography. Several studies have recently shown that geographic variation exists in opioid prescribing for various disease states. Curtis *et al* examined schedule II opioid analgesics and found significant variation at the county level, with the presence of a statewide prescription monitoring programs being a factor strongly associated with less opioid prescribing.[58] Webster *et al* examined opioid prescribing for acute lower back pain and found that geographic variation exists and that nearly four-fifths of the between-state variation can be explained by

state level factors.[59] Recent unpublished work suggests that geographic variation in chronic opioid treatment for fibromyalgia syndrome is similar to that seen in other conditions treated with opioid analgesics.[72]

Fibromyalgia syndrome, also labeled FMS or simply fibromyalgia, is an idiopathic, functional disorder characterized by chronic widespread pain and diffuse tenderness.[2] Although the etiology of fibromyalgia remains unclear, it is becoming increasingly evident that disordered central pain processing is the primary source of the syndrome. Fibromyalgia is diagnosed in approximately 5% of women [9] and 1.6% of men in the US.[53] This translates to more than 6 million patients in the US alone. Patients suffering from fibromyalgia are burdened with significantly increased healthcare utilization and costs compared to similar controls.[19]

According to a 2004 review published in the *Journal of the American Medical Association*, opioids have no evidence of efficacy for use in fibromyalgia syndrome.[21] Current guidelines for the treatment of fibromyalgia do not consider opioids a valid treatment alternative.[61] Despite the lack of evidence of efficacy for their use in fibromyalgia syndrome, the pattern of prescribing in fibromyalgia has mirrored that chronic non-malignant pain in general.[4] This elevated use is troublesome not only due to the lack of efficacy presented, but also because of the myriad societal and individual adverse effects associated with opioid use.[34] These include the common adverse effects seen

with acute (constipation, pruritus, respiratory depression, nausea, vomiting, delayed gastric emptying, sexual dysfunction, muscle rigidity and myoclonus, sleep disturbance, pyrexia, diminished psychomotor performance, cognitive impairment, dizziness, and sedation) as well as chronic (hormonal and immune effects, abuse and addiction, tolerance, and hyperalgesia) use of these medications. Opioid-induced hyperalgesia is of particular concern in fibromyalgia patients, because treatment with these medications may not only be inefficacious, but also may result in the manifestation of a separate pain condition. Although opioid treatment may result in hyperalgesia in any patient, the dysregulated opioidergic pathways seen in fibromyalgia patients creates greater concern.[32] Furthermore, possible altered functioning in descending cortical structures of fibromyalgia patients may decrease efficacy of strong opioids that ignore the noradrenergic aspect of pain seen in fibromyalgia.[42]

Only one study was found that examines geographic variation of opioid prescribing across time. Zerzan *et al* examined the variation in use of opiates in state Medicaid programs between 1996 and 2002.[69] This study showed significant increases in the level of opiate prescribing and in the variation seen in that prescribing. The coefficients of variation for the prescribing of opiates increased from 38.5% in 1996 to 49.6 in 2002.[69] Unpublished work shows that the coefficient of variation for chronic opioid use in fibromyalgia syndrome is 36.2%.[72] This is slightly lower than other findings in geographic variation of

opioid prescribing due to the chronic nature of the outcome variable.

Many leading researchers in the geographic variation literature have stated that geographic variation of an intervention is a sign of inappropriate use.[60] In general, the interpretation of whether this inappropriate use is under- or overutilization is indeterminable using standard methods. However, the chronic use of opioids for the treatment of fibromyalgia provides a unique situation due to the current treatment guideline's statement that "strong opioids are not recommended".[61]

The current study seeks to build on recent unpublished work, which found large state level geographic variation in chronic opioid use among fibromyalgia patients. This study found that contributing factors examined in fibromyalgia generally followed patterns established in other conditions treated with opioid. The percentage of patients that were female and the percentage of the population with previous illicit opioid use were both positive predictors of chronic opioid utilization; while state population, age between 45 and 64, physician prevalence, and fibromyalgia prevalence within a geography all were negatively associated with opioid use.

Disease prevalence as a predictor of evidence-based medicine has not been studied in the literature previously, but may indicate increased dissemination of information and peer-to-peer physician interaction for diseases such as fibromyalgia. By utilizing panel data methods more commonly seen in social

sciences, the current study seeks to isolate within state variation. We aim first to assess the extent of geographic variation at the state level for opioid utilization in patients suffering from fibromyalgia syndrome across the nation between the years 2007 and 2009. We hypothesize that significant geographic variation exists at the state level for opioid prescribing in this population and that both prevalence and variation will increase each year. Second, we aim to examine the effect of prescription monitoring programs and various other factors on the rate of chronic opioid use at the state level. Based on previous work[72], we hypothesize that physician prevalence, fibromyalgia prevalence, state population and percent of patients between 45 and 64 will be negatively associated with chronic opioid use, whereas female gender and prior illicit opioid use rate will be positively associated at the state level.

B: Materials and methods

Data Source

The University of Kentucky Institute for Pharmaceutical Outcomes and Policy has a licensing agreement for the i3 Invision Data Mart (IVDM) for 2007 through 2009. We obtained de-identified patient information from January 1, 2007 to December 31, 2009 from the IVDM. The IVDM is a nationally representative de-identified sample of 15 million patients from a commercial health plan across the United States and includes commercially insured patients as well as patients in Medicaid managed care plans. The data are collected at the patient level, and consist of

eligibility and enrollment information (eligibility date, eligibility span, health plan type), demographic information (gender, age, state), medical (inpatient, outpatient, professional services, including ICD-9-CM, DRG, CPT-4, revenue code and links to participating providers), pharmacy (prescriber, NDC, day supply, quantity), and laboratory (type of test and results) data for approximately 15 million patients each year.

Study Cohort Definitions

The dataset was searched for patients with fibromyalgia syndrome as identified by *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-CM-9) code 729.1 (myalgia and myositis unspecified). Only patients between ages 18-64 were considered for this study. The reasons for this restriction are utilization patterns may differ for children, and missing data problems are more common for those eligible for Medicare. Patients with malignancies were excluded from analysis because medical care patterns may differ for these patients. From this sample a sub-subsample of patients who had eligibility for the entire study period (January 1, 2007 to December 31, 2009) were selected as a panel. The University of Kentucky Institutional Review Board provided approval for this study via a blanket data use agreement for IVDM.

Outcome Variable

Chronic opioid therapy was the primary outcome of interest for this study. Chronic opioid therapy is defined as receiving greater than 183 days of opioid therapy in a given calendar year.

Similar outcome measures have been used in the past to describe chronic opioid use.[62] This individual level outcome variable is aggregated at the state level to provide a rate of chronic opioid use for each of the 3 years of the study for each state. Receipt of opioids was based on paid prescription claims with National Drug Codes (NDC) for opioid medications. Each claim is associated with a day supply calculated at the pharmacy level based on directions for use from the prescriber. Using American Hospital Formulary Service Codes[63] and verifying with Pharmaprojects Therapeutics Class Codes[64], drugs were divided into two classes, opioids and non-opioids (including tramadol).

Independent variables

State level variables were adapted from two previous studies measuring geographic variation in opioid use. Curtis *et al*[58] included proportion of females, rate of illicit drug use, state rate of surgeons, presence of a statewide prescription monitoring program, and proportion of population in younger and older age groups. Webster *et al*[59] extended this framework by including other economic and quality variables including unemployment rates, median income, physician disciplinary sanctions, and healthcare quality rankings. We adapted these variables for longitudinal analysis of our data and outcome based on results from our previous cross-sectional analysis resulting in the following time variant variables: prevalence of fibromyalgia within a state, state prevalence of physicians, proportion of females within our patient sample, state population,

state unemployment rate, state median income, rate of illicit opioid use, rate of physician disciplinary sanctions, presence of statewide prescription monitoring program, healthcare quality ranking, and proportion of state between 45 and 64 years of age. State unemployment rate and median income were observed in July of each year. Physician discipline sanction rates were taken from Public Citizen.[65] Healthcare quality state rankings were taken from The Commonwealth Fund[66] for 2007 and 2009, an average of the two values was used for 2008. State demographic and economic data was taken from US Census and Department of Labor data.

Data Analysis

State level geographic variation was measured using standard deviation, ratio of maximum to minimum, and coefficient of variation. The coefficient of variation is the ratio of the standard deviation of the prevalence rates to the mean rate among states. Dispersion statistics were calculated for each year. To analyze potential contributing factors to chronic opioid use among fibromyalgia patients we performed multiple time series regressions across states: between effects, fixed effects, and random effects. All calculations and analyses, including geographic variation analysis, were performed using Stata v11.2. Map generation was performed using ‘spmap’ and ‘uscoord’ within Stata. For all evaluations a three-year panel was analyzed for 2007, 2008, and 2009.

C: Results

This panel included 107369 patients from the 48 contiguous states and the District of Columbia who were eligible for the entire 36 months of the study. The patients were 68.2% female and average of 46.3 years of age in July 2008. Overall chronic opioid use did grow annually though not at a statistically significant rate. Both bivariate and multivariate regression showed time as an insignificant contributor to chronic opioid use in fibromyalgia syndrome. Mean chronic opioid therapy grew from 9.13% in 2007 to 10.62% (Table 1). All three measures of dispersion showed large geographic variation, but no difference was seen in this variation across time. The coefficient of variation ranged from 36.3% in 2008 to 36.6% in 2009. There was an approximately fivefold difference between the state with the minimum amount of chronic opioid therapy (New York in 2007 and South Dakota in 2008 and 2009) and the maximum amount (West Virginia all three years).

Multivariate linear regression using the between effects estimator showed both the prevalence of fibromyalgia and the prevalence of physicians within a state had significant negative associations with chronic opioid use among fibromyalgia patients (Table 2). In addition, median income was positively associated with chronic opioid use. Other predicted relationships were not found to be significant under this model.

When assuming a fixed effect model the results of the multivariate regression changes significantly. Neither

fibromyalgia nor physician prevalence are significantly associated with chronic opioid use. Chronic opioid use in fibromyalgia syndrome does continue to rise with the unemployment rate and fall with median income, however. Further analysis of state fixed effects can be seen in Table 5 and Figure 1. Although fixed effects are not appropriate for ranking, comparison of the top and bottom quartiles is possible. States in the Southeast and Western Unites States are generally liberal prescribers of chronic opioid therapy while those in the Northeast and Plains are conservative.

A random effects regression was performed and the results can be seen in Table 5. Results are similar to those seen in the between effects model though with the addition of the unemployment rate as a positive predictor of chronic opioid use. However, the results of the Hausman specification test indicate that the coefficients of the between effects estimation and those of the fixed effects estimation are significantly different ($p>X^2=0.01$), making the random effects estimation inappropriate for this data.

D: Discussion

Geographic Variation: Existence in Fibromyalgia

The primary aim of this study was to highlight the geographic variation in chronic opioid use for patients with fibromyalgia syndrome. We examined a panel of over 100000 fibromyalgia patients eligible for treatment within the i3 Invision Data Mart for 36 consecutive months between January 2007

and December 2009. We found about 1 in 10 patients meeting these criteria received chronic opioid therapy over this period of time. This rate did not fluctuate significantly year-to-year. Utilization seen in this study is similar to the rate seen in a cross-sectional study of chronic opioid use in fibromyalgia syndrome (11.7%).[72] Geographic variation in chronic opioid therapy did exist in this data. A fivefold difference was seen between patients in the state with the lowest use rate (New York in 2007 and South Dakota in 2008 and 2009, 4%) and that with the highest use rate (West Virginia, 19-20%). The coefficient of variation was around 36.5% for each year. These differences were stable across time, consistent with that seen in the cross-sectional analysis, and similar to those seen in other studies analyzing geographic variation of opioid prescribing.[58,59,69] Zerzan *et al* did see significant increases in both mean opioid prescribing and geographic variation over the study period.[69] There are two important differences between that study and the present study, however. First, their study period spanned seven years versus the present study's three years. This increased period of monitoring is better suited to picking up time dependent variation. Second, the outcome of interest in Zerzan *et al* was opioid prescribing in general, not chronic therapy for a specific disease.

Geographic Variation: Effect of Various Models

In order to investigate the association of state-level variables with chronic opioid use in fibromyalgia syndrome we looked at three different models. The first was the between

effects model; in this model we average variation within states across time. This results in a similar model to the one seen in the cross-sectional analysis, where we do not attempt to observe within state variation; as such, the results are comparable to those seen in the cross-sectional analysis. The two prevalence factors of interest, physician and disease prevalence, are both significantly associated with less chronic opioid use. This can be explained based on increased knowledge dissemination or peer-to-peer physician interaction resulting in better practice. Also, the median income of a state is negatively associated with chronic opioid use; states with higher median income have fewer fibromyalgia patients receiving chronic opioid therapy.

The fixed effects model examines the within state variation, assuming that a state's error component is correlated with the explanatory variables. In this study the independent variable coefficients generated by the fixed effects model are significantly different from those generated in the between effects model, as indicated by the rejection of the null hypothesis of the Hausman specification test. Findings of the fixed effect model indicate that only state level economic indicators are significantly associated with chronic opioid use in fibromyalgia syndrome. States with lower median income and higher unemployment are more likely to have fibromyalgia patients treated with chronic opioid therapy. Fixed effects for each state relative to the District of Columbia can be seen in Figure 1 and Table 4. Although we are not able to directly rank states

according to fixed effects, a comparison of those with very low fixed effects to those with very high fixed effects is appropriate and enlightening. We can see a definite geographic pattern develop for states that liberally use chronic opioid therapy in the treatment of fibromyalgia syndrome. These states largely overlap with states identified by Curtis *et al* as high claim rate states for controlled-release oxycodone.[58]

E: Strengths and weaknesses of specific models

Use of the between effects estimator is largely a repeat of the cross-sectional analysis previously performed.[72] However, this study model is an appropriate one, and the reiteration shows that the results of the cross-sectional analysis are robust to inclusion of only patients eligible for the entire three-year study period. In addition, the between effects estimator is not required to meet the assumption that error terms of states be correlated with explanatory variables. However, the impetus for time-series analysis and the major weakness of the cross-sectional approach is the requirement to ignore within state heterogeneity. The fixed-effects model adjusts for this heterogeneity using repeated measures of time variant factors for each state. The significant differences seen in the coefficients from these two models suggest that within state identity is a strong predictive factor for chronic opioid use in fibromyalgia syndrome. Given the inclusion of only three time periods for the study, the fixed effect coefficients may be biased. Considering the chronic nature of the outcome of interest and the large

geographic units analyzed, a panel with more time-periods would be very informative.

F: Conclusions

The goals of this study were to assess the level of geographic variation in chronic opioid therapy for the treatment of patients suffering from fibromyalgia syndrome and identify factors associated with this variation. Findings show that geographic variation of this outcome is similar to that seen in other studies of opioid prescribing. The present study also shows that geographic variation is stable over the study period (2007-2009) for the panel. Using the between effects estimator in a multivariate time-series regression we showed that both the prevalence of fibromyalgia and the prevalence of physicians within a state are significantly associated with less chronic opioid use for the treatment of fibromyalgia syndrome. The relationship between disease prevalence and evidence-based practice has not been seen in the fibromyalgia or pain literature previously. However, an explanation used by Webster *et al* for the relationship between physician prevalence and opioid use may be applicable[59]: as the prevalence of the disease increases information dissemination and peer-to-peer interaction regarding the treatment of the disease may also increase. Analysis using the fixed effects estimator suggests that state identity is significantly associated with chronic opioid use in the treatment of fibromyalgia syndrome.

While these findings illustrate the role of characteristics outside of the individual patient that may partially determine the rate of chronic opioid use in certain populations, state-level characteristics are only a small part of the a wider story. The next chapter will look at another characteristic outside of individual patient that may contribute to the level of chronic opioid therapy seen in fibromyalgia patients: provider type.

Table 3.1: Geographic variation in chronic opioid therapy for fibromyalgia

Year	Mean (%)	SD	Max/Min	CoV
2007	9.13	3.32	4.92	36.4
2008	9.83	3.57	5.36	36.3
2009	10.62	3.78	4.60	35.6

Table 3.2: Between effects regression, chronic opioid use

	Coef.	SE	P
FMS prevalence (%)	-2.972	0.965	0.004
FMS female (%)	0.218	0.116	0.067
State population	-0.001	0.001	0.061
State age 45-64 (%)	-0.310	0.220	0.168
Unemployment rate	0.001	0.003	0.826
Median income ($)	-0.001	0.001	0.045
Illicit opioid use (%)	0.007	0.004	0.140
Physician prevalence (per 100k)	-0.001	0.001	0.035
Physician disciplinary action (per 100K)	0.001	0.001	0.823
Healthcare quality rank	0.001	0.001	0.456
Prescription monitoring program	0.016	0.009	0.098
Constant	0.143	0.134	0.293
R^2= [within=0.038] [between=0.624] [overall=0.527] [SD(u_i+e_i)=0.024] [F(11,37)=5.58] [Prob>F=0.001]			

Table 3.3: Fixed effects regression, chronic opioid use

	Coef.	SE	P
FMS prevalence (%)	1.405	0.975	0.156
FMS female (%)	0.003	0.225	0.990
State population	-0.001	0.001	0.986
State age 45-64 (%)	-0.406	0.546	0.461
Unemployment rate	0.003	0.001	0.001
Median income ($)	-0.001	0.001	0.016
Illicit opioid use (%)	-0.001	0.002	0.743
Physician prevalence (per 100k)	-0.001	0.001	0.095
Physician disciplinary action (per 100K)	-0.001	0.001	0.107
Healthcare quality rank	-0.001	0.001	0.852
Prescription monitoring program	-0.007	0.004	0.076
Constant	0.334	0.311	0.289
R^2: [within=0.422] [between=0.142] [overall=0.165] [*sigma u*=0.033] [*sigma e*=0.012] [*rho*=0.892]			

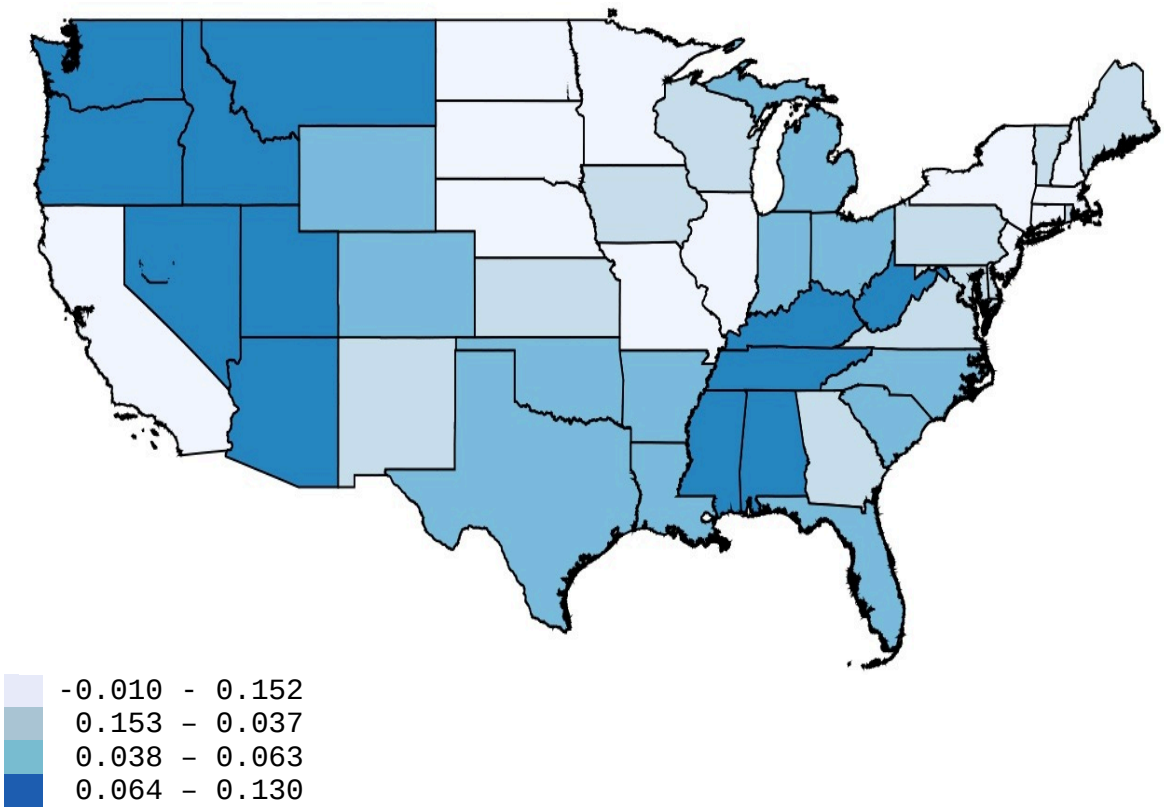
Table 3.4: Fixed effect of state on chronic opioid use in FMS

	Coef.	SE	P
South Dakota	-0.010	0.034	0.774
New York	-0.010	0.023	0.679
Minnesota	-0.007	0.024	0.757
New Jersey	-0.006	0.018	0.739
District of Columbia	0.000	0.000	1.000
New Hampshire	0.001	0.014	0.932
Massachusetts	0.004	0.016	0.789
California	0.005	0.021	0.833
North Dakota	0.005	0.048	0.909
Nebraska	0.010	0.025	0.705
Illinois	0.012	0.016	0.447
Missouri	0.013	0.020	0.515
Connecticut	0.015	0.018	0.399
Virginia	0.016	0.022	0.475
Iowa	0.021	0.022	0.349
Georgia	0.022	0.018	0.224
Maine	0.023	0.019	0.219
Rhode Island	0.024	0.022	0.288
Kansas	0.024	0.025	0.338
Wisconsin	0.027	0.022	0.230
Delaware	0.030	0.011	0.007
Maryland	0.031	0.015	0.045
New Mexico	0.031	0.026	0.236
Pennsylvania	0.037	0.015	0.017
Vermont	0.037	0.019	0.049
Wyoming	0.037	0.013	0.005
Texas	0.038	0.015	0.015
Michigan	0.043	0.015	0.006
Louisiana	0.046	0.020	0.024
Arkansas	0.047	0.027	0.083
Colorado	0.049	0.021	0.021
Ohio	0.049	0.023	0.034
Florida	0.058	0.020	0.004
Indiana	0.060	0.019	0.002
South Carolina	0.060	0.024	0.013
North Carolina	0.060	0.022	0.009
Oklahoma	0.063	0.017	0.001
Washington	0.065	0.014	0.001
Idaho	0.068	0.017	0.001
Mississippi	0.071	0.023	0.001
Montana	0.071	0.013	0.001
Alabama	0.079	0.023	0.001
Arizona	0.081	0.023	0.001
Oregon	0.081	0.018	0.001
Tennessee	0.086	0.024	0.001
Kentucky	0.086	0.022	0.001
Nevada	0.092	0.017	0.001
Utah	0.111	0.013	0.001
West Virginia	0.130	0.019	0.001

Table 3.5: Random effects regression, chronic opioid use

	Coef.	SE	P
FMS prevalence (%)	**-1.611**	0.647	0.013
FMS female (%)	0.107	0.147	0.466
State population	-0.001	0.001	0.107
State age 45-64 (%)	-0.149	0.376	0.692
Unemployment rate	**0.003**	0.001	0.001
Median income ($)	**-0.001**	0.001	0.001
Illicit opioid use (%)	0.003	0.002	0.167
Physician prevalence (per 100k)	**-0.001**	0.001	0.001
Physician disciplinary action (per 100K)	-0.001	0.001	0.225
Healthcare quality rank	0.001	0.001	0.465
Prescription monitoring program	0.002	0.004	0.616
Constant	0.175	0.177	0.322
R^2= [within=0.352] [between=0.504] [overall=0.486] [Wald-X^2(11)=168.45] [Prob>X^2=0.001] [*sigma*_u=0.023] [*sigma*_e=0.012] [*rho*=0.796]			

Figure 3.1: Fixed effect of state on chronic opioid use in fibromyalgia, relative to DC



Chapter 4: The role of practitioner type in determining chronic opioid use in fibromyalgia syndrome

The previous two chapters focused on state-level, structural characteristics that may affect a large number of patients collectively. These factors as well as the identity of a state were shown to be significantly associated with chronic opioid use in fibromyalgia patients. However these high-level factors only explain part of the variation seen in this practice. This chapter focuses on another factor that is grouped outside of the individual patients but at a higher level of granularity than the state: diagnosing provider type.

A: Background

Fibromyalgia syndrome, also labeled FMS or simply fibromyalgia, is an idiopathic, functional disorder characterized by chronic widespread pain and diffuse tenderness.[2] Although the etiology of fibromyalgia remains unclear, it is becoming increasingly evident that disordered central pain processing is the primary source of the syndrome. Fibromyalgia is diagnosed in approximately 5% of women in the US[9] and 1.6% of men.[53] In the US this translates to more than 6 million patients. Patients suffering from fibromyalgia are burdened with significantly increased healthcare costs and utilization compared to similar controls.[19]

Treatment of fibromyalgia syndrome typically focuses on the two most troublesome aspects of the disorder: pain and lack of restorative sleep. Treatment is generally multimodal, consisting

of pharmacologic agents and non-pharmacologic therapies such as massage or acupuncture. Unfortunately, one of the increasingly common medication classes of choice for the treatment of pain associated with fibromyalgia syndrome is the opioid analgesics class. According to a 2004 review published in the *Journal of the American Medical Association* (JAMA), opioids have no evidence of efficacy for use in fibromyalgia patients.[21] Chronic opioid therapy for the control of chronic nonmalignant pain of many types has increased tremendously over the past decade.[32] Despite the lack of evidence of efficacy for their use in fibromyalgia syndrome, the pattern of use in fibromyalgia has mirrored that of use in chronic non-malignant pain.[4]

Given the complicated and multifaceted nature of FMS it is not surprising that patients suffering from this disorder see a variety of providers. These providers include not only physicians, both primary care and various specialists, but also midlevel providers, such as nurse practitioners and physician assistants, and complementary providers, such as chiropractors. This diverse group of providers makes up the integrated care team that a fibromyalgia patient may be exposed to in their course of care.

There is a wealth of evidence in many disease states detailing different prescribing practices exhibited by various physician specialties and different care patterns exhibited by different provider types. Specialist care has been shown to be superior in myocardial infarction, stroke, asthma, and rheumatoid arthritis while primary care practitioners excel in care for

conditions such as hypertension, diabetes, and low back pain.[73] Furthermore, specialists have been shown to have better clinical scenario knowledge in their area of expertise, but are generally more expensive caregivers.[73] Physician specialty has also been shown to be associated with the early utilization of new prescription drugs.[74] This is especially relevant in fibromyalgia as the approved therapies are new to the market while more established medications such as opioids have utilization trends that are troubling given the lack of evidence supporting their use.

There is some evidence in the literature that suggests the prescribing rate of opioid pain medications is affected by the specialty of the prescribing physician. In a study examining the prescribing of schedule II pain medications, Rose *et al* found that specialists were significantly more likely to prescribe opioid medications than their primary care counterparts.[75] The authors attribute this difference to the possible reluctance of generalists to utilize certain medication classes due to an increased likelihood of review as a result of seeming overuse in a population that may not warrant the use of CII pain medications.[75] Again this is especially relevant in the study of patients suffering from fibromyalgia syndrome due to the strong case against the use of opioid medications for treatment. Not only is the failure rate of opioid use a greater concern in patients with fibromyalgia, there is also an increased concern of misuse or abuse among this population due to characteristics

commonly seen in these patients. For example, risk factors commonly associated with nonmedical use of opioids include anxiety and mood disorders, each a common comorbidity seen in patients with fibromyalgia.[50]

When examining a separate nonmalignant chronic pain condition, lower back pain, Carey *et al* found that healthcare utilization varied significantly depending on whether the primary provider was a generalist (primary care), orthopedic surgeon (specialist), or chiropractor (allied health).[76] Patients seeing chiropractors were likely to have more healthcare visits and use fewer medications both in general and for pain. Primary care practitioners were found to be the most cost efficient provider for treatment of low back pain. Despite the apparent differences seen in the utilization of healthcare services no differences were found in health outcomes for the patients included in that study. Time to functional recovery, return to work, and complete recovery from low back pain were similar across all three groups.[76]

The literature currently features studies highlighting differences in prescribing practices in fibromyalgia among physician specialties, including disparities in the level of prescribing of muscle relaxants, anxiolytics, hypnotics, and anti-epileptics;[77] and also shows differences in opioid prescribing practices across physician specialties.[75] However, no studies could be found that address the role of provider type in the prescribing of opioids chronically for patients suffering

from fibromyalgia syndrome. The research question posed in this study addresses the role of provider category and, more specifically, physician specialty on the prescribing of opioids chronically in patients suffering from fibromyalgia syndrome.

Only provider category or specialty is considered in this analysis. Factors both at higher aggregation levels, such as state-level characteristics, and at lower aggregation levels, such as patient-specific characteristics (gender, age, etc.) are considered elsewhere. Using this strategy, two research goals are accomplished. First, the raw effect of provider type is examined, answering the very broad question of the effect of receiving a diagnosis from a certain provider type on patient care. There are limitations associated with this approach; these limitations are addressed later. The second research goal accomplished is the determination of propensity associated with various diagnosing provider types on the prescribing of opioid therapy in a patient. These propensities can be used in an overarching research program examining chronic opioid use in fibromyalgia patients in conjunction with variables captured at both greater and lesser levels of granularity to provide a propensity index that takes a broad look at patient identity rather than focusing on patient specific characteristics exclusively. The use of this propensity index can then be applied to similar patients for the identification of a suitable control group for fibromyalgia patients. This process is described elsewhere.

Given the unadjusted nature of the independent variables we hypothesize that specialists, especially those associated with pain treatment (*e.g.*, anesthesiologists, physical medicine) will be correlated with higher levels of chronic opioid use. Furthermore, we predict that midlevel providers (i.e. nurse practitioners, physician assistants) will be associated with lower chronic opioid use due to limited opioid prescribing rights in general. Beyond these two predicted trends there is also a question as to the effect of having a chiropractor as diagnosing provider. Because there is no previous literature surrounding this topic we do not make a prediction as to what effect this may have.

B: Materials and methods

Data Source

The University of Kentucky Institute for Pharmaceutical Outcomes and Policy has a licensing agreement for the i3 Invision Data Mart (IVDM) for the years 2007-2009. We obtained de-identified patient information from January 1, 2007 to December 31, 2009 from the IVDM. The IVDM is a nationally representative de-identified sample of 15 million patients from a commercial health plan across the United States and includes commercially insured patients as well as patients in Medicaid managed care plans. The data are collected at the patient level, and consist of eligibility and enrollment information (eligibility date, eligibility span, health plan type), demographic information (gender, age, state), medical (inpatient, outpatient,

professional services, including ICD-9-CM, DRG, CPT-4, revenue code and links to participating providers), pharmacy (prescriber, NDC, day supply, quantity), and laboratory (type of test and results) for approximately 15 million patients each year.

Study Cohort Definitions

The dataset was searched for patients with fibromyalgia syndrome as identified by *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-CM-9) code 729.1 (myalgia and myositis unspecified). Patients with at least one claim between January 1, 2007 and December 31, 2009 were included in the sample. Only patients between ages 18-64 were considered for this study. The reasons for this restriction are utilization patterns may differ for children, and missing data problems are more common for those eligible for Medicare. Patients with malignancies were excluded from analysis because medical care patterns may differ for these patients. The University of Kentucky Institutional Review Board provided approval for this study via a data use agreement for the IVDM.

For each patient identified as having fibromyalgia syndrome a table containing information describing healthcare service utilization was compiled. This table contains the diagnoses assigned to the patient at each visit as well as the provider associated with these diagnoses. Patients were then assigned a diagnosing provider based on their first claim in the IVDM with a diagnosis of fibromyalgia syndrome (ICD-9 CM 729.1).

Outcome Variable

Chronic opioid therapy was the primary outcome of interest for this study. Chronic opioid therapy is defined as receiving a day supply in excess of one-half the total eligibility span for an individual patient. Similar outcome measures have been used in the past to describe chronic opioid use.[62] This is a binary outcome with patients either being recipients of chronic opioid therapy or not.

Independent variables

The structure of the i3 IVDM is such that several comparisons can be made at different levels of aggregation of provider type. The most aggregated level looks at the difference in patients diagnosed with fibromyalgia initially in the data by either a physician (primary care of specialist) versus an allied health professional (nurse practitioner, physician assistant, chiropractor, etc.). A second more detailed comparison can be made that divides physicians into primary care versus specialists and allied health professionals into various categories. Finally a comparison that divides physicians into various specialties can be examined at the highest level of granularity. The divisions used for this final division are: anesthesiologist, chiropractor, emergency medicine, family medicine, general surgeon, internal medicine, neurology, nurse practitioner, orthopedic surgeon, physical medicine, physician assistant, physiotherapist, and rheumatologist. Using each of these divisions we can examine the impact of various role identities as a diagnosing provider may

have on the prescribing practices of opioids chronically in patients.

Data analysis

Because the outcome of interest is a binary variable assigning individual patients as either receiving opioid therapy chronically or not, a logistic regression is used to examine the contribution of various provider role divisions. Several logistic regressions are performed, due to the problem of multiple comparisons and multiple regressions being used, all alpha levels are assumed to be 0.001 with all intervals considered at the 99.9% confidence level. In addition to multivariate logistic regression at multiple levels, a bivariate regression comparing provider division at the middle aggregation level is performed. Data aggregation and cleaning were done using Oracle SQL Developer and SAS v.10; data analysis was performed in STATA 11.

C: Results

As can be seen in Table 1 the type of provider associated with the first diagnosis of fibromyalgia for a patient in the sample varies widely. The majority of the diagnosing providers are concentrated between primary care physicians and chiropractors, while the rest are spread among various physician specialties and midlevel providers. Of the total 571192 patients examined in the data, 213231 or nearly 40% had their first diagnosis of fibromyalgia in the data from a chiropractor. Of the physician specialties, rheumatologists were the most common diagnosing physicians for fibromyalgia, followed by

anesthesiologists (this includes pain management specialists). Neurologists only account for 1.6% of initial diagnoses. Examination of subsequent diagnoses for each patient shows a much greater proportion of specialist diagnoses compared to primary care and chiropractic diagnoses.

Table 2 highlights the association of physician versus allied health professional for prescribing opioids chronically in patients. If the entirety of the 571192 patients is included in the analysis then diagnosis by a physician versus an allied health professional is associated with a 6.62 odds ratio and a marginal effect of 0.12 representing an increased likelihood of receiving opioids chronically. This effect is statistically significant at an alpha level less than 0.001. However, much of this effect is likely due to inclusion of chiropractors with the midlevel practitioners. As seen in Table 3, if we exclude patients diagnosed by chiropractors and compare the diagnosis by a midlevel practitioner to a physician we see this difference disappear. Tables 2 and 3 display results from the highest level of aggregation, which compares physicians to non-physicians.

Table 4 increases the granularity of the data, breaking apart physicians into primary care and specialist and breaking allied health professionals into chiropractors, nurse practitioners, and physician assistants. Based on this division we can rank these various providers based on how likely patients diagnosed by them are to receive opioid therapy chronically. Based on this ranking scheme and the associated marginal effects,

patients diagnosed by chiropractors are far less likely to receive opioid therapy chronically than others; this is followed by primary care patients, then nurse practitioner and physician assistant patients (not significantly different), and finally patients seeing specialists.

Using this same level of granularity Table 5 shows head-to-head bivariate odds ratios comparing each of these provider types. All of these comparisons are significantly different at an alpha of less than 0.001, except when looking at the difference between nurse practitioners and physician assistants, which is not significant.

Finally, Table 6 examines provider grouping at the highest level of granularity. Allied health professionals and primary care physicians are not affected by this disaggregation but specialists are broken into several categories including rheumatology, anesthesiology, physical medicine, emergency medicine, neurology, orthopedics, and general surgery. The marginal effects of these categories are shown in Table 6. Provider types who are least likely to diagnose patients receiving chronic opioid therapy are seen at the top and those most likely at the bottom. With the exception again of the difference between nurse practitioner and physician assistant each bivariate comparison is statistically significant at a p-value less than 0.001.

D: Discussion

The aim of this study was twofold. First, we sought to highlight the role of diagnosing practitioner in the prescribing of opioids for chronic use in patients suffering from fibromyalgia syndrome. In order to show the correlation of various provider groups with chronic opioid prescribing we broke the data down in several ways highlighting different levels of granularity available in the i3 Invision Data Mart. Using these categorizations we were able to support both of the research hypotheses. First, specialists were more likely to diagnose patients receiving chronic opioid therapy. This is not unexpected as no control for patient severity or other patient characteristics is attempted. A gatekeeper has likely referred a patient who receives a diagnosis of fibromyalgia from a specialist to that specialist either for management of fibromyalgia or a comorbid condition. This theory is supported by the very large proportion of subsequent diagnoses by specialists following primary diagnosis from another provider in the data. This is an unfortunate effect of treating the data as one three-year cross-section of data. The prediction that midlevel practitioners would be less likely to see patients receiving chronic opioid therapy was not supported by this data. Exclusion of chiropractic patients in Table 3 shows that midlevel practitioners are very similar to physicians as a whole in this when it comes to opioid prescribing. Further as the level of granularity increases these midlevel practitioners remain

moderate prescribers of chronic opioid therapy for fibromyalgia patients.

Given the lack of previous literature on the topic, patients receiving chiropractic care was the most surprising finding. Patients whose initial diagnosis in the data was from a chiropractor were much less likely to receive chronic opioid therapy. There are several possible explanations for this. First, chiropractors do not have prescribing rights for medications. This could reduce the total number of medication and also the likelihood of receiving chronic opioid therapy. Second, patients visiting chiropractors may be suffering from less severe symptoms than others who are seeing a specialist for instance. Finally, patients seeing a chiropractor may be patients receiving more integrated team-based care. If this is the case the members of this team may also be more likely to follow evidence-based guidelines in the treatment of fibromyalgia, which strongly caution against the use of opioids in this disease state. The percentage of patients receiving chiropractic treatment in this study is surprising given the small amount of evidence supporting its use in the literature. However studies have shown that patients suffering from musculoskeletal pain disorders show similar outcomes and greater satisfaction when seeing a chiropractor.[78]

In addition to these findings the second research goal of this study was to examine the role of diagnosing provider category on the overall propensity of fibromyalgia patients to

receive chronic opioid therapy. To this end, raw effects of provider type ignoring patient level characteristics were used. Integration of provider type into a propensity index for chronic opioid use will help to identify an appropriate control group when examining fibromyalgia patients, a task that has proven difficult in the existing literature.

E: Limitations

There are several limitations to this study that threaten the internal and external validity. First, the identification of the first diagnosing provider may not be strongly linked to the prescribing provider. This is a limitation of the dataset itself, as prescribing physician data is encrypted and cannot be linked directly to diagnosing provider data. This is a problem of construct validity; however, the large study population used supports the assumption that, on average, patients diagnosed by a certain physician will be treated by the same physician. This assumption supported by the fact that four-fifths of the patients in the study sample saw only one provider for fibromyalgia during the entire three-year cross-section.

Second, the generalizability of these findings is questionable. What does it mean that patients diagnosed by specialists are more likely to receive chronic opioid therapy? This may signal that these patients are either suffering from more severe fibromyalgia symptoms or have higher rates of comorbid conditions. As discussed, however, the use of opioid medications in patients suffering from fibromyalgia is not

recommended in the literature. Moreover, the use of these medications even for comorbid conditions is inadvisable due to the pathophysiology of the disease that compounds the deleterious effects of this medication class.

F: Conclusions

Although patient level characteristics such as demographics, severity of condition, and comorbid conditions are extremely important in the study of drug utilization patterns, focus on this level of factors exclusively ignores aggregated factors at the provider or geographic level. To this effect, geographic variation of chronic opioid use in the fibromyalgia patient population has been examined previously and the current study looks at the effect of diagnosing provider categorization on the prescribing of these medications. Findings from this study indicate that the level of chronic opioid use in patients is highly correlated with the diagnosing provider type. Patients undergoing chiropractic care are much less likely to receive chronic opioid therapy while those diagnosed by specialists are much more likely when compared to midlevel and primary care practitioners. Based on these findings further study into the effects of chiropractic care on patients suffering from fibromyalgia is warranted, due to the lack of evidence currently available.

Beyond these independent findings this study also provides an important building block in the aggregation of a propensity index that will identify fibromyalgia patients likely to receive

chronic opioid therapy. In addition to state- and patient-level factors these findings will be used to identify an adequate control group for comparison in healthcare costs and outcomes associated with evidence based medicine versus chronic opioid therapy in this patient population. This chapter, and the two previous, highlighted the association of group characteristics determined above the patient level; however, these group characteristics are not able to explain fully the variation seen in chronic opioid use among fibromyalgia patients. The following chapter looks at the role of patient-level characteristics such as demographics, comorbid conditions, and concurrent medication use.

Table 4.1: Patient count by provider type

Specialty	N=571912		
Allied Health	37.9%		
--Chiropractor		98.4%	
--Nurse Practitioner		1.0%	
--Physician Assistant		0.6%	
Physician	62.1%		
--Primary Care		67.7%	
----Family Practice			63.5%
----Internal Medicine			36.5%
--Specialist		32.3%	
----Rheumatology			24.5%
----Anesthesiology			22.4%
----Physical Medicine			19.7%
----Emergency Medicine			17.0%
----Neurology			8.4%
----Orthopedics			4.6%
----General Surgery			3.4%

Table 4.2: Chronic opioid prescribing by diagnosing provider type, high aggregation

Provider Type	OR	SE	CI Low (99.9%)	CI High (99.9%)	MFX
Physician	6.62	0.09	6.31	6.93	0.12
Allied Health	Reference				

Table 4.3: Chronic opioid prescribing by diagnosing provider type, high aggregation (excluding chiropractors)

Provider Type	OR	SE	CI Low (99.9%)	CI High (99.9%)	MFX
Physician	0.93	0.04	0.80	1.09	-0.01
Allied Health	Reference				

Table 4.4: Chronic opioid prescribing by diagnosing provider type, medium aggregation

Provider Type	OR	SE	CI Low (99.9%)	CI High (99.9%)	MFX
Primary care	0.62	0.05	0.48	0.79	-0.03
Specialist	1.69	0.13	1.12	2.17	0.04
Chiropractor	0.13	0.01	0.10	0.16	-0.12
Nurse practitioner	0.99	0.09	0.72	1.35	-0.01
Physician assistant	Reference				

Table 4.5: Comparison of chronic opioid utilization by diagnosing provider type, bivariate odds ratio (standard error), medium aggregation

	Primary care	Specia-list	Chiropr-actor	Nurse practi-tioner	Physician Assistant
Primary care	-	0.403	4.794	0.550	0.615
	-	(0.003)	(0.075)	(0.030)	(0.046)
Specialist	2.480	-	11.889	1.365	1.5224
	(0.023)	-	(0.186)	(0.075)	(0.115)
Chiropractor	0.209	0.084	-	0.115	0.128
	(0.003)	(0.001)	-	(0.006)	(0.010)
Nurse practitioner	1.817	0.733	8.711	-	1.117
	(0.100)	(0.040)	(0.490)	-	(0.104)
Physician assistant	1.627	0.656	7.800	0.895	-
	(0.123)	(0.049)	(0.596)	(0.083)	-

Table 4.6: Chronic opioid prescribing by diagnosing provider type, low aggregation

Provider Type	OR	SE	CI Low (99.9%)	CI High (99.9%)	MFX
Chiropractor	0.13	0.01	0.10	0.16	-0.12
General surgeon	0.29	0.02	0.24	0.35	-0.05
Emergency medicine	0.46	0.04	0.35	0.60	-0.04
Family practitioner	0.63	0.05	0.49	0.80	-0.03
Internal medicine	0.61	0.05	0.48	0.78	-0.03
Orthopedic surgeon	0.89	0.08	0.67	1.18	-0.01
Nurse practitioner	0.99	0.09	0.72	1.35	-0.01
Physician assistant	Reference				
Rheumatologist	1.34	0.10	1.05	1.73	0.02
Neurologist	1.59	0.13	1.23	2.06	0.04
Physical medicine	1.66	0.13	1.29	2.14	0.04
Anesthesiologist	4.56	0.35	3.55	5.85	0.18

Chapter 5: The role of patient characteristics in determining chronic opioid use in fibromyalgia syndrome

The previous three chapters focused on high-level factors that are shown to be associated with chronic opioid use in fibromyalgia patients. However, no analysis of the characteristics surrounding this practice would be complete without looking closely at individual patients and the variation seen in demographics, comorbid conditions, and concurrent medication use between them.

A: Background

Fibromyalgia syndrome, also labeled FMS or simply fibromyalgia, is an idiopathic, functional disorder characterized by chronic widespread pain and diffuse tenderness.[2] Fibromyalgia is only diagnosed in approximately 5% of women[9] and 1.6% of men[10] in the general population. This disorder affects over 6 million patients in the United States. Fibromyalgia syndrome is associated with significant clinical and economic burden to patients, the healthcare system, and society as a whole. Fibromyalgia is generally considered a disorder that occurs in women between 20 and 50 years of age; while this is the typical presentation, fibromyalgia occurs in males, children, adolescents and the elderly. Prevalence of fibromyalgia syndrome increases until age 80, after which it declines.[12] Higher prevalence rates are seen in relatives of patients suffering from fibromyalgia suggesting both environmental and genetic factors leading to the disorder.[9]

The primary clinical characteristic of fibromyalgia is diffuse, widespread pain often accompanied by tenderness and fatigue. The diagnosis of fibromyalgia is generally a difficult and tenuous endeavor, which involves ruling out differential diagnoses such as rheumatoid arthritis, systemic lupus erythematosus, and other conditions that present with nondescript pain as a major complaint. In 1990, the American College of Rheumatology developed diagnostic criteria for fibromyalgia syndrome.[13] These criteria focus on the pain and tenderness associated with the disease. Practitioners palpate 18 pressure points throughout the body; patients exhibiting abnormal tenderness in 11 of the 18 points, in addition to a three-month history of bilateral, widespread pain in multiple segments of the body, are said to have fibromyalgia.[13]

Patients suffering from fibromyalgia have been shown to be burdened with increased healthcare utilization and costs compared to similar controls. The London Fibromyalgia Epidemiology Study compared four groups: fibromyalgia patients, patients with widespread pain but no fibromyalgia diagnosis, patients accessing healthcare without widespread pain, and a group of controls. This study showed fibromyalgia patients accessing pain-related medication more often and having significantly greater average healthcare costs than those with general widespread pain.[10] Another study, utilizing a US-based health-insurance database, found that total annual healthcare costs for fibromyalgia sufferers averaged $9573 versus $3291 for age and sex matched

controls.[19] Statistically significant differences were seen across all cost types including: inpatient care, outpatient care, pain-related medications, other medications, and other medical care.[79]

Treatment of fibromyalgia syndrome typically focuses on the two most troublesome aspects of the disorder: pain and lack of restorative sleep. Management is generally multimodal, consisting of pharmacologic agents and non-pharmacologic therapies such as massage or acupuncture. According to a 2004 review published in the *Journal of the American Medical Association*, pharmacologic therapies for fibromyalgia can be divided according to the level of existing efficacy evidence: strong, modest, weak, or none.[21]

Medications considered to have strong efficacy evidence include amitriptyline and possibly other tri-cyclic antidepressants (TCA) and cyclobenzaprine (though cyclobenzaprine is associated with a significant adverse drug effect profile that makes use less than ideal). In addition, the Food and Drug Administration (FDA) has approved three medications for the treatment of fibromyalgia syndrome. In 2007, the FDA approved pregabalin, an alpha-2 delta ligand, which reduces calcium influx at nerve terminals and therefore reduces the release of several relevant neurochemicals.[28] Pregabalin has been shown to be superior to placebo in reducing pain and fatigue, improving sleep index scores, improving both patient and clinician global impression of change, and improving four of eight SF-36 domains.[29] One year following the approval of pregabalin, the FDA approved

duloxetine. Duloxetine, a balanced serotonin, norepinephrine reuptake inhibitor (SNRI), has been shown in two randomized placebo controlled trials to improve fibromyalgia symptoms across many domains in women with and without major depressive disorder.[30] In 2009, the FDA approved a third drug for use in fibromyalgia known as milnacipran. Milnacipran is another balanced serotonin, norepinephrine reuptake inhibitor (SNRI), which was shown to be superior to placebo in pain response, patient global impression of change, fatigue, cognition, and several SF-36 domains.[31] In addition to medications with strong evidence of efficacy, selective serotonin reuptake inhibitors (SSRIs) are considered to have modest evidence of efficacy.

Many medications are considered to have no evidence of efficacy in the treatment of fibromyalgia syndrome. Classes of medication that fall into this category include opioids, glucocorticoids, non-steroidal anti-inflammatory drugs, benzodiazepines, and hypnotics.[21] Although not included in this review, serotonin antagonist reuptake inhibitors (SARI) such as trazadone and nefazadone have no evidence of efficacy in treatment of fibromyalgia, though they have shown efficacy in symptoms associated with the disorder such as pain.[80] Bupropion, the only FDA approved member of the norepinephrine, dopamine reuptake inhibitor (NDRI) class, has shown efficacy in the treatment of neuropathic pain,[81] but was not included in the review either. Anticonvulsants also are not included in the *JAMA*

review, but atypical anticonvulsants such as gabapentin have shown efficacy in treatment of fibromyalgia.[82]

Many of these medication classes see widespread use among patients suffering from fibromyalgia despite the lack of efficacy evidence. One of the most concerning trends associated with this over the past decade is the increased use of opioids in nonmalignant pain in general and fibromyalgia in particular. Not only is the failure rate of opioid use a greater concern in patients with fibromyalgia compared to the general nonmalignant pain population, there is also an increased concern of misuse or abuse among this population due to characteristics commonly seen in these patients. Risk factors commonly associated with nonmedical use of opioids include anxiety and mood disorders, each a common comorbidity seen in patients with fibromyalgia.[50] In addition low self-rated health status, commonly seen in fibromyalgia, increases the propensity toward misuse or abuse of opioid medications.[50] Beyond these reasons there is also increased concern of adverse effect presentation in patients with fibromyalgia for several reasons. Fibromyalgia patients report adverse effects and intolerance to treatment at elevated rates.[51]

Given this increased concern it is important to study the contributing factors associated with chronic opioid use in the fibromyalgia patient population. Past work has highlighted contributing factors at the geographic- and provider-level, providing insight into associations that affect the propensity for a patient to receive opioid therapy chronically, independent

of characteristics specific to that individual. The current study seeks to extend this knowledge by showing associations between chronic opioid use in patients suffering from fibromyalgia syndrome and patient-specific characteristics including demographics, comorbidities, and concurrent medications. Specifically, comorbid conditions examined in patients can be seen in Table 1 and concurrent medication classes can be seen in Table 2. Given the related nature of fibromyalgia with mental and mood disorders, musculoskeletal diseases, and ill-defined conditions we predict each of these classes of comorbid conditions will be associated with increased complexity of presentation and therefore increased propensity for chronic opioid use in patients. Additionally, considering the adverse drug effect profiles and lack of evidence supporting use of benzodiazepines, hypnotics, and muscle relaxants, we predict increased chronic opioid use in patients receiving these medication classes. Conversely, we predicts patients receiving selective-serotonin reuptake inhibitors, anticonvulsants (including pregabalin and gabapentin), selective-norepinephrine reuptake inhibitors, and tricyclic antidepressants will be associated with lower levels of chronic opioid use because use of these medications is supported by evidence in the current literature.

B: Materials and methods

Data Source

The University of Kentucky Institute for Pharmaceutical Outcomes and Policy has a licensing agreement for the i3 Invision Data Mart (IVDM) for the years 2007-2009. We obtained de-identified patient information from January 1, 2007 to December 31, 2009 from the IVDM. The IVDM is a nationally representative de-identified sample of 15 million patients from a commercial health plan across the United States and includes commercially insured patients as well as patients in Medicaid managed care plans. The data are collected at the patient level, and consist of eligibility and enrollment information (eligibility date, eligibility span, health plan type), demographic information (gender, age, state), medical claims (inpatient, outpatient, professional services, including ICD-9-CM, DRG, CPT-4, revenue code and links to participating providers), pharmacy claims (prescriber, NDC, day supply, quantity), and laboratory claims (type of test and results) for approximately 15 million patients each year.

Study Cohort Definitions

The dataset was queried for patients with fibromyalgia syndrome as identified by *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-CM-9) code 729.1 (myalgia and myositis unspecified). Patients with at least one claim between January 1, 2007 and December 31, 2009 were included in the sample. Only patients between ages 18-64 were considered

for this study. The reasons for this restriction are utilization patterns may differ for children, and missing data problems are more common for those eligible for Medicare. Patients with malignancies were excluded from analysis because medical care patterns may differ for these patients. The University of Kentucky Institutional Review Board provided approval for this study via a data use agreement for the IVDM. For each patient identified as having fibromyalgia syndrome, tables containing demographic, comorbidity, and concurrent medication use were created for the entirety of the three-year cross-section of data.

Outcome Variable

Chronic opioid therapy was the primary outcome of interest for this study. Chronic opioid therapy is defined as receiving a day supply in excess of one-half the total eligibility span for an individual patient. Similar outcome measures have been used in the past to describe chronic opioid use.[62] This is a binary outcome with patients either being recipients of chronic opioid therapy or not.

Independent Variables

Independent variables are divided into three categories: demographics, comorbidities, and concurrent medications. Demographic variables include gender (male or female) and age. Age was calculated from the date of birth to the eligibility start date in the data. Patients were excluded from analysis if they were less than 18 years of age or greater than 64 years of age. Comorbidities were determined by having a positive diagnosis

determined by International Classification of Disease 9 (ICD-9) in the data during eligibility. Codes included in each comorbidity class can be seen in Table 1. Concurrent medications were determined using each patient's prescription history for the entire cross-section. A single prescription for a medication was considered positive. Medication classifications were determined using Therapeutic Class Codes (TCC). Categorization these therapeutic class codes can be seen in Table 2.

Data analysis

Because the outcome of interest is a binary variable assigning individual patients as either receiving opioid therapy chronically or not, a logistic regression is used to examine the association of various types of patient characteristics to chronic opioid use in this patient population. Logistic regressions using robust standard errors are performed for each category of patient characteristic; due to the problem of multiple comparisons and multiple regressions being used all alpha levels are assumed to be less than 0.01 with all intervals being at the 99% confidence level. Data aggregation and cleaning were done using Oracle SQL Developer and SAS v.10 while data analysis was performed in STATA 11.

C: Results

The study sample included 619302 patients suffering from fibromyalgia syndrome. Mean age was 44.4 years, and two-thirds of the patients were women. Patient sex and age were both statistically positive associates of chronic opioid use.

Demographic factors only account for about one-tenth the variance attributed to comorbid conditions and about one-twentieth that of concurrent medications. Table 3 shows the number of patients prescribed a medication falling into each of the categories highlighted in Table 1. The majority of patients in the study population had at least one prescription for an opioid medication. Other interesting medication classes include benzodiazepines where one-fourth of the patients had received a prescription, and hypnotics where almost one-fifth had received a prescription. Neither of these medications have demonstrated efficacy in the treatment of fibromyalgia syndrome. Also of interest from Table 3 is selective serotonin reuptake inhibitors (SSRIs), a class of medication recommended for use in fibromyalgia patients, were used in 23% or patients. Selective norepinephrine reuptake inhibitors such as duloxetine and minalcipran, FDA approved medications for fibromyalgia, were used in 12% of patients. The anticonvulsant class also was present in over one-fifth of patients, which can be explained by the presence of gabapentin and pregabalin, two medications commonly used in fibromyalgia patients.

Table 4 shows the logistic regression that displays odds ratios for each medication class representing association between that medication class and chronic opioid use in patients. Classes containing opioids were excluded from this regression. Table 4 is arranged with medication classes independently and negatively associated with chronic opioid use in patients at the top and

those independently and positively associated with chronic opioid use at the bottom. Although marginal effects cannot be directly compared for magnitude the arrangement of the medication classes from top to bottom allows relative comparisons for contributions to chronic opioid use in patients. Given the very large sample size we are examining, each of the medication classes is statistically significant at the 99.9% confidence level except selective norepinephrine, reuptake inhibitors (NDRIs), which are only used in 7% of the sample. Of the medication classes mentioned in Table 3, benzodiazepines and hypnotics each are in the bottom half of Table 4. Also at the bottom of the table is the anticonvulsant class with a large positive marginal effect for chronic opioid use. Another interesting point is non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids are at the top of Table 4 with a slightly negative marginal effect. Other classes associated with predicted directions are SNRIs and TCAs; each of these classes is seen in the middle of Table 4.

Beyond looking at drug classes we also examined the association of the presence of various comorbid conditions with chronic opioid use. Table 5 has these comorbid conditions listed and the number and portion of patients suffering from each disease category. The top of this table has chronic opioid use. This is the outcome of interest and is seen in just over 10% of patients in the data. This means that over 10% of patients in the study population received a day supply of opioids greater than

one-half of their eligibility period in the data. Nearly 90% of patients in this data suffered from another condition classified as “Symptoms, signs and ill-defined conditions”. This class contains many common ailments including fatigue, which afflicted nearly half of these patients and other nondescript conditions such as anxiety or gastric related symptoms. Conditions unrelated to pain, the musculoskeletal system, or neurology were also abundant. Diseases of the respiratory, circulatory, and digestive system, were present in 70%, 48%, and 46% of patients, respectively. Other conditions affecting the musculoskeletal system were present in nearly 70% of patients including back pain in over 30% and arthritis in one-fourth.

Table 6 shows the logistic regression with odds ratios for the association of comorbid conditions with chronic opioid use in this patient population. Independent variables are ordered in Table 6 according to their relative marginal effect. Diseases at the top of the table such as diseases of the respiratory system and others have little association and possibly slightly negative associations with chronic opioid use in fibromyalgia patients. Diseases at the bottom of Table 6, including migraine, back pain with neuropathic involvement, arthritis, and depression, are each associated with increased chronic opioid use. Again, given the very large sample size nearly every association, with the exception of those with very small marginal effects, is statistically significant at the 99.9% confidence level. One exception to this is diabetes, which has an extremely small

marginal effect but due to prevalence greater than 10% in the population still is significantly and positively associated with chronic opioid use in this population.

D: Discussion

This study was undertaken to accomplish two research goals. The first is an independent objective that seeks to fill a gap in the literature. Although studies have looked at predictors of medication use in fibromyalgia patients at the patient level no study to date has looked specifically at the effect of geographic, provider, and patient characteristics on the utilization of opioid medications chronically; this study fills that gap. Secondly, the results of this study serve to show the contribution of patient-level factors to chronic opioid use in this patient population. The contribution of demographic information, comorbid conditions, and concurrent medication use when combined with previously gathered information on the contribution of physician-level factors and structural factors can be used to identify an appropriate control group to assess the effect chronic opioid use in patients suffering from fibromyalgia syndrome, a significant gap in the current literature.

Concurrent medication use is very high in this population with four-fifths receiving a medication other than an opioid in the data. Nearly three-fifths received an opioid prescription during their eligibility, a number significantly elevated over the general population, which generally sees rates of about 20%

for annual opioid prescription receipt. Non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and naproxen, were used in nearly 45% of patients and glucocorticoids in over 30%. Neither class was associated with increased chronic opioid use however. This is likely due to the myriad uses for these medications. Both muscle relaxants and benzodiazepines are associated with significant side effect profiles; although muscle relaxants are not currently considered a scheduled substance each of these medication classes has literature supporting their potential as drugs of abuse.[83] This can be said of hypnotics as well, though hypnotics fall in the middle of the classes when it comes to marginal effect on chronic opioid use. The use of multiple classes of potential drugs of abuse is troubling especially given the increased propensity for misuse that is reported in this patient population.[51] Medications with efficacy evidence are seen spread throughout the table, each with positive marginal effects, but seen at various magnitudes. This suggests no association between utilization of evidence supported medications and chronic opioid use, and not a strict substitution of one for the other.

Comorbid conditions examined included a wide range of disease states. In general, those diseases associated with an independent pain condition are found to have large and positive marginal effects on chronic opioid use in this patient population. This is as predicted, as many patients with fibromyalgia are also afflicted with other central and musculoskeletal pain disorders

that require treatment. However, given the increased concern for many adverse effects from these medications in this population, opioids should still be considered a line of last defense even in other independent conditions. Additionally, many of the diseases considered are chronic and neuropathic in nature increasing the concern for use even in the absence of fibromyalgia syndrome. This is due to the constantly increasing dose required for treatment over long periods of time as well as the significant short- and long-term adverse effects seen in patients. Generally diseases with little correlation with pain such as diseases of the respiratory, digestive, and circulatory system were found near the top of the table with marginal effects being either very small or negative.

Overall, it can be seen that the presence of comorbid conditions and concurrent medications increases the likelihood of chronic opioid use in patients suffering from fibromyalgia syndrome. This likely represents a latent disease severity variable. Although the combination of demographic data, comorbidities, and concurrent medications represent explanations of nearly one-fourth of the variance seen in chronic opioid use in this population, over 75% of this variation is not explained by this variable set. This is likely due to the contribution of factors at larger levels of aggregation such as provider-level factors and structural factors such as geographic variation, but there are also unobserved and unobservable factors in this

patient population due to the secondary database nature of this study. This is one of several limitations seen in this study.

E: Limitations

As mentioned, the presence of comorbid conditions and concurrent medications likely represents partial explanation of a latent disease severity variable. No retrospective fibromyalgia severity index currently exists for use in studies of this type, however. The inclusion of these patient-level variables in a broader analysis could partially compensate for this. Another limitation of the data source is the records used exclusively refer to prescription medications and ignore over-the-counter (OTC) drugs. This could significantly alter the use of NSAIDs medications specifically but may also have effects on diagnosis of conditions such as GERD, depression, migraine and others which may be controlled using medication available OTC. Finally, all weaknesses generally associated with secondary database such as only being able to observe which medications are filled, not which are actually taken, apply to this study as well.

F: Conclusions

Previous work has focused on characteristics of the fibromyalgia patient population at lower levels of granularity, specifically the provider- and structural-level. These characteristics are able to explain large amounts of variation seen in chronic opioid use in fibromyalgia patients. However, patient-level characteristics such as demographics, comorbid conditions, and concurrent medications are an important part of

understanding the factors that are associated with chronic opioid use in fibromyalgia patients. The current study shows that comorbid conditions are present at high levels in this patient population and medications, including opioids, are being utilized at an elevated rate compared to the general population.

These results are important not only as independent findings, but also because they demonstrate the need for an adequate comparison group when studying outcomes in fibromyalgia patients. Comparison to the general population or even to patients diagnosed with another pain disorder is not sufficient for outcomes research in this disease state. Given these findings, the development of a propensity index utilizing the contribution of factors captured at the structural, provider, and patient level is needed. In the following chapters the use of a propensity index for comparisons of healthcare costs associated with chronic opioid use by fibromyalgia patients, of the healthcare costs associated with fibromyalgia, and of the costs associated with the interaction of chronic opioid use and fibromyalgia will be presented.

Table 5.1: Comorbid conditions and associated ICD-9 codes

Variable	ICD-9
Diabetes	250-250.xx
Mental and mood disorders	
--Anxiety	300.01, 300.3, 309.81, 300.23, 300.21, 300.22, 300.2, 300.20, 300.29, 300.02, 293.84, 309.21, 300.0, 300.00, 300.09, 300.10
--Depression	300.4, 309.0, 309.1, 296.5, 296.2, 296.3, 290.21, 282.84, 286.20, 296.xx, 298.0
--Tension headache	307.81
Migraine	346-346.xx
Diseases of the circulatory system	390-459.xx
Diseases of the respiratory system	460-519.x
Diseases of the digestive system	
--GERD	530.11, 530.81
--Gastritis	535.0-535.5
Diseases of the musculoskeletal system	
--Back pain	722.92-722.93, 722.4-722.5, 722.81, 722.91, 723.1, 723.5-723.6
--Arthritis	711.00-716.xx
Symptoms, signs and ill-defined conditions	
--Fatigue	780.71, 780.79
--Headache	784
--Chest pain	786.5-786.5x
--Abdominal pain	789.0-789.0x
--Anxiety-related symptoms	780.4, 785.0-785.1, 786.01, 786.05, 786.09
--Gastric-related symptoms	787.0, 787.01-787.03, 787.1-787.3, 787.9, 787.91, 787.99
Painful neuropathic disorders	
--Diabetic neuropathy	250.6x, 357.2
--Post-herpetic neuropathy	531.x
--Back pain with neuropathic involvement	721.41-721.42, 721.91, 722.1, 722.10, 722.11, 722.2, 722.70, 722.72-722.73, 724.0x, 724.3, 724.4
--Neck pain with neuropathic involvement	721.1, 722.0, 722.71, 723.0, 723.4
--Causalgia	337.2x, 353.2-353.4, 354.4, 355.7x, 355.9, 729.2
--Phantom limb pain	353.6
--Trigeminal neuralgia	350.1
--Atypical facial pain	350.2, 352.1
--Other painful neuropathies	353.0, 353.1, 353.8, 353.9, 354.0-354.5, 354.8, 354.9, 355.0-355.6, 355.8
Sleep disorders	780.51-780.52, 307.41, 307.42, 307.49, 780.53, 780.57, 786.03, 347.0x-47.1x, 780.5, 780.50, 780.54-780.56, 780.58-780.59

Table 5.2: Concurrent medications and Therapeutic Class Codes

Medication class	Therapeutics Class Codes
Opioids	H3A
NSAIDs	S2B, H3E
Glucocorticoids	P5A
Muscle Relaxants	H6H
Benzodiazepines	H2F
SSRIs	H3S
Anticonvulsants	H4B
Hypnotics	H2E
SNRIs	H7C
TCAs	H2U
Triptans	H3F
Codeine Combinations	H3U, H3X
NDRIs	H7D
SARIs	H7E
Migraine Combinations	H3K, H3L, H3M, H3R

Table 5.3: Concurrent medication use prevalence

Medication class	Users	Mean	SD
Opioids	354860	0.573	0.495
NSAIDs	267538	0.432	0.495
Glucocorticoids	203750	0.329	0.470
Muscle Relaxants	203750	0.329	0.470
Benzodiazepines	148632	0.240	0.427
SSRIs	143059	0.231	0.422
Anticonvulsants	130053	0.210	0.408
Hypnotics	105281	0.170	0.376
SNRIs	73697	0.119	0.323
TCAs	47067	0.076	0.264
Triptans	44590	0.072	0.259
Codeine Combinations	41493	0.067	0.250
NDRIs	43351	0.070	0.255
SARIs	33442	0.054	0.230
Migraine Combinations	22295	0.036	0.187

Table 5.4: Logistic regression, effect of concurrent medications on chronic opioid use

	OR	SE	P	MFX
NSAIDs	0.828	0.009	0.001	-0.011
Glucocorticoids	0.950	0.010	0.001	-0.003
NDRIs	0.956	0.015	0.005	-0.003
SSRIs	1.054	0.012	0.001	0.003
SARIs	1.348	0.022	0.001	0.019
Migraine Combinations	1.492	0.029	0.001	0.027
TCAs	1.525	0.022	0.001	0.029
Hypnotics	1.598	0.018	0.001	0.031
SNRIs	1.686	0.020	0.001	0.036
Triptans	2.032	0.030	0.001	0.054
Benzodiazepines	2.162	0.023	0.001	0.054
Muscle Relaxants	2.867	0.030	0.001	0.073
Anticonvulsants	3.255	0.035	0.001	0.095

Table 5.5: Comorbid condition prevalence

Variable	Number	Mean	SD
Chronic opioid use	63655	0.103	0.304
Diabetes	72387	0.117	0.321
Mental and mood disorders	180102	0.291	0.454
--Anxiety	119674	0.193	0.395
--Depression	94819	0.153	0.360
--Tension headache	19661	0.032	0.175
Migraine	69938	0.113	0.317
Diseases of the circulatory system	298227	0.482	0.500
Diseases of the respiratory system	430823	0.696	0.460
Diseases of the digestive system	288307	0.466	0.499
--GERD	129198	0.209	0.406
--Gastritis	320	0.001	0.023
Diseases of the musculoskeletal system	420582	0.679	0.467
--Back pain	199454	0.322	0.467
--Arthritis	152452	0.246	0.431
Symptoms, signs and ill-defined conditions	540386	0.873	0.333
--Fatigue	236056	0.381	0.486
--Headache	118	0.000	0.014
--Chest pain	164204	0.265	0.441
--Abdominal pain	191973	0.310	0.462
--Anxiety-related symptoms	187117	0.302	0.459
--Gastric-related symptoms	145307	0.235	0.424
Painful neuropathic disorders	257744	0.416	0.493
--Diabetic neuropathy	9099	0.015	0.120
--Post-herpetic neuropathy	4263	0.007	0.083
--Back pain with neuropathic involvement	159916	0.258	0.438
--Neck pain with neuropathic involvement	95003	0.153	0.360
--Causalgia	54553	0.088	0.283
--Phantom limb pain	95	0.000	0.012
--Trigeminal neuralgia	2180	0.004	0.059
--Atypical facial pain	3154	0.005	0.493
--Other painful neuropathies	62306	0.101	0.301
Sleep disorders	118569	0.191	0.393

Table 5.6: Logistic regression, effect of comorbid condition on chronic opioid use

	OR	SE	P	MFX
Diseases of the respiratory system	0.732	0.007	0.001	-0.023
Anxiety-related symptoms	0.851	0.009	0.001	-0.011
Chest pain	0.931	0.010	0.001	-0.005
Tension headache	0.931	0.021	0.002	-0.005
Fatigue	0.942	0.009	0.001	-0.004
Gastritis	0.971	0.162	0.860	-0.002
GERD	0.991	0.011	0.449	-0.001
Abdominal pain	1.016	0.011	0.137	0.001
Diabetes	1.079	0.015	0.001	0.006
Headache	1.160	0.323	0.595	0.011
Diseases of the circulatory system	1.207	0.012	0.001	0.013
Gastric-related symptoms	1.209	0.013	0.001	0.014
Other painful neuropathies	1.203	0.063	0.001	0.014
Atypical facial pain	1.252	0.015	0.001	0.017
Neck pain with neuropathic involvement	1.299	0.081	0.001	0.021
Trigeminal neuralgia	1.339	0.013	0.001	0.021
Back pain	1.404	0.015	0.001	0.026
Sleep disorders	1.421	0.045	0.001	0.029
Diabetic neuropathy	1.581	0.017	0.001	0.036
Anxiety	1.578	0.021	0.001	0.038
Causalgia	1.676	0.069	0.001	0.045
Post-herpetic neuropathy	1.727	0.020	0.001	0.045
Depression	2.160	0.021	0.001	0.065
Arthritis	2.223	0.021	0.001	0.067
Back pain with neuropathic involvement	2.598	0.030	0.001	0.092
Migraine	9.810	2.303	0.001	0.371

Chapter 6: The association between chronic opioid use in fibromyalgia syndrome and healthcare costs

Chapter 2 through Chapter 5 focuses on revealing characteristics associated with chronic opioid use in fibromyalgia syndrome. This chapter attempts to control these characteristics to find the true effect of chronic opioid use on healthcare costs in fibromyalgia patients. Control of these characteristics through stratification of the patients sample allows for comparison of similar patients and therefore a more accurate measure of costs differences associated with this therapy choice.

A: Background

Fibromyalgia syndrome, also labeled FMS or simply fibromyalgia, is an idiopathic, functional disorder characterized by chronic widespread pain and diffuse tenderness.[2] Although the hallmark symptom of fibromyalgia is dispersed pain, the syndrome is also characterized by fatigue, non-restorative sleep, and cognitive difficulties.[2] There are many unanswered questions regarding both etiology and treatment of fibromyalgia. Although the literature has increased due to the recent introduction of medications approved for the indication of fibromyalgia, research addressing issues such as cost of care and healthcare utilization for patients receiving medications other than those currently under patent is less than rigorous, outdated, or nonexistent.

Fibromyalgia is only diagnosed in approximately 5% of women[9] and 1.6% of men[10] in the general population affecting over

6 million patients in the United States. Fibromyalgia syndrome is associated with significant clinical and economic burden to patients, the healthcare system, and society as a whole. Fibromyalgia is generally considered a disorder that occurs in women between 20 and 50 years of age; while this is the typical presentation, fibromyalgia occurs in males, children, adolescents and the elderly. Prevalence of fibromyalgia syndrome increases until age 80, after which it declines.[12] Higher prevalence rates are seen in relatives of patients suffering from fibromyalgia suggesting involvement of both environmental and genetic factors in development of the disorder.[9] In 1990, the American College of Rheumatology developed diagnostic criteria for fibromyalgia syndrome.[13] These criteria focus on the pain and tenderness associated with the disease. Practitioners palpate 18 pressure points throughout the body; patients exhibiting abnormal tenderness in 11 of the 18 points, in addition to a three-month history of bilateral, widespread pain in multiple segments of the body, are said to have fibromyalgia.[13]

Treatment of fibromyalgia syndrome typically focuses on the two most troublesome aspects of the disorder: pain and lack of restorative sleep. Management is generally multimodal, consisting of pharmacologic agents and non-pharmacologic therapies such as massage or acupuncture. According to a 2004 review published in the *Journal of the American Medical Association* pharmacologic therapies for fibromyalgia can be divided according to the level of existing efficacy evidence:

strong, modest, weak, or none.[21] Many medications are considered to have no evidence of efficacy in the treatment of fibromyalgia syndrome. Classes of medication that fall into this category include opioids, glucocorticoids, non-steroidal anti-inflammatory drugs, benzodiazepines, and hypnotics.[21]

Despite this lack of efficacy evidence, several of these medication classes see widespread use among patients suffering from fibromyalgia. One of the most concerning trends associated with medication utilization over the past decade is the increased use of opioids in nonmalignant pain in general and fibromyalgia in particular. Not only is the failure rate of opioid use a greater concern in patients with fibromyalgia compared to the general nonmalignant pain population, there is also an increased concern of misuse or abuse among this population due to characteristics commonly seen in these patients. Risk factors commonly associated with nonmedical use of opioids include anxiety and mood disorders, each a common comorbidity seen in patients with fibromyalgia.[50] In addition low self-rated health status, commonly seen in fibromyalgia, increases the propensity toward misuse or abuse of opioid medications.[50] Beyond these reasons there is also increased concern of adverse effect presentation in patients with fibromyalgia for several reasons, including reports of adverse effects and intolerance to treatment at elevated rates.[51]

Patients suffering from fibromyalgia are burdened with increased healthcare costs and utilization patterns compared to

similar controls. The London Fibromyalgia Epidemiology Study compared four groups: fibromyalgia patients, patients with widespread pain but no fibromyalgia diagnosis, patients accessing healthcare without widespread pain, and a group of controls. This study showed fibromyalgia patients accessing pain-related medication more often and having significantly greater average healthcare cost than those with general widespread pain.[10] Another study, utilizing a US-based health-insurance database, found that total annual healthcare costs for fibromyalgia sufferers averaged $9573 versus $3291 for age and sex matched controls.[19] Statistically significant differences were seen across all cost types including: inpatient care, outpatient care, pain-related medications, other medications, and other medical care.[79] These totals ignore the increased personal and societal burden due to pain and interference of the illness on the patients' daily lives.

Although costs associated with chronic opioid use have not been examined in fibromyalgia syndrome specifically, the economic burden of chronic opioid use in general chronic pain patients compared to nonusers matched on characteristics such as age, sex, geographic region, insurance type, and Charlson comorbidity index has been examined.[84] Leider *et al* found that medical and prescription costs each differed significantly when comparing chronic opioid users to nonusers. Annualized medical costs averaged $18092 for users and only $3565 for nonusers. Annualized prescription costs mirrored this trend, averaging $4956 for chronic opioid users and only $1410 for nonusers.[84]

Based on this literature and findings previously discussed, we predict fibromyalgia patients receiving chronic opioid therapy to have medical and prescription costs that are elevated significantly over nonusers. However, the existence of this difference would not be very informative, as the cause of the increase may have little to do with the disease itself but may instead be the result of other factors at the geographic-, provider-, or patient-level as previously described.[72,85,86] In order to control for these differences, stratification based on propensity to receive chronic opioid therapy determined by factors at multiple levels will be used.

Using this approach, fibromyalgia patients can be stratified into deciles based on their propensity to received chronic opioid therapy. We predict that as the propensity to receive chronic opioid therapy increases the differences seen in healthcare costs, both medical and prescription, will decrease though still remain elevated for chronic opioid users. The rationale for this prediction is that the propensity to receive chronic opioid therapy is an indicator of latent variables such as disease severity and patient overall health that are unobservable in a secondary database study. For instance, as propensity for chronic opioid use increases fibromyalgia severity likely increases; refractory patients may receive a therapy not supported by evidence because other, more appropriate, choices have not been successful. Another example, as overall health decreases and patient presentation becomes complicated by other

comorbidities and concurrent medications propensity to receive chronic opioid therapy for the control of one or more symptoms will increase.

This study will examine the raw difference in medical and prescription costs between chronic opioid users and nonusers with fibromyalgia syndrome. It will then detail the development of a propensity index for chronic opioid use in fibromyalgia patients. Finally, it will examine the difference in medical and healthcare costs seen in fibromyalgia patients receiving chronic opioid therapy from those not controlling for the propensity to receive this therapy.

B: Materials and methods

Data source

The University of Kentucky Institute for Pharmaceutical Outcomes and Policy has a licensing agreement for the i3 Invision Data Mart (IVDM) for the years 2007-2009. We obtained de-identified patient information from January 1, 2007 to December 31, 2009 from the IVDM. The IVDM is a nationally representative de-identified sample of 15 million patients from a commercial health plan across the United States and includes commercially insured patients as well as patients in Medicaid managed care plans. The data are collected at the patient level, and consist of eligibility and enrollment information (eligibility date, eligibility span, health plan type), demographic information (gender, age, state), medical (inpatient, outpatient, professional services, including ICD-9-CM, DRG, CPT-4, revenue

code and links to participating providers), pharmacy (prescriber, NDC, day supply, quantity), and laboratory (type of test and results) for approximately 15 million patients each year.

Study cohort definitions

The dataset was queried for patients with fibromyalgia syndrome as identified by *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-CM-9) code 729.1 (myalgia and myositis unspecified). Patients with at least one claim between January 1, 2007 and December 31, 2009 were included in the sample. Only patients between ages 18 and 64 were considered for this study. The reasons for this restriction are utilization patterns may differ for children, and missing data problems are more common for those eligible for Medicare. Patients with malignancies were excluded from analysis because medical care patterns may differ for these patients. The University of Kentucky Institutional Review Board provided approval for this study via a blanket data use agreement for the IVDM.

Outcome variables

Two outcome variables of interest were collected: medical costs and prescription costs. These were collected based on medical and prescription charges collected in the IVDM. Charged amounts were used in all analyses of healthcare costs. Charges were summed at the patient level and then annualized to control for differing eligibility spans across patients.

Independent variables

Independent variables were collected at the state, provider, and patient level as described previously. The variables were used to develop a propensity index using logistic regression coefficients. Propensity to receive chronic opioid therapy was then used to divide patients into deciles.

Data analysis

Median medical and prescription costs were examined due to the skewness of cost data unless otherwise noted. The statistical significance of cost data between chronic opioid users and nonusers was calculated using two-group t-tests without an assumption of homoscedasticity. Data extraction was completed using Oracle SQL Developer and SAS v10, while statistical analyses were all completed in STATA v11.

C: Results

The study sample consisted of 549340 patients suffering from fibromyalgia syndrome taken from the IVDM; of these approximately 10% were chronic opioid users. Mean age was 44 years and approximately two-thirds were women. Table 1 shows patient characteristics for chronic opioid users and nonusers. To determine which characteristics differed between these two groups two-group t-tests were used assuming heteroskedasticity. In general, chronic opioid users were older and more likely to be female. They also suffered from more comorbid conditions and were more likely to be taking concurrent medications whether these medications were pain related or not. Chronic opioid users were

less likely to be diagnosed by a chiropractor, and more likely, in general, to be diagnosed by a physician specialist. This is especially true of anesthesiology, which according to the definitions included in the IVDM includes pain management physicians. States also varied widely in the proportion of their patients receiving chronic opioid therapy, this can be seen more clearly in Table 2.

Due to the vast differences seen between chronic opioid users and nonusers in this population a propensity score was developed. This index assigns a score for each patient in the fibromyalgia sample from the IVDM that represents his or her propensity toward receiving chronic opioid therapy. The contribution of each variable independent of the others can be seen in Table 2. The vast majority of variables are significantly and independently correlated either negatively or positively with chronic opioid use. In general these associations agree at least in direction with findings previously reported.[72,85,86]

Comorbid conditions that are neuropathic or pain-related increase the likelihood of receiving opioids chronically while more general disease states are either not associated or negatively associated in general. Concurrent medications used in the treatment of fibromyalgia or other neuropathic or pain-related disorders are also positively associated with chronic opioid use, while medications such as NSAIDs or glucocorticoids that are used for a wide variety of indications are negatively associated. As previously reported,[85] chiropractors are strongly

and negatively associated with chronic opioid use while many specialists, especially in anesthesiology, are positively associated. State correlations varied widely with states in the Northeast being negatively associated with chronic opioid use while states in the South and Mountain West were positively associated with it, generally.

Figure 1 shows the k-density plot of the propensity score. Nonusers of chronic opioid therapy have propensity scores with slightly lower variance and increased right skewness when compared to chronic opioid users, although the range of scores seen for the two groups was similar. Mean propensity overall was -2.99, for opioid nonusers it was -3.24, and for chronic opioid users it was -0.88. Table 3 shows the results of the propensity score being broken into deciles. There is a clear association between the propensity score identification as either a chronic opioid user or as a nonuser, as the proportion of chronic opioid users increases from less than 1% in the first decile to 50% in the tenth with a smooth increase over the deciles.

In Figure 2 the difference between annualized medical charges between chronic opioid nonusers and users can be seen. Chronic opioid users have annualized medical costs about three times higher than nonusers in fibromyalgia syndrome ($18193 vs. $6130). However, if each of these groups is broken apart according to their propensity to receive chronic opioid therapy we can see the groups are heterogeneous. While chronic opioid nonusers display medical charge characteristic that increase in a

clear trend, the chronic opioid users have medical charges that resemble a positive parabola.

Similar to Figures 2 and 3, which illustrate the differences in annualized medical charges between chronic opioid users and nonusers Figures 4 and 5 show differences in annualized prescription charges. In Figure 4, we see that prescription charges are about six times greater for fibromyalgia patients who are also chronic opioid users than for nonusers ($6087 vs. $935). Looking at Figure 5, however, illustrates again that these groups are different. Again chronic opioid users show a steady increase in prescriptions costs over the deciles, but users show a parabolic trend that decreases in general between deciles one and four before increasing between deciles five and ten.

Finally Figure 6 shows the ratio of healthcare costs between the two groups for each decile. We can see that over the deciles from one to ten the ratio of annualized prescription charges for users decreases consistently (7.2 to 2.2). A similar but less pronounced change is seen in medical charges (2.4 to 1.4).

D: Discussion

The goals of this research study are twofold: to highlight the increased healthcare costs associated with chronic opioid use in fibromyalgia syndrome and to develop a propensity index for identification of fibromyalgia patients at increased risk of receiving opioid therapy chronically.

To address the first goal, overall differences in medical and prescription costs between fibromyalgia patients receiving chronic opioid therapy versus those who are not receiving this therapy were examined. There is a clear distinction between these groups seen in Figures 2 and 4. Chronic opioid users had medical charges three times higher than nonusers and prescription charges six times higher. This is consistent with the literature discussed previously which shows in other disease states both medical and prescription costs are significantly elevated in chronic opioid users.

However, attribution of this difference in cost purely to chronic opioid use is not possible using this simple comparison. As shown in Table 1 chronic opioid users and nonusers are different in many ways: comorbidity prevalence, medication use, provider type, and geographic location. To more effectively compare these groups like patients must be grouped.

The second research goal helps to clarify this difference. Using a set of independent variables that describe patient demographics, comorbid conditions, concurrent medications, diagnosing provider, and state of residence we developed a propensity index with an outcome variable of chronic opioid use. The two groups have propensity scores that overlap greatly and allow for the stratification of the study sample into deciles describing their propensity to receive chronic opioid therapy. The cost trends are highly varied and the disparities seen from decile to decile in both medical and prescription costs differ

between chronic opioid users and nonusers. Figures 3 and 5 illustrate this heterogeneity.

Using this propensity index and dividing the groups into deciles based on likelihood of receiving chronic opioid therapy we are able to see a comparison of patients with a high or low propensity for receiving chronic opioid therapy. Using these comparisons we can see that a clear trend is present. Figure 6 shows that differences seen in both medical and prescription costs between chronic opioid users and nonusers are present in each decile. However, it is evident that as the propensity toward chronic opioid use increases these differences decrease. In chronic opioid users with a very small propensity for chronic opioid use prescription costs are over seven times higher than nonusers and medical costs nearly 2.5 times greater while those with a high propensity for use have differences of only two and 1.5, respectively. This shows that propensity to receive chronic opioid therapy plays a significant role in the accumulation of medical and prescription costs and that this role differs depending on whether patients actually receive this therapy or not.

E: Limitations

As with other claims-based retrospective database studies our research is subject to errors in coding, the IVDM is primarily a claims database and data gathered is not done so with specific research in mind. Another limitation specific to claims-based research in fibromyalgia syndrome is the lack of a specific

ICD-9 code to identify these patients, though the coding scheme used is generally accepted in this literature area. In addition, patient charges were used as the healthcare cost markers in this data. Although the median charges for users and nonusers of chronic opioids and for fibromyalgia patients in general agree with those seen previously in the literature,[19,79,84] the affect of chronic opioid use in fibromyalgia patients has not previously been studied. Finally, the generalizability of this study is also questionable. Because a large number of variables were used to create a propensity score to balance patients according to likelihood of receiving chronic opioid use, only the propensity itself is balanced on average. This does nothing to answer questions as to what factors in particular should caution practitioner to be especially wary of prescribing opioids in fibromyalgia patients.

F: Conclusions

This study shows both that in fibromyalgia patient chronic opioid use is associated with higher medical and prescription costs and that propensity to receive chronic opioid therapy is associated with these costs and varies according to whether the patient actually receives this therapy choice. The findings show that even after balancing observable factors between opioid users and nonusers (demographic, comorbidities, concurrent medications, provider type, geographic location) healthcare costs will be higher for fibromyalgia patients receiving this chronic opioid therapy.

While chronic opioid use is already strongly discouraged for patients suffering from fibromyalgia syndrome in the literature, there are no previous economic outcomes studies in the literature to support this caution. This study adds to that literature and also develops a propensity index that can be used for comparing fibromyalgia patients receiving chronic opioid therapy to control patients with similar propensities for receiving that therapy choice. Using a patient's propensity to receive a fibromyalgia diagnosis, the following chapter creates a matching algorithm to select similar control patients from a nationally representative database. Chapter 7 is a comparison of healthcare costs between fibromyalgia patients and this well-matched control group.

Table 6.1: Patient characteristics, by chronic opioid use

Variable	Nonuser n=491134	SD	User n=58206	SD	P
Demographics					
Age	43.754	11.82	46.912	9.99	0.00
Female	0.652	0.476	0.740	0.43	0.00
Comorbid conditions					
Diabetes	0.106	0.308	0.156	0.36	0.00
Anxiety	0.177	0.382	0.351	0.47	0.00
Depression	0.138	0.345	0.306	0.46	0.00
Tension headache	0.031	0.174	0.051	0.21	0.00
Migraine	0.097	0.296	0.271	0.44	0.00
Circulatory system	0.454	0.498	0.606	0.48	0.00
Respiratory system	0.692	0.462	0.714	0.45	0.00
GERD	0.196	0.397	0.294	0.45	0.00
Gastritis	0.000	0.022	0.001	0.02	0.01
Back pain	0.314	0.464	0.496	0.50	0.00
Arthritis	0.217	0.412	0.453	0.49	0.00
Fatigue	0.364	0.481	0.467	0.49	0.00
Headache	0.000	0.014	0.000	0.01	0.04
Chest pain	0.250	0.433	0.338	0.47	0.00
Abdominal pain	0.295	0.456	0.406	0.49	0.00
Anxiety-related	0.288	0.453	0.377	0.48	0.00
Gastric-related	0.217	0.412	0.347	0.47	0.00
Diabetic neuropathy	0.012	0.108	0.030	0.17	0.00
Post-herpetic	0.006	0.075	0.016	0.12	0.00
Back pain with	0.239	0.427	0.488	0.50	0.00
Neck pain with	0.145	0.352	0.283	0.45	0.00
Causalgia	0.078	0.268	0.193	0.39	0.00
Trigeminal neuralgia	0.003	0.055	0.008	0.08	0.00
Atypical facial pain	0.005	0.067	0.011	0.10	0.00
Other neuropathic	0.093	0.291	0.176	0.38	0.00
Sleep disorders	0.178	0.382	0.333	0.47	0.00
Concurrent medications					
Anticonvulsants	0.168	0.374	0.597	0.49	0.00
Benzodiazepines	0.206	0.405	0.536	0.49	0.00
Glucocorticoids	0.313	0.464	0.457	0.49	0.00
NSAIDS	0.418	0.493	0.549	0.49	0.00
Muscle relaxants	0.295	0.456	0.676	0.46	0.00
Hypnotics	0.147	0.354	0.395	0.48	0.00
TCAs	0.063	0.243	0.202	0.40	0.00
SSRIs	0.214	0.410	0.394	0.48	0.00
SNRIs	0.098	0.297	0.328	0.46	0.00
NDRIs	0.064	0.245	0.135	0.34	0.00
SARIs	0.045	0.208	0.154	0.36	0.00
Triptans	0.058	0.233	0.215	0.41	0.00
Anti-migraine	0.028	0.166	0.107	0.30	0.00
Provider type					
Anesthesiology	0.026	0.159	0.192	0.39	0.00
Chiropractor	0.365	0.481	0.079	0.26	0.00
General surgery	0.007	0.084	0.006	0.07	0.00
Emergency medicine	0.033	0.178	0.025	0.15	0.00
Family medicine	0.255	0.436	0.258	0.43	0.10
Internal medicine	0.148	0.355	0.146	0.35	0.29
Orthopedic surgery	0.008	0.091	0.012	0.11	0.00
Nurse practitioner	0.002	0.050	0.004	0.06	0.00
Physician assistant	0.002	0.045	0.003	0.05	0.00
Rheumatology	0.043	0.202	0.092	0.28	0.00
Neurology	0.014	0.117	0.036	0.18	0.00
Physical medicine	0.032	0.176	0.087	0.28	0.00

Table 6.1: Patient characteristics, by chronic opioid use (continued)

Variable	Nonuser n=491134	SD	User n=58206	SD	P
State					
Alabama	0.007	0.084	0.012	0.10	0.00
Arkansas	0.009	0.097	0.013	0.11	0.00
Arizona	0.037	0.189	0.047	0.21	0.00
California	0.055	0.227	0.033	0.17	0.00
Colorado	0.036	0.185	0.036	0.18	0.91
Connecticut	0.007	0.081	0.005	0.07	0.00
District of Columbia	0.001	0.034	0.001	0.02	0.00
Delaware	0.001	0.027	0.001	0.02	0.53
Florida	0.098	0.298	0.137	0.34	0.00
Georgia	0.079	0.269	0.070	0.25	0.00
Iowa	0.009	0.094	0.007	0.08	0.00
Idaho	0.003	0.051	0.003	0.05	0.27
Illinois	0.029	0.169	0.019	0.13	0.00
Indiana	0.016	0.125	0.021	0.14	0.00
Kansas	0.010	0.101	0.009	0.09	0.00
Kentucky	0.008	0.090	0.012	0.11	0.00
Louisiana	0.015	0.120	0.017	0.13	0.00
Massachusetts	0.009	0.097	0.006	0.07	0.00
Maryland	0.018	0.131	0.020	0.13	0.00
Maine	0.001	0.030	0.001	0.02	0.07
Michigan	0.007	0.083	0.007	0.08	0.25
Minnesota	0.055	0.228	0.036	0.18	0.00
Missouri	0.038	0.190	0.030	0.17	0.00
Mississippi	0.008	0.087	0.011	0.10	0.00
Montana	0.001	0.027	0.001	0.02	0.26
North Carolina	0.033	0.179	0.043	0.20	0.00
North Dakota	0.003	0.055	0.001	0.03	0.00
Nebraska	0.008	0.091	0.006	0.07	0.00
New Hampshire	0.001	0.038	0.001	0.03	0.02
New Jersey	0.022	0.146	0.011	0.10	0.00
New Mexico	0.007	0.084	0.007	0.08	0.63
Nevada	0.006	0.075	0.009	0.09	0.00
New York	0.039	0.193	0.016	0.12	0.00
Ohio	0.054	0.226	0.070	0.25	0.00
Oklahoma	0.009	0.096	0.012	0.10	0.00
Oregon	0.005	0.072	0.008	0.09	0.00
Pennsylvania	0.013	0.113	0.014	0.11	0.01
Rhode Island	0.010	0.099	0.009	0.09	0.08
South Carolina	0.010	0.100	0.012	0.11	0.00
South Dakota	0.003	0.053	0.001	0.03	0.00
Tennessee	0.021	0.143	0.030	0.17	0.00
Texas	0.126	0.331	0.118	0.32	0.00
Utah	0.007	0.083	0.012	0.10	0.00
Virginia	0.022	0.148	0.020	0.13	0.00
Vermont	0.000	0.013	0.000	0.00	0.02
Washington	0.008	0.090	0.011	0.10	0.00
Wisconsin	0.035	0.183	0.032	0.17	0.00
West Virginia	0.002	0.040	0.004	0.05	0.00
Wyoming	0.001	0.029	0.001	0.02	0.07

Table 6.2: Logistic regression, propensity for chronic opioid use

Variable	Coef	SE	P
Demographics			
Age	-0.184	0.012	0.001
Female	0.006	0.001	0.001
Comorbid conditions			
Diabetes	0.046	0.016	0.005
Anxiety	0.005	0.013	0.724
Depression	0.010	0.014	0.459
Tension headache	-0.183	0.026	0.001
Migraine	0.245	0.016	0.001
Circulatory system	0.066	0.012	0.001
Respiratory system	-0.319	0.012	0.001
GERD	-0.111	0.013	0.001
Gastritis	0.106	0.194	0.584
Back pain	0.048	0.012	0.001
Arthritis	0.550	0.012	0.001
Fatigue	-0.187	0.011	0.001
Headache	0.118	0.314	0.706
Chest pain	-0.142	0.013	0.001
Abdominal pain	-0.050	0.012	0.001
Anxiety-related symptoms	-0.203	0.012	0.001
Gastric-related symptoms	0.026	0.013	0.045
Diabetic neuropathy	0.172	0.036	0.001
Post-herpetic neuralgia	0.481	0.047	0.001
Back pain with neuropathy	0.551	0.012	0.001
Neck pain with neuropathy	0.022	0.014	0.119
Causalgia	0.181	0.015	0.001
Trigeminal neuralgia	-0.150	0.066	0.022
Atypical facial pain	0.031	0.058	0.591
Other neuropathic disorders	-0.055	0.015	0.001
Sleep disorders	-0.091	0.013	0.001
Concurrent medications			
Anticonvulsants	0.916	0.012	0.001
Benzodiazepines	0.757	0.012	0.001
Glucocorticoids	-0.085	0.011	0.001
NSAIDS	-0.340	0.011	0.001
Muscle relaxants	0.754	0.012	0.001
Hypnotics	0.477	0.012	0.001
TCAs	0.360	0.015	0.001
SSRIs	0.146	0.012	0.001
SNRIs	0.492	0.013	0.001
NDRIs	0.026	0.017	0.127
SARIs	0.311	0.017	0.001
Triptans	0.816	0.017	0.001
Anti-migraine combinations	0.485	0.021	0.001
Provider type			
Anesthesiology	1.572	0.026	0.001
Chiropractor	-0.992	0.026	0.001
General surgery	-0.201	0.068	0.003
Emergency medicine	0.117	0.037	0.002
Family medicine	0.216	0.022	0.001
Internal medicine	0.153	0.024	0.001
Orthopedic surgery	0.294	0.050	0.001
Nurse practitioner	0.550	0.084	0.001
Physician assistant	0.729	0.093	0.001
Rheumatology	0.460	0.027	0.001
Neurology	0.356	0.035	0.001
Physical medicine	0.871	0.028	0.001

Table 6.2: Logistic regression, propensity for chronic opioid use (continued)

State			
Alabama	0.452	0.202	0.025
Arkansas	0.205	0.201	0.309
Arizona	0.365	0.198	0.065
California	-0.102	0.198	0.607
Colorado	0.104	0.198	0.598
Connecticut	-0.230	0.209	0.270
District of Columbia	-0.588	0.283	0.038
Delaware	0.086	0.268	0.747
Florida	0.215	0.197	0.273
Georgia	-0.117	0.197	0.551
Iowa	-0.065	0.205	0.751
Idaho	0.318	0.219	0.146
Illinois	-0.166	0.199	0.406
Indiana	0.350	0.199	0.079
Kansas	0.050	0.204	0.806
Kentucky	0.529	0.202	0.009
Louisiana	0.033	0.200	0.871
Massachusetts	-0.268	0.206	0.193
Maryland	0.003	0.200	0.987
Maine	0.005	0.271	0.984
Michigan	0.299	0.205	0.144
Minnesota	-0.132	0.198	0.505
Missouri	-0.062	0.198	0.756
Mississippi	0.246	0.203	0.226
Montana	0.336	0.265	0.204
North Carolina	0.182	0.198	0.357
North Dakota	0.009	0.236	0.968
Nebraska	-0.174	0.207	0.401
New Hampshire	-0.528	0.246	0.032
New Jersey	-0.488	0.202	0.016
New Mexico	-0.009	0.205	0.966
Nevada	0.667	0.204	0.001
New York	-0.673	0.200	0.001
Ohio	0.272	0.197	0.168
Oklahoma	0.529	0.202	0.009
Oregon	0.607	0.205	0.003
Pennsylvania	0.332	0.201	0.098
Rhode Island	-0.191	0.203	0.348
South Carolina	0.192	0.202	0.341
South Dakota	-0.084	0.242	0.727
Tennessee	0.418	0.199	0.035
Texas	-0.090	0.197	0.649
Utah	0.561	0.203	0.006
Virginia	-0.061	0.199	0.761
Vermont	0.093	0.539	0.863
Washington	0.284	0.203	0.161
Wisconsin	-0.002	0.198	0.993
West Virginia	0.562	0.218	0.010
Wyoming	(Omitted)		
Constant	-3.763	0.199	0.001

Table 6.3: Propensity score deciles, by chronic opioid use

Decile	Nonuser	User	Total
1	54,819	115	**54,934**
2	54,708	226	**54,934**
3	54,509	425	**54,934**
4	54,184	750	**54,934**
5	53,665	1,269	**54,934**
6	52,679	2,255	**54,934**
7	50,854	4,080	**54,934**
8	47,321	7,612	**54,933**
9	40,975	13,960	**54,935**
10	27,420	27,514	**54,934**
Total	**491,134**	**58,206**	**549,340**

Figure 6.1: Propensity prediction for chronic opioid use

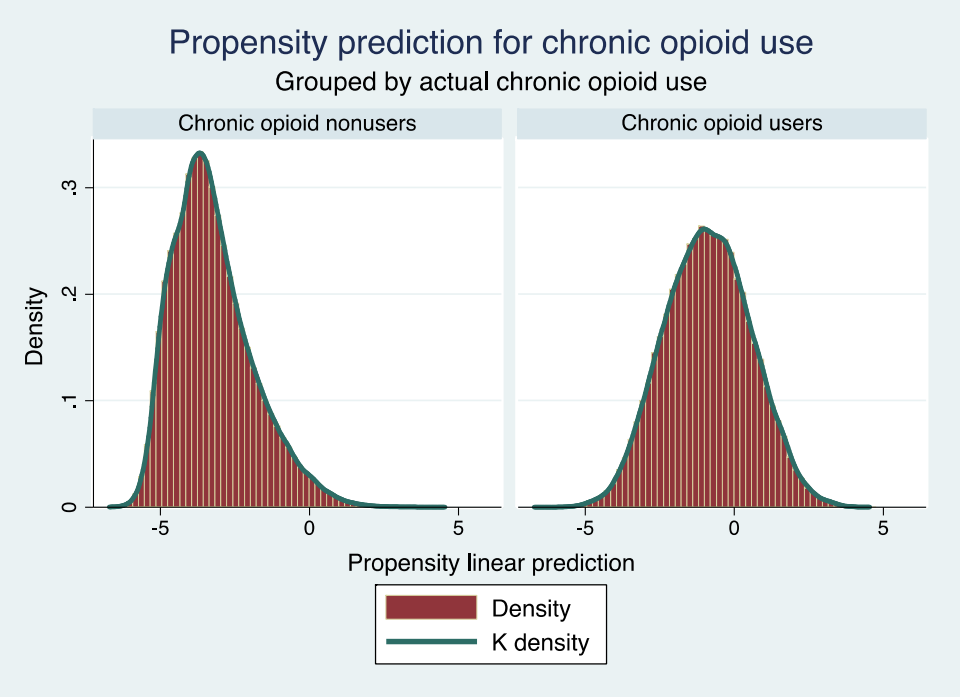


Figure 6.2: Annualized medical charges based on chronic opioid use

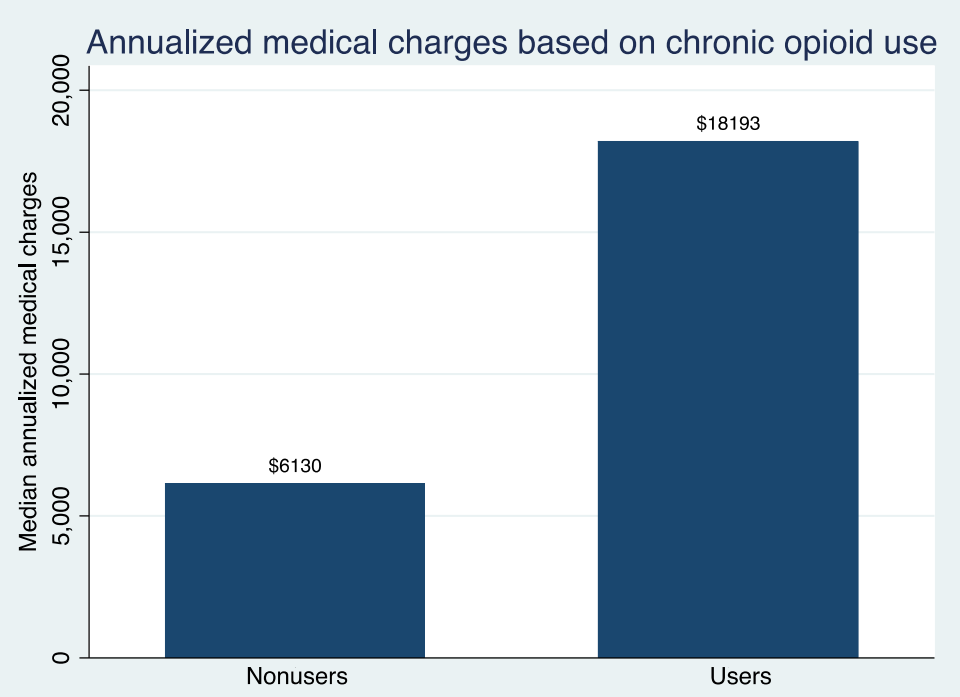


Figure 6.3 Medical charges, grouped by propensity to receive chronic opioid therapy decile

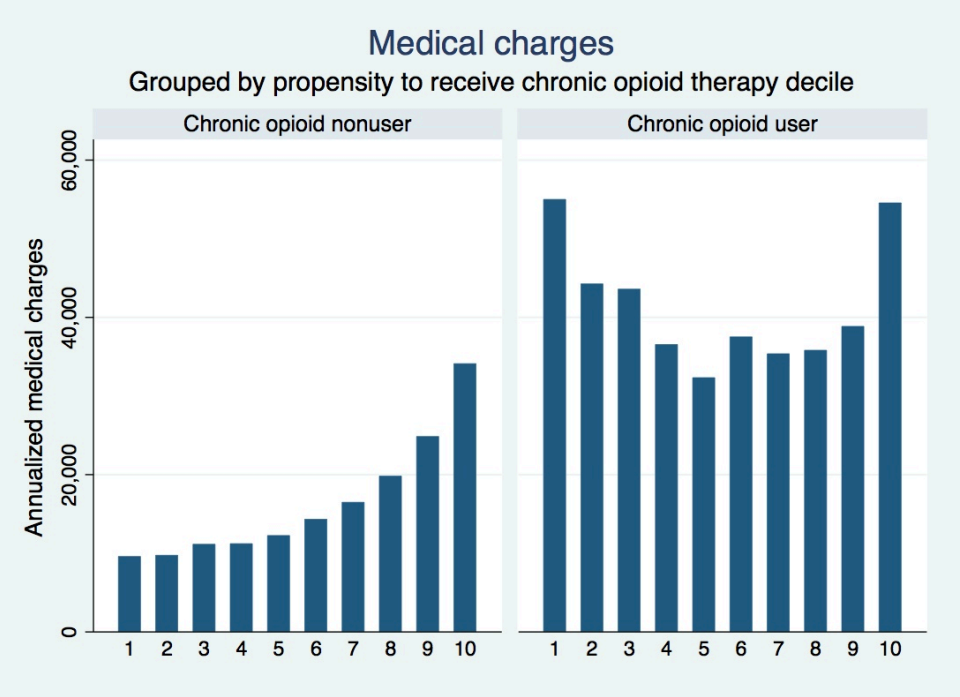


Figure 6.4: Annualized prescription charges based on chronic opioid use

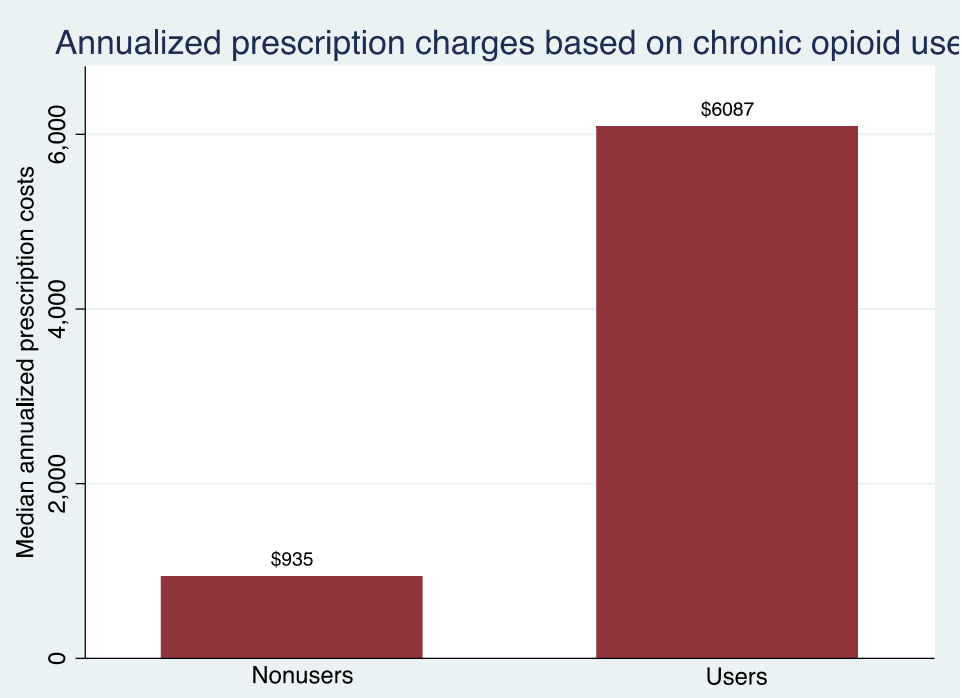


Figure 6.5: Prescription charges, grouped by propensity to use chronic opioid therapy decile

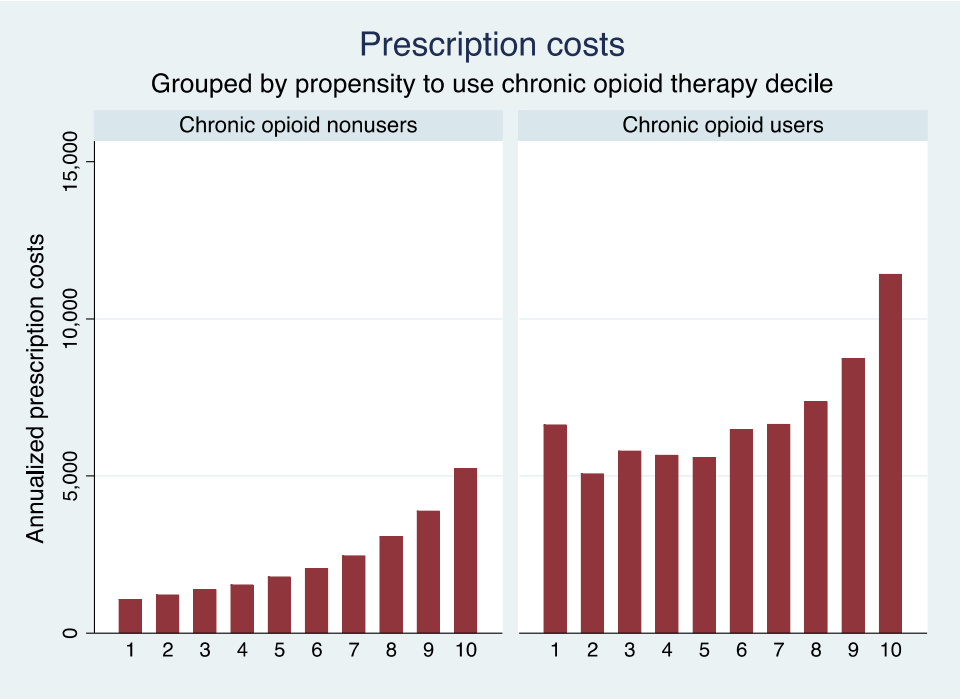
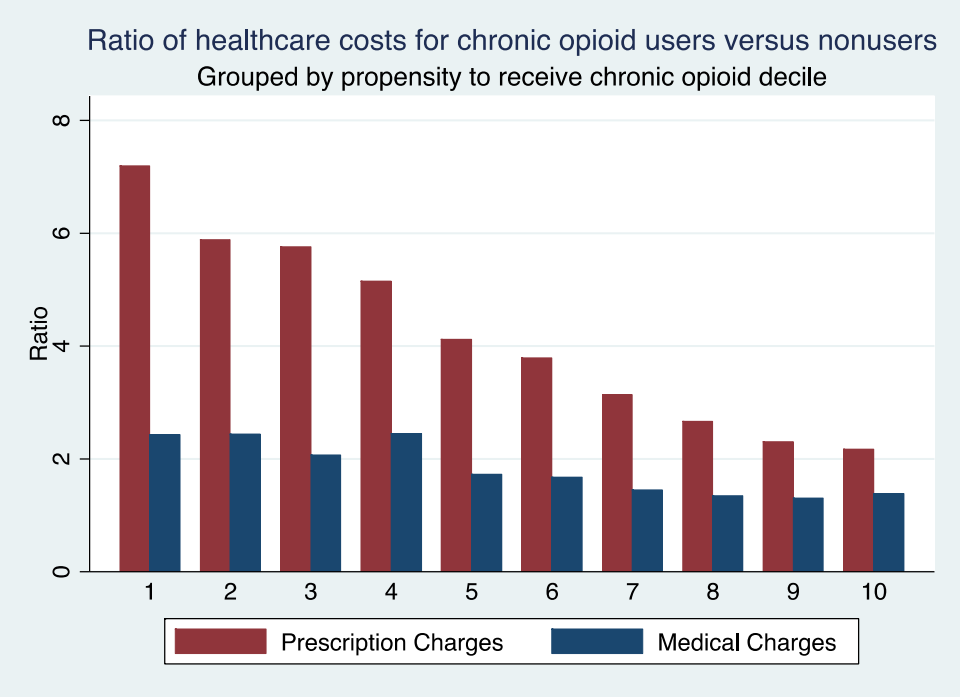


Figure 6.6: Ratio of healthcare costs for chronic opioid users versus nonusers



Chapter 7: A propensity score matched assessment of costs associated with fibromyalgia syndrome

Chapter 2 through Chapter 5 focuses on revealing characteristics associated with chronic opioid use in fibromyalgia syndrome. Identification of these characteristics highlights the fact that finding a comparison group for patients suffering from fibromyalgia syndrome is a difficult endeavor. Using propensity score techniques identified in the previous chapter, this study constructs a matching algorithm based on the likelihood of a patient receiving a fibromyalgia diagnosis considering characteristics at the state-, provider-, and patient-level.

A: Background

Fibromyalgia syndrome, also labeled FMS or simply fibromyalgia, is an idiopathic, functional disorder characterized by chronic widespread pain and diffuse tenderness.[2] This disorder affects over 6 million patients in the United States and is associated with significant clinical and economic burden to patients, the healthcare system, and society as a whole. There are several characteristics, physiological and clinical, that separate fibromyalgia patients from those with general chronic nonmalignant pain. Though the theoretical case is strong, there is a lack of evidence specifically analyzing utilization and cost characteristics of patients using opioids chronically in this disease state.

Although the hallmark symptom of fibromyalgia is dispersed pain, the syndrome is also characterized by fatigue, non-restorative sleep, and cognitive difficulties.[2] There are many unanswered questions regarding both etiology and treatment of fibromyalgia. Although the literature has grown due to the recent introduction of medications approved for the indication of fibromyalgia, research addressing issues such as cost of care, off-label treatment patterns, or healthcare utilization for patients receiving medications other than those currently under patent is less than rigorous, outdated, or nonexistent.

Although the etiology of fibromyalgia remains unclear, it is becoming increasingly evident that disordered central pain processing is the primary source of the syndrome.[4] Research has shown that fibromyalgia patients have shifted pain response profiles when exposed to either pressure[5] or thermal[6] stimuli. Fibromyalgia is not an organic disorder characterized by a structural or functional abnormality; rather it is considered a functional somatic syndrome. These disorders are identified by symptoms, suffering, and disability.[7] Other examples of somatic pain syndromes include irritable bowel syndrome, temporomandibular disorder, and vulvodynia. Each of these syndromes is characterized by nondescript, regional pain without an underlying mechanistic cause.[4]

Idiopathic chronic generalized musculoskeletal pain is present in 10% to 12% of the general population.[8] Most patients suffering from this type of chronic pain also meet the clinical

criteria often used to identify patients suffering from fibromyalgia syndrome. Despite the similarities in description however fibromyalgia is only diagnosed in approximately 5% of women[9] and 1.6% of men[10] in the general population. The difference in diagnosis rates seen between chronic nonmalignant pain and fibromyalgia syndrome can partially be attributed to the nature of fibromyalgia, which is not a homogeneous pain condition. Rather, the disorder can be observed along a spectrum where at one end pain and tenderness are the exclusive symptoms, and at the other, pain is accompanied by significant psychological and cognitive detriment.[11] This spectrum is multidimensional and is not a definite indicator of severity. Patients may exhibit severe pain symptoms exclusively or have moderate pain but suffer from mental clouding, irritable bowel, or numerous other symptoms.

Fibromyalgia is generally considered a disorder that occurs in women between 20 and 50 years of age. Although this is the typical presentation, fibromyalgia occurs in males, children, adolescents and the elderly. Fibromyalgia is increasingly prevalent until age 80, after which prevalence declines.[12] Higher prevalence rates are seen in relatives of patients suffering from fibromyalgia suggesting both environmental and genetic factors leading to the disorder.[9]

Patients suffering from fibromyalgia have been shown to be burdened with increased healthcare utilization and costs compared to similar controls. Several studies examining the costs of fibromyalgia in various forms, and in comparison to various

control groups, have been conducted. In 1999 a study, utilizing a US-based health-insurance database, found that total annual healthcare costs for fibromyalgia sufferers averaged $9573 versus $3291 for age and sex matched controls.[19] Statistically significant differences were seen across all cost types including: inpatient care, outpatient care, pain-related medications, other medications, and other medical care.[19]

In 2003, Robinson *et al* compared fibromyalgia claimants with a general sample of privately insured individuals. Using this approach, fibromyalgia patients had total annual costs of $5945 versus only $2486 for controls. The authors suggest, “when a claim for FM is present, considerable costs are involved”, but also “disability and comorbidities greatly increase the burden of FM”.[87]

Two years later in an attempt to compare fibromyalgia to more similar patients, Boonen *et al* looked at fibromyalgia, chronic low back pain, and ankylosing spondylitis. This study employed a cost journal approach and found both low back pain (8533EU) and fibromyalgia (7813EU) to be significantly more expensive than ankylosing spondyloses (3205EU) due mainly to direct non-medical costs and productivity costs.[88]

The London Fibromyalgia Epidemiology Study, published in 2007, compared four groups: fibromyalgia patients, patients with widespread pain but no fibromyalgia diagnosis, patients accessing healthcare without widespread pain, and a group of controls. This study showed fibromyalgia patients accessing pain-related

medication more often and having significantly greater average healthcare cost than those with general widespread pain.[10]

In 2009, Silverman *et al* compared fibromyalgia patients to rheumatoid arthritis patients. Using a large secondary claims database of privately insured individuals with fibromyalgia, rheumatoid arthritis, or both, this study showed that expenses for fibromyalgia patients ($10911) are similar to those with rheumatoid arthritis ($10716).[89] Direct medical costs for fibromyalgia patients were approximately equal to those seen in rheumatoid arthritis patients, and while both groups had high prevalence of comorbidities fibromyalgia patients had more emergency department, physician, and physical therapy appointments than rheumatoid arthritis patients.[89]

Most recently Palacio *et al* used a propensity score approach that compared fibromyalgia patients to a random sample taken from a private health insurance database and matched according to sex, age, and the Deyo-Charlson modified comorbidity index, an index looking at 17 comorbidities. Using this approach, mean annualized medical costs were calculated to be $6407.28 for FMS patients and only $4274.88 for matched controls.[90] Corresponding prescription costs were $1604.76 and $1086.72, respectively.[90] The Palacio study is the best example of a control sample being used to date, but as admitted by the authors, this study was limited by the lack of matching for conditions not contained in the comorbidity index used, “conditions that were more frequent among fibromyalgia patients”.[90]

The development of the cost literature surrounding the disease of fibromyalgia over the past ten years, with the culmination in the recent article published by Palacio *et al* shows the struggle for an adequate control group for comparison with this disease state. Previous work by this author has shown that the approach taken by Palacio *et al* is not sufficient to control for the factors that go into determining costs of patients suffering from fibromyalgia syndrome. This work shows that determinants of costs differ at not only the patient level, but the provider and structural (geographic) level as well.[72,85,86] In addition, the use of a propensity score measure that looks only at age, sex, and a small set of comorbid conditions may not be sufficient to control for patient factors such as other comorbidities not contained in the index, as well as concurrent medications that differ in fibromyalgia patients compared to these controls.

The purpose of this study is to compare medical and prescription costs between fibromyalgia patients and a well-matched control group. A propensity score taking into account demographics, geographic location, diagnosing provider type, comorbid conditions, and concurrent medication classes will be used to match patients. Based on previous literature we hypothesize that although patients suffering from fibromyalgia syndrome will have elevated medical and prescription costs this elevation has been exaggerated in previous literature and will be tempered by the use of an appropriately chosen control group.

B: Materials and methods

Data source

The University of Kentucky Institute for Pharmaceutical Outcomes and Policy has a licensing agreement for the i3 Invision Data Mart (IVDM) for the years 2007-2009. We obtained patient information from January 1, 2007 to December 31, 2009 from the IVDM. The IVDM is a nationally representative de-identified sample of 15 million patients from commercial health plans across the United States. Data are collected at the patient level, and consist of eligibility and enrollment information (eligibility date, eligibility span, health plan type), demographic information (gender, age, state), medical claims (inpatient, outpatient, professional services, including ICD-9-CM, DRG, CPT-4, revenue code and links to participating providers), pharmacy claims (prescriber, NDC, day supply, quantity), and laboratory claims (type of test and results) for approximately 15 million patients each year. For the purposes of this study the entire three-year data slice was considered as a single cross-section.

Study cohort definitions

The dataset was queried for patients with fibromyalgia syndrome as identified by *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-CM-9) code 729.1 (myalgia and myositis unspecified). Patients with at least one claim between January 1, 2007 and December 31, 2009 were included in the sample. Only patients between ages 18 and 64 were considered for this study. The reasons for this restriction are

utilization patterns may differ for children, and missing data problems are more common for those eligible for Medicare. Patients with malignancies were excluded from analysis because medical care patterns may differ for these patients. The University of Kentucky Institutional Review Board provided approval for this study.

A control group was selected using the same inclusion and exclusion criteria as for the patients except where ICD-9 code 729.1 was used for the identification of fibromyalgia syndrome a list of ICD-9 codes for related disorders was used for identification of controls with similar disease states. The list of diseases and corresponding IDC-9 codes can be found in Table 1.

Outcome variables

Two outcome variables of interest were collected: medical costs and prescription costs. These were collected based on medical and prescription charges collected in the IVDM. Charged amounts were used in all analyses of healthcare costs. Charges were summed at the patient level and then annualized to control for differing eligibility spans across the sample. The top and bottom one-percent of annualized medical and annualized prescription charges were dropped to control for outliers.

Independent variables

Independent variables were collected at the state, provider, and patient level as described previously. The variables were used to develop a propensity index using logistic regression coefficients. Propensity to be diagnosed with fibromyalgia

syndrome was determined from these variables and then, using a simple matching nearest neighbor algorithm, a one-to-one match was constructed of fibromyalgia patients and controls.

Data analysis

Natural log of medical and prescription costs were examined due to the skewness of cost data unless otherwise noted. The statistical significance cost differences between fibromyalgia patients and controls was calculated using two-group t-tests before and after the matching algorithm was carried out. Data extraction was completed using Oracle SQL Developer and SAS v10, the matching process was carried out using Fortran, and all statistical analyses were completed in STATA v12.

C: Results

A total of 1919409 controls were identified in the IVDM to match to 494369 fibromyalgia patients. Table 2 shows demographic information, comorbid conditions, concurrent medication classes, diagnosing provider types, and geographic locations for the patients and controls before the matching process was completed. Using the propensity for being diagnosed with fibromyalgia syndrome as evidenced by the coefficients obtained from a logistic regression, patients and controls were matched one-to-one using a nearest neighbor algorithm matching the closest propensity scores. These coefficients and the resulting characteristic balance can also be seen in Table 2.

The algorithm resulted in 445912 matched pairs of controls and patients for a sample total of 891824. Calculating the

coefficient of variation for all included variables shows that variation among controls and patients across all variables was reduced from 20% to 4%. Significant differences among patients and controls are designated with an asterisk both before and after the matching schema, as are significant coefficients obtained from the first stage logistic regression.

The matching results in a sample that is an average of 44 years old and two-thirds female. As expected in a population with fibromyalgia, many pain comorbidities are present at rates elevated from the general population, including back pain, neuropathic pain disorders, as well as fatigue and sleep disorders. We also see that medication classes typically used to treat these disorders see increased use: these include benzodiazepines, NSAIDs, hypnotics, and muscle relaxants. Diagnosing provider varies, but chiropractors and primary care physicians are most common. Geographic variation between patients and controls varies by state but is controlled sufficiently by the matching process.

Figure 1 shows the distribution of the natural log of annualized medical costs for the entire population. The natural log of these costs resembles a normal distribution though kurtosis is slightly elevated. Figure 2 shows the same figure for prescription charges, which are skewed left of normal.

Overall, medical costs were higher for fibromyalgia patients both before and after the matching process. Fibromyalgia patients had annualized medical costs of $14315 for the total

patient sample of 494369 compared to $13007 for the 1919409 controls. This is a 10% elevation in annualized medical costs for patients over controls before the propensity score matching. After the matching, we see medical costs of $13941 for 445912 fibromyalgia patients and $13802 for their matched pairs. This is a difference of only 1%. A 90% reduction in the difference is seen.

Similar results are seen for prescription charges, though somewhat larger differences are seen. Before matching, fibromyalgia patients had mean annualized prescription charges of $2463, compared to only $1974 for controls. This is a 25% difference between patients and controls. After matching the charges are $2378 and $2266, respectively. This is a difference of only 5% and represents a reduction of 80% as a result of the matching process.

D: Discussion

This study is a first for the fibromyalgia literature, employing an extensive propensity score matching technique that attempts to balance patients and controls on comorbid conditions, concurrent medications, diagnosing providers, and geographic location. The literature to date has shown elevated costs among fibromyalgia patients as compared to various control sets with the only consensus being that fibromyalgia patients have a significantly higher burden of illness.

Table 2 highlights the results of the propensity score matching. Because the study sample is so expansive, containing

nearly half a million matched pairs, significant differences in individual variables are seen both before and after the matching process. However, the variation between the groups overall is reduced 5-fold by the matching process. This reduction in variation in observed variables serves to create a more appropriate control group so the association of a diagnosis of fibromyalgia with healthcare costs can be examined.

Based on previous published literature[19,88,89] and unpublished work by this author[72,85,86], we predicted fibromyalgia costs were overstated due to the use of disparate and inappropriate control groups in the past. As seen in Figures 3 and 4, the differences in healthcare costs is considerably reduced when comparing fibromyalgia patients to a well-matched control group. Though the differences are reduced drastically, both medical and prescription costs associated with fibromyalgia remain elevated by a statistically significant amount.

Until recently, studies comparing fibromyalgia patients to controls matched on age and sex at best. Using this approach various results were collected including costs overall being about three times higher for fibromyalgia patients.[19] A recent study utilized a more advanced model, matching patients using the Charlson-Deyo comorbidity index. The authors found medical and prescription costs to be elevated by approximately 50%, signaling a decrease in cost differences between cases and controls as variation in observed variables was reduced. The present study extends this work by employing an extensive propensity score

model built on multiple classes of observed variables reducing the difference seen in fibromyalgia patients and controls further. Though a difference is still seen in cost measures this difference is reduced by approximately 90% through the matching process.

E: Limitations

In addition to limitations generally applicable to secondary database research such as the possibility of miscoding and the use of charges as a proxy for actual healthcare costs, the following limitation are worth noting. First, the validity of ICD-9 code 729.1 as an identifier of fibromyalgia within the IVDM has not been validated; however, the decision to use the code is consistent with previous research done in this area. Identification of concurrent medications also has a significant omission. Patients were not identified according to use of opioids in the dataset. This omission was a conscious decision of the researcher as chronic opioid use among fibromyalgia patients may be endogenous to other comorbid conditions. This research question is examined elsewhere. Despite this omission opioid use is balanced after the matching process to an extent similar to other concurrent medication classes with differences between fibromyalgia patients and their matches being approximately one percent. Finally, there is a possibility of “overmatching” due to the lengthy list variables controlled for in the propensity score. Each group of variables has been shown to vary significantly among fibromyalgia patients, however.[72,85,86] Given this variation

and the large number of matched pairs available for analysis, “overmatching” is not a significant concern.

F: Conclusions

Both medical and prescription costs were shown to be significantly elevated in fibromyalgia patients when compared to well-matched controls. The introduction of an extensive propensity score-matching schema reduces the elevation seen in costs by approximately 90%; however, costs remain elevated by 1% for medical costs and 5% for prescription costs. The reductions seen in these measures draws into question whether the elevations seen in costs associated with fibromyalgia seen in previous literature are a result of the diagnosis itself or the complicated nature of the disorder which is associated with increased comorbidity prevalence and concurrent medication use, as well as differing healthcare utilization patterns and geographic variation.

While using a well-matched group of controls largely controls the contribution to healthcare costs associated with a fibromyalgia diagnosis, the impact of chronic opioid therapy on patients with and without fibromyalgia is not addressed in this study. Using similar techniques and a propensity score identifying the likelihood of being a fibromyalgia patient receiving chronic opioid therapy, the following chapter analyzes the effect this treatment choice has on healthcare costs.

Table 7.1: List of disease states used for control identification

Diseases of the musculoskeletal system	
--Back pain	722.92-722.93, 722.4-722.5, 722.81, 722.91, 723.1, 723.5-723.6
--Arthritis	711.00-716.xx
Symptoms, signs and ill-defined conditions	
--Fatigue	780.71, 780.79
--Headache	784
--Chest pain	786.5-786.5x
--Abdominal pain	789.0-789.0x
--Anxiety-related symptoms	780.4, 785.0-785.1, 786.01, 786.05, 786.09
--Gastric-related symptoms	787.0, 787.01-787.03, 787.1-787.3, 787.9, 787.91, 787.99
Painful neuropathic disorders	
--Diabetic neuropathy	250.6x, 357.2
--Post-herpetic neuropathy	531.x
--Back pain with neuropathic involvement	721.41-721.42, 721.91, 722.1, 722.10, 722.11, 722.2, 722.70, 722.72-722.73, 724.0x, 724.3, 724.4
--Neck pain with neuropathic involvement	721.1, 722.0, 722.71, 723.0, 723.4
--Causalgia	337.2x, 353.2-353.4, 354.4, 355.7x, 355.9, 729.2
--Phantom limb pain	353.6
--Trigeminal neuralgia	350.1
--Atypical facial pain	350.2, 352.1
--Other painful neuropathies	353.0, 353.1, 353.8, 353.9, 354.0-354.5, 354.8, 354.9, 355.0-355.6, 355.8

Table 7.2: Patient characteristics, before and after propensity score match

	All		Pr(FMS)	Matched	
	Contro	FMS		Control	FMS
	Demographics				
Female	0.611	0.663*	-0.006*	0.657	0.655
Age	44.6	44.2*	0.044*	44.0	44.2*
	Comorbid conditions				
Diabetes	0.110	0.110	-0.010	0.106	0.109*
Anxiety	0.153	0.195*	-0.009	0.189	0.188
Depression	0.116	0.154*	0.001	0.149	0.147*
Tension headache	0.023	0.033*	0.147*	0.034	0.032*
Migraine	0.086	0.114*	0.045*	0.111	0.109*
Circulatory system	0.450	0.471*	-0.011*	0.458	0.466*
Respiratory system	0.633	0.698*	0.137*	0.694	0.689*
GERD	0.172	0.206*	0.038*	0.198	0.199
Gastritis	0.000	0.000*	0.003	0.001	0.001
Back pain	0.360	0.335*	-0.030*	0.351	0.341*
Arthritis	0.196	0.242*	0.231*	0.228	0.230
Fatigue	0.271	0.376*	0.311*	0.362	0.358*
Headache	0.000	0.000*	0.330*	0.001	0.001
Chest pain	0.217	0.257*	0.026*	0.247	0.250*
Abdominal pain	0.247	0.304*	0.080*	0.295	0.294
Anxiety-related	0.243	0.295*	0.053*	0.285	0.285
Gastric-related	0.175	0.227*	0.086*	0.218	0.217
Diabetic neuropathy	0.019	0.013*	-0.565*	0.012	0.013*
Post-herpetic	0.005	0.006*	-0.161*	0.006	0.006
Back pain with	0.305	0.267*	-0.286*	0.279	0.273*
Neck pain with	0.152	0.161*	0.139*	0.167	0.161*
Causalgia	0.085	0.089*	-0.070*	0.092	0.089*
Trigeminal	0.003	0.003*	-0.348*	0.003	0.003
Atypical facial	0.004	0.005*	0.008	0.004	0.005
Other neuropathic	0.119	0.102*	-0.165*	0.099	0.102*
Sleep disorders	0.145	0.194*	0.099*	0.187	0.185*
	Concurrent medications				
Anticonvulsants	0.145	0.209*	0.269*	0.196	0.195
Benzodiazepines	0.195	0.239*	0.041*	0.232	0.231
Glucocorticoids	0.297	0.329*	0.003	0.320	0.322
NSAIDS	0.410	0.436*	0.007	0.423	0.429*
Muscle relaxants	0.289	0.335*	0.131*	0.321	0.326*
Hypnotics	0.129	0.170*	0.079*	0.165	0.162*
TCAs	0.045	0.076*	0.312*	0.069	0.069
SSRIs	0.193	0.234*	0.012*	0.229	0.227*
SNRIs	0.073	0.120*	0.271*	0.112	0.110*
NDRIs	0.056	0.071*	-0.001	0.070	0.068*
SARIs	0.036	0.056*	0.121*	0.052	0.051
Triptans	0.056	0.074*	-0.008	0.071	0.070*
Anti-migraine	0.027	0.036*	0.001	0.035	0.035
	Practitioner type				
Chiropractor	0.364	0.358*	-	0.435	0.377*
General surgery	0.004	0.007*	0.573*	0.006	0.006*
Emergency medicine	0.023	0.034*	0.318*	0.026	0.031*
Family medicine	0.234	0.273*	0.070*	0.240	0.267*
Internal medicine	0.137	0.159*	0.052*	0.135	0.155*
Orthopedic surgery	0.106	0.010*	-2.500*	0.010	0.011
Nurse practitioner	0.002	0.003*	0.353*	0.002	0.003*
Physician assistant	0.002	0.002*	0.279*	0.002	0.002*
Rheumatology	0.022	0.051*	0.524*	0.042	0.043*
Neurology	0.037	0.017*	-0.940*	0.016	0.018*
Physical medicine	0.034	0.041*	0.120*	0.039	0.040*
Anesthesiology	0.036	0.045*	0.103*	0.045	0.045

Table 7.2: Patient characteristics, before and after propensity score match (continued)

	State				
Alabama	0.007	0.008*	-0.051*	0.007	0.007*
Arkansas	0.009	0.010*	-0.043*	0.010	0.010
Arizona	0.038	0.039*	-0.070*	0.041	0.039*
California	0.047	0.050*	0.092*	0.053	0.051*
Colorado	0.035	0.036*	-0.017	0.037	0.036
Connecticut	0.006	0.006*	0.144*	0.006	0.006
District of Columbia	0.001	0.001*	-0.208*	0.001	0.001
Delaware	0.001	0.001*	-0.260*	0.001	0.001
Florida	0.114	0.101*	-0.140*	0.100	0.102*
Georgia	0.084	0.080*	-0.105*	0.079	0.080
Iowa	0.009	0.009*	0.008	0.009	0.009
Idaho	0.003	0.003*	-0.234*	0.003	0.003
Illinois	0.028	0.028	0.027*	0.030	0.029*
Indiana	0.016	0.016*	-0.019	0.016	0.016
Kansas	0.010	0.011	-0.015	0.011	0.011*
Kentucky	0.009	0.009	-0.111*	0.009	0.009
Louisiana	0.016	0.014*	-0.154*	0.014	0.014*
Massachusettes	0.010	0.009*	-0.102*	0.009	0.009*
Maryland	0.018	0.018*	-0.004	0.017	0.018*
Maine	0.001	0.001*	-0.217*	0.001	0.001
Michigan	0.008	0.007*	-0.149*	0.007	0.007
Minnesota	0.047	0.051*	0.040*	0.050	0.050
Missouri	0.037	0.037	-0.036*	0.039	0.038*
Mississippi	0.007	0.008*	0.063*	0.007	0.007
Montana	0.001	0.001*	-0.224*	0.001	0.001
North Carolina	0.034	0.035*	-0.007	0.034	0.034*
North Dakota	0.002	0.003*	0.317*	0.003	0.003*
Nebraska	0.008	0.008*	0.078*	0.008	0.008
New Hampshire	0.002	0.001*	-0.335*	0.001	0.001
New Jersey	0.019	0.021*	0.075*	0.020	0.021
New Mexico	0.007	0.006*	-0.249*	0.006	0.007
Nevada	0.006	0.006*	0.014	0.006	0.006
New York	0.029	0.036*	0.228*	0.037	0.035*
Ohio	0.058	0.057*	-0.129*	0.054	0.057*
Oklahoma	0.010	0.010*	-0.168*	0.010	0.010
Oregon	0.006	0.005*	-0.174*	0.005	0.006
Pennsylvania	0.015	0.013*	-0.115*	0.013	0.013*
Rhode Island	0.012	0.010*	-0.257*	0.010	0.010*
South Carolina	0.010	0.011*	0.017	0.010	0.011
South Dakota	0.002	0.003*	0.264*	0.003	0.003*
Tennessee	0.020	0.022*	0.045*	0.022	0.022*
Texas	0.120	0.126	-	0.129	0.124*
Utah	0.007	0.007	-0.107*	0.007	0.007
Virginia	0.020	0.022*	0.133*	0.022	0.022
Vermont	0.000	0.000*	-0.216	0.000	0.000
Washington	0.012	0.008*	-0.497*	0.008	0.008*
Wisconsin	0.036	0.033*	-0.081*	0.031	0.034*
West Virginia	0.002	0.002	-0.184*	0.002	0.002*
Wyoming	0.001	0.001*	-0.058	0.001	0.001*

Figure 7.1: Distribution of annualized medical charges, histogram

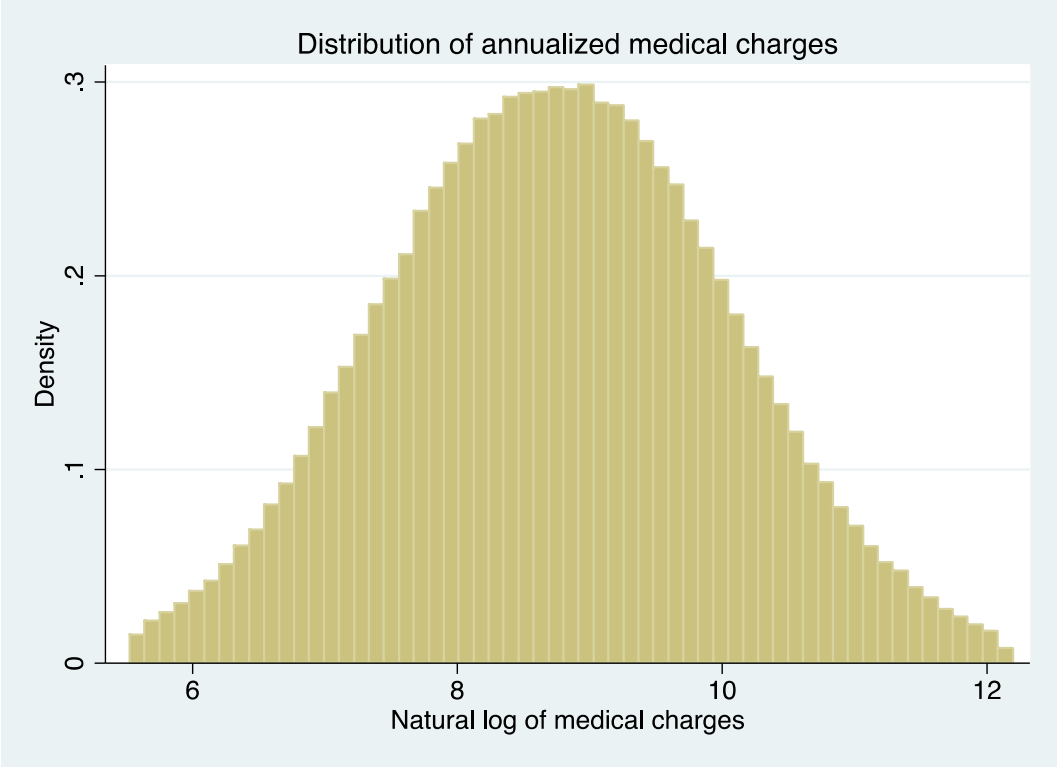


Figure 7.2: Distribution of annualized prescription charges, histogram

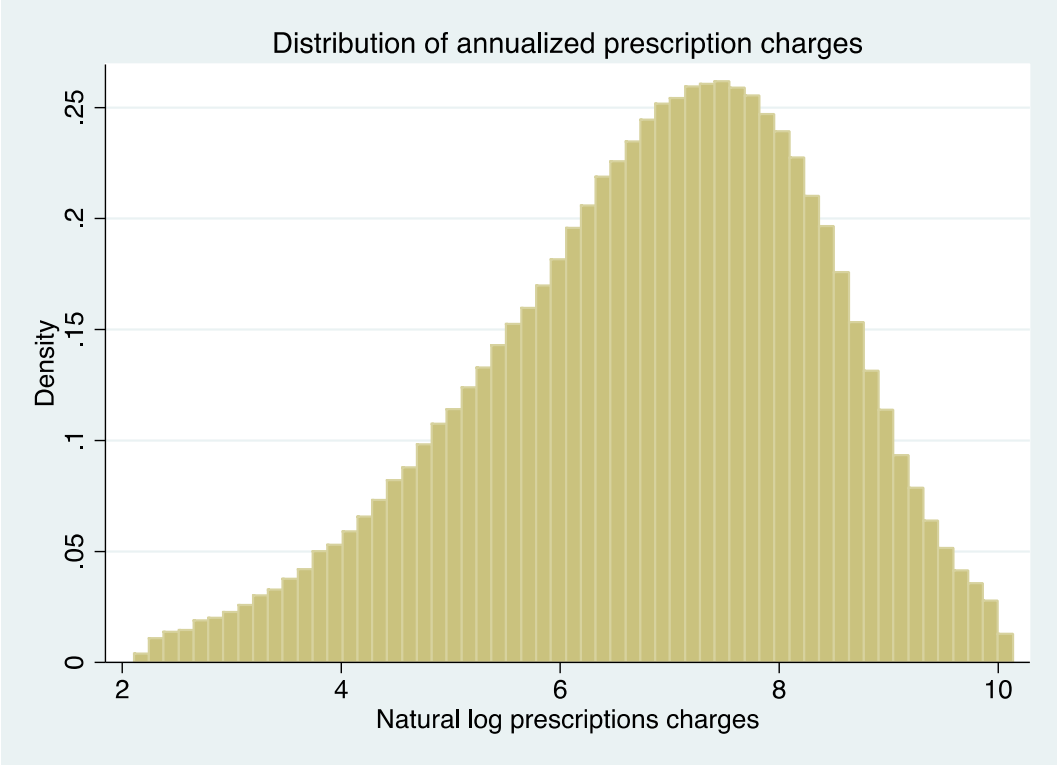


Figure 7.3: Annualized medical charges, before and after propensity score match

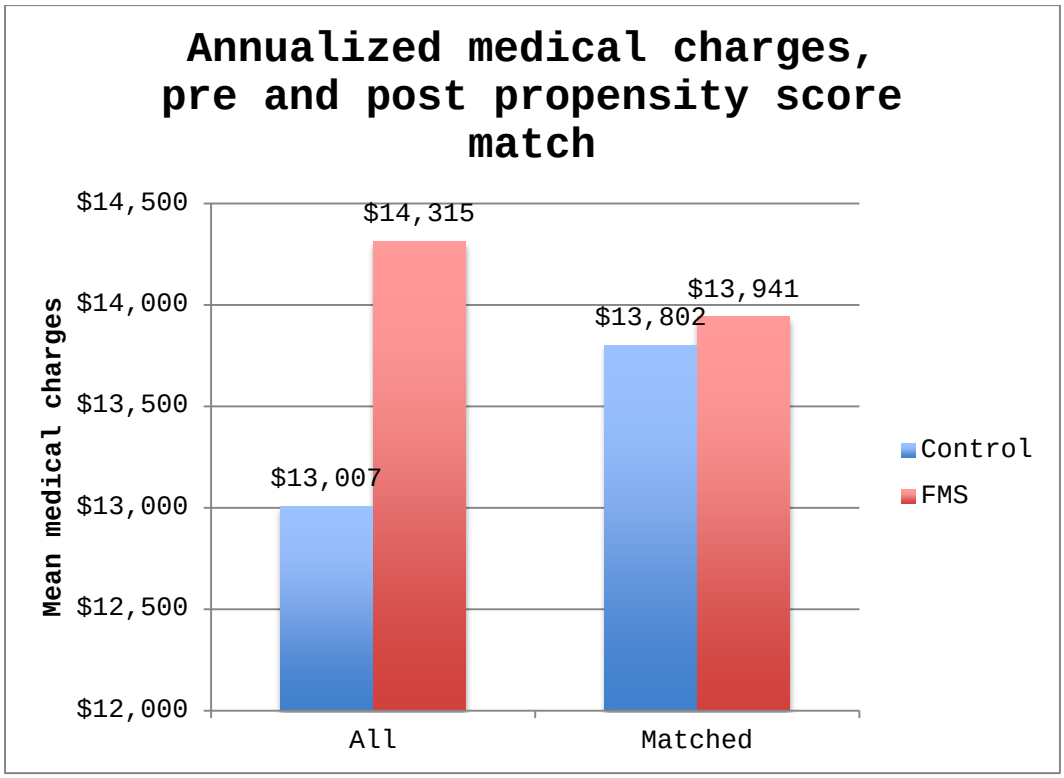
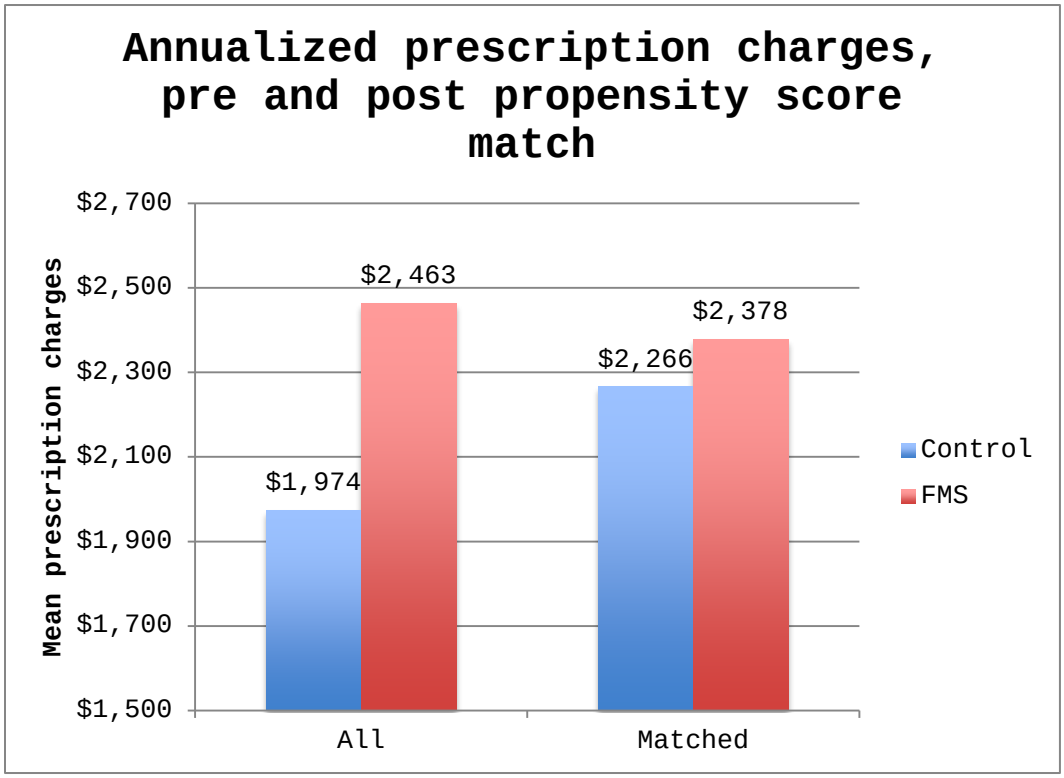


Figure 7.4: Annualized prescription charges, before and after propensity score match



Chapter 8: A propensity score matched assessment of costs associated with chronic opioid use in fibromyalgia syndrome

Chapter 7 focuses on the impact a diagnosis of fibromyalgia has on healthcare costs. However issue equally important to clinical practice is the effect the use of chronic opioid therapy in fibromyalgia patients has on healthcare costs. This chapter, using propensity matching introduced in Chapter 7, analyzes the impact of the interaction of chronic opioid therapy and fibromyalgia syndrome.

A: Background

Chronic pain research is a difficult endeavor due to the subjective and heterogeneous nature of the disorder. One approach to answering these research questions is to look at individual chronic pain ailments. Fibromyalgia syndrome, due to the nature of the disorder, the recent development of medication with proven safety and efficacy, the significant burden of illness it inflicts on sufferers, and the wide range of treatment alternatives currently in use without efficacy evidence, is an ideal disease state for this goal.

Fibromyalgia syndrome, also labeled FMS or simply fibromyalgia, is an idiopathic, functional disorder characterized by chronic widespread pain and diffuse tenderness.[2] This disorder affects over 6 million patients in the United States and is associated with significant clinical and economic burden to patients, the healthcare system, and society as a whole. Over the past decade a troubling trend has manifested, the increased

prescribing and utilization of opioids for the treatment of chronic nonmalignant pain.

In his book *Powerful Medicines*, Dr. Jerry Avorn describes medication use according to a triad of characteristics: benefits, risks, and costs. By applying this theoretical framework to chronic opioid use in fibromyalgia syndrome, a clear case against their use can be formulated. The benefits of use of these medications in this disorder are not clear. There is no evidence supporting the efficacy of opioid use in this disorder. The risks associated with use of these medications are severe and varied; both personal and societal risks are described in detail below. Finally, the costs of opioid use in this population are negligible when only the prescription cost is considered. However, when considering treatment failure, adverse effects, and indirect costs, both to the individual and society, the cost becomes a serious concern.

There are several characteristics, physiological and clinical, that separate fibromyalgia patients from those with general chronic nonmalignant pain. Though the theoretical case against use of this therapy choice is strong, there is a lack of evidence specifically comparing utilization and cost characteristics of patients using opioids chronically in this disease state and those receiving evidence-based therapy.

Treatment of fibromyalgia syndrome typically focuses on the two most troublesome aspects of the disorder: pain and lack of restorative sleep. Treatment is generally multimodal, consisting

of pharmacologic agents and non-pharmacologic therapies such as massage or acupuncture. According to a 2004 review published in the *Journal of the American Medical Association*, pharmacologic therapies for fibromyalgia can be divided according to the level of existing efficacy evidence: strong, modest, weak, or none.[21] In addition to classifying medications with moderate and strong evidence for efficacy, the authors of the 2004 clinical review on fibromyalgia treatment also described classes of medications with no evidence for efficacy. The following medication classes were designated as such: corticosteroids, non-steroidal anti-inflammatory drugs, benzodiazepines, and other hypnotics. Opioid analgesics are also included in this category. However, despite the lack of evidence supporting the use of opioids for the treatment of fibromyalgia, evidence suggests widespread and increasing clinical utilization.[4]

Opioid use in chronic nonmalignant pain is a divisive subject in the current literature. Current guidelines suggest guarded use of opioids chronically in nonmalignant pain and these recommendations are based on moderate quality evidence at best.[32] The use of opioids chronically in fibromyalgia patients deserves extra scrutiny for several reasons. First, the use of opioids in fibromyalgia patients ignores the complicated presentation of the disorder discussed above. Although opioids may temporarily control the pain experienced in this disorder, their use ignores the other aspects of the disorder including non-restorative sleep, fatigue, and irritable bowel.

Patients suffering from fibromyalgia may also have altered endogenous opioid activity. A study utilizing positron emission tomography found that patients suffering from fibromyalgia syndrome exhibit decreased mu-opioid receptor availability in areas of the brain key to pain and nociception processing.[48] There are two possible explanations for the demonstrated reduced availability. First, endogenous enkephalins levels are elevated in patients with fibromyalgia, even when compared to patients suffering from chronic low back pain.[49] Elevated endogenous ligands in these patients may explain the reduced availability of receptors to opioids, decreasing their effectiveness in fibromyalgia patients. Another possible explanation is the increased presence of endogenous ligands may lead to down regulation of opioid receptors.

Not only is the failure rate of opioid use a greater concern in patients with fibromyalgia, there is also an increased concern of misuse or abuse among this population due to characteristics commonly seen in these patients. Risk factors commonly associated with nonmedical use of opioids include anxiety and mood disorders, each a common comorbidity seen in patients with fibromyalgia.[50] In addition low self-rated health status, commonly seen in fibromyalgia, increases the propensity toward misuse or abuse of opioids.[50]

Beyond these reasons there is also increased concern of adverse effect presentation in patients with fibromyalgia for several reasons. Fibromyalgia patients report adverse effects and

intolerance to treatment at elevated rates.[51] In addition to the increased reporting of adverse effects in general there are also concerns with the way certain specific adverse effects seen with opioid use may affect fibromyalgia patients. Constipation is a hallmark effect seen with opioid use and may be of increased concern in patients suffering from the irritable bowel symptoms commonly associated with fibromyalgia. Other adverse effects such as sedation and mental clouding are also of particular concern in patients with fibromyalgia due to the possible pre-existing presence of these problems due to the disorder.

Despite all these concerns, the use of opioids in the treatment of fibromyalgia continues with 37.4% of patients receiving short-acting opioids and 8.3% receiving long-acting opioids with an average of 124 and 243 days of therapy annually, respectively.[51]

There have been no previous studies into the effect of this treatment choice on healthcare costs associated with fibromyalgia syndrome. However, unpublished work by this author shows that variation exists in geographic location, diagnosing provider type, comorbid conditions, and concurrent medications among fibromyalgia patients receiving chronic opioid therapy compared to those who are not.[72,85,86,91] Given this variation identification of the effect of chronic opioid use on healthcare costs is a difficult endeavor.

In order to isolate the effect of this treatemnt choice in fibromyalgia patients we will employ a difference-in-difference

model that examines the difference seen in costs associated with chronic opioid use in fibromyalgia patients compared to the difference seen in control patients. Using this technique, we predict that both medical and prescription costs for fibromyalgia patients receiving chronic opioid therapy will be significantly elevated. The introduction of well-matched pairs will temper the difference between cases and controls but fibromyalgia patients receiving chronic opioid therapy will have significantly greater costs than their matched counterparts.

B: Materials and methods

Data source

The University of Kentucky Institute for Pharmaceutical Outcomes and Policy has a licensing agreement for the i3 Invision Data Mart (IVDM) for the years 2007-2009. We obtained patient information from January 1, 2007 to December 31, 2009 from the IVDM. The IVDM is a nationally representative de-identified sample of 15 million patients from commercial health plans across the United States. Data are collected at the patient level, and consist of eligibility and enrollment information (eligibility date, eligibility span, health plan type), demographic information (gender, age, state), medical claims (inpatient, outpatient, professional services, including ICD-9-CM, DRG, CPT-4, revenue code and links to participating providers), pharmacy claims (prescriber, NDC, day supply, quantity), and laboratory claims (type of test and results) for approximately 15 million

patients each year. For the purposes of this study the entire three-year data slice was considered as a single cross-section.

Study cohort definitions

The dataset was queried for patients with fibromyalgia syndrome as identified by *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-CM-9) code 729.1 (myalgia and myositis unspecified). Patients with at least one claim between January 1, 2007 and December 31, 2009 were included in the sample. Only patients between ages 18 and 64 were considered for this study. The reasons for this restriction are utilization patterns may differ for children, and missing data problems are more common for those eligible for Medicare. Patients with malignancies were excluded from analysis because medical care patterns may differ for these patients. The University of Kentucky Institutional Review Board provided approval for this study.

A control group was selected using the same inclusion and exclusion criteria used for the patients except where ICD-9 code 729.1 was used for the identification of fibromyalgia syndrome a list of ICD-9 codes was used for identification of controls with similar disease states. The list of diseases and corresponding IDC-9 codes can be found in Table 1.

Outcome variables

Two outcome variables of interest were collected: medical costs and prescription costs. These were collected based on medical and prescription charges collected in the IVDM. Charged

amounts were used in all analyses of healthcare costs. Charges were summed at the patient level and then annualized to control for differing eligibility spans across the sample. The top and bottom one-percent of annualized medical and annualized prescription charges were dropped to control for outliers.

Independent variables

Independent variables were collected at the state, provider, and patient level as described previously.[72,85,86] The variables were used to develop a propensity index using logistic regression coefficients. Propensity to be diagnosed with fibromyalgia syndrome and treated with chronic opioid therapy was determined from these variables and then using a simple matching algorithm a one-to-one match was constructed of fibromyalgia patients and controls.

Data analysis

Natural log of medical and prescription costs were examined due to the skewness of cost data unless otherwise noted. The difference-in-difference of cost outcomes is determined in two methods. The first is difference-in-difference by ordinary least squares. This method assumes fixed effects for chronic opioid use and fibromyalgia with an interaction between the effects. With these assumptions a simple linear regression of the fixed effects and the interaction will difference attributable to chronic opioid use in this disease state. The second method uses the propensity for a patient to be diagnosed with fibromyalgia syndrome and treated with chronic opioid therapy to match

patients to controls. After matching the statistical significance of cost differences between fibromyalgia patients receiving chronic opioid therapy and controls was calculated using two-group t-tests before and after the matching algorithm was carried out. Data extraction was completed using Oracle SQL Developer and SAS v10, the matching process was carried out using Fortran, and all statistical analyses were completed in STATA v12.

C: Results

A total sample of 2413778 was identified in the IVDM as meeting inclusion criteria. Of these 50159 were fibromyalgia patients receiving chronic opioid therapy. The comparison of various independent variables in these two groups can be seen in Table 2. Table 2 also reports logistic regression coefficients used to match fibromyalgia patients receiving chronic opioid therapy to controls based on propensity to meet both of these conditions, and the resulting independent variables for matched patients and controls. Differences in these variables that are significant at $p < 0.05$ are denoted with an asterisk as are statistically significant logistic regression coefficeints. Although many independent variables remain different for the 48333 matched pairs of patients and controls the coefficient of variation among of the variables as a whole is decreased from 50% to 5%.

The difference-in-difference for fibromyalgia patients receiving chronic opioid therapy compared to others was derived via two methods. The first utilized a simple linear regression

that took into account fibromyalgia status, chronic opioid therapy receipt, and the interaction between the two. Using this limited variable set we found that the difference-in-difference attributable to chronic opioid therapy in fibromyalgia syndrome is 7.3% for annual medical charges and 1.3% for annual prescription charges.

To better grasp these differences we then used a propensity score matching technique to identify 48333 pairs of individuals who were matched based on their propensity to be fibromyalgia patients receiving chronic opioid therapy. Matching results in a sample that is an average of 47 years old and that is three-fourths female. As expected in a population with fibromyalgia patients receiving chronic pain treatment, many pain comorbidities are present at rates elevated from the general population, including back pain, neuropathic pain disorders, as well as fatigue and sleep disorders. We also see that medication classes typically used to treat these disorders see increased use: these include benzodiazepines, NSAIDs, hypnotics, and muscle relaxants. Diagnosing provider varies but primary care physicians as well as anesthesiologists (pain treatment), rheumatologists, and neurologists are abundant. Geographic variation between patients and controls varies by state but is controlled well by the matching process.

Overall, medical costs were higher for fibromyalgia patients receiving chronic opioid therapy both before and after the matching process. Fibromyalgia patients receiving chronic

opioid therapy had annualized medical costs of $28552 for the total patient sample of 50159 compared to $12946 for the 2363619 controls. This is a 120% elevation in annualized medical costs for patients over controls before the propensity score matching. After matching, we see medical costs of $28209 for 48333 fibromyalgia patients and $24471 for their matched pairs. This is a difference of only 15%; nearly a 90% reduction in the difference is seen.

Similar results are seen for prescription charges, though larger differences are seen. Before matching fibromyalgia patients receiving chronic opioid therapy had mean annualized prescription charges of $7075, compared to only $1968 for controls. This is a 260% difference between patients and controls. After matching the charges are $7012 and $4861, respectively. This is a difference of only 44% and represents a reduction of over 80% as a result of the matching process.

D: Discussion

Little reseach has been done looking at the effect of treatment using chronic opioid therapy in patients suffering from fibromyalgia syndrome. Although anecdotal evidence suggests that response to this therapy is poor,[51] the true effect is unknown. This study is novel for the fibromyalgia literature for several reasons. It is the first study to attempt to see the unique effects that may be present in fibromyalgia patients being treated with opioids chronically, it is the first to utilize an

extenisive propensity score to isolate this effect, and it is the first to examine the economic outcomes of this treatment choics.

Fibromyalgia patients present with a unique pathophysiology that is not fully understood. Many of the characteristics that set this disease apart from other neuropathic disorders also increase the concern associated with the use of opioids chroncically for these patients. Because of this we set out to see if fibromyalgia patients treated with chronic opioid therapy would be affected to a greater extent than others as indicated by increased medical and prescription costs.

We had two sets of findings. The first uses the principles ordinary least squares to isolate the interaction of chronic opioid therapy in fibromyalgia patients above the effects seen from fibromyalgia or chronic opioid therapy individually. This approach showed that, in addition to the increase seen in consequences associated with chronic opioid use or fibromyalgia, the interaction of the two, or the difference-in-difference, was 7.3% annually for medical charges and 1.3% for prescription charges. This represent nearly $2000 in medical costs and $100 in prescription costs annually.

Our second set of findings utilized propensity score methods to balance patients and controls based on their propensity to be a fibromyalgia patient receiving chronic opioid therapy. Propensity score matching allowed us to balance these patients across a large number of observed variables, resulting in 48333 matched pairs of individuals. We predicted that the

costs associated with chronic opioid use in fibromyalgia patients would be tempered through the use of well-matched pairs but would still represent a significant portion of both annual medical and prescription costs. This was shown to be the case, as even after the use of propensity score matching, chronic opioid therapy in patients suffering from fibromyalgia syndrome was associated with a 15% increase in annual medical costs and a 44% increase in annual prescription costs.

E: Limitations

These two sets of findings may seem to be at odds with each other. However, the first approach using ordinary least squares assumes fixed effects for both fibromyalgia syndrome and chronic opioid use with an interaction term, while the propensity score model does not require these assumptions. The propensity score model balances patients and controls across all observed factors while the difference-in-difference model utilizes the entire sample.

Aside from the assumptions imposed by the ordinary least squares model other limitations to these findings exist. Limitations generally applicable to secondary database research such as the possibility of miscoding and the use of charges as a proxy for actual healthcare costs are applicable here. In addition, the validity of ICD-9 code 729.1 as an identifier of fibromyalgia within the IVDM has not been validated, however the decision to use the code is consistent with previous research done in this area. Finally, there is a possibility of

“overmatching” due to the lengthy list variables controlled for in the propensity score. Each group of variables has been shown to vary significantly among fibromyalgia patients, however.[72,85,86] Given this variation and the large number of matched pairs available for analysis however “overmatching” is not a significant concern.

F: Conclusions

Both medical and prescription costs were shown to be significantly elevated in patients suffering from fibromyalgia syndrome and receiving chronic opioid therapy, even when using a well-matched group of controls. The propensity score used for matching reduced variation across independent variables by 90%; however, costs remain elevated by 15% for medical costs and 44% for prescription costs. There is no literature currently available examining the effect of chronic opioid therapy in fibromyalgia syndrome, unpublished work by this author though shows that in well-matched individuals a fibromyalgia diagnosis results in a 1% increase in annual medical costs and 5% increase in annual prescription costs. These differences are an order of magnitude smaller than the differences associated with chronic opioid therapy in these individuals.

Given the theoretical balance of risk and benefits associated with chronic opioid therapy in fibromyalgia syndrome the detrimental effect of this treatment choice is not surprising. This study is the first to provide strong evidence of increased healthcare costs associated with the utilization of

chronic opioid therapy, a practice not supported by evidence, in patients suffering from fibromyalgia syndrome.

The effect the interaction of chronic opioid therapy and fibromyalgia has on healthcare costs is a complicated issue. Taking the finding of this chapter in the context of the previous seven chapters is necessary. Chapter 9 will summarize the results and conclusions of each of the previous chapters and explain how these findings fit together, as well as how they fit into the greater fibromyalgia literature.

Table 8.1: List of disease states used for control identification

Diseases of the musculoskeletal system	
--Back pain	722.92-722.93, 722.4-722.5, 722.81, 722.91, 723.1, 723.5-723.6
--Arthritis	711.00-716.xx
Symptoms, signs and ill-defined conditions	
--Fatigue	780.71, 780.79
--Headache	784
--Chest pain	786.5-786.5x
--Abdominal pain	789.0-789.0x
--Anxiety-related symptoms	780.4, 785.0-785.1, 786.01, 786.05, 786.09
--Gastric-related symptoms	787.0, 787.01-787.03, 787.1-787.3, 787.9, 787.91, 787.99
Painful neuropathic disorders	
--Diabetic neuropathy	250.6x, 357.2
--Post-herpetic neuropathy	531.x
--Back pain with neuropathic involvement	721.41-721.42, 721.91, 722.1, 722.10, 722.11, 722.2, 722.70, 722.72-722.73, 724.0x, 724.3, 724.4
--Neck pain with neuropathic involvement	721.1, 722.0, 722.71, 723.0, 723.4
--Causalgia	337.2x, 353.2-353.4, 354.4, 355.7x, 355.9, 729.2
--Phantom limb pain	353.6
--Trigeminal neuralgia	350.1
--Atypical facial pain	350.2, 352.1
--Other painful neuropathies	353.0, 353.1, 353.8, 353.9, 354.0-354.5, 354.8, 354.9, 355.0-355.6, 355.8

Table 8.2: Patient characteristics, before and after propensity score match

	All		Pr(FMS)	Matched	
	Control	FMS,Op		Control	FMS,Op
	Demographics				
Female	0.619	0.738*	0.002*	0.730	0.735
Age	44.5	46.8*	0.058*	46.9	46.8
	Comorbid conditions				
Diabetes	0.110	0.146*	0.008	0.145	0.146
Anxiety	0.158	0.345*	0.009	0.333	0.340*
Depression	0.120	0.294*	-0.010	0.278	0.289*
Tension headache	0.025	0.050*	-0.056*	0.048	0.049
Migraine	0.088	0.268*	0.244*	0.248	0.262*
Circulatory system	0.451	0.591*	0.021	0.586	0.588
Respiratory system	0.645	0.705*	-0.169*	0.693	0.703*
GERD	0.176	0.282*	-0.050*	0.271	0.279*
Gastritis	0.001	0.001*	-0.047	0.001	0.001
Back pain	0.352	0.492*	-0.026*	0.489	0.487
Arthritis	0.200	0.446*	0.595*	0.430	0.441*
Fatigue	0.289	0.457*	0.077*	0.438	0.453*
Headache	0.001	0.001*	0.391	0.001	0.001
Chest pain	0.223	0.322*	-0.084*	0.311	0.320*
Abdominal pain	0.256	0.392*	0.020	0.382	0.389*
Anxiety-related	0.251	0.358*	-0.148*	0.344	0.355*
Gastric-related	0.182	0.328*	0.040*	0.315	0.323*
Diabetic neuropathy	0.017	0.026*	-0.135*	0.026	0.025
Post-herpetic	0.005	0.014*	0.221*	0.014	0.014
Back pain with	0.293	0.484*	0.246*	0.487	0.479*
Neck pain with	0.151	0.279*	0.184*	0.270	0.274
Causalgia	0.084	0.185*	0.136*	0.180	0.181
Trigeminal	0.003	0.007*	-0.035*	0.007	0.007
Atypical facial	0.004	0.010*	0.067	0.009	0.010
Other neuropathic	0.114	0.171*	-0.081*	0.167	0.169
Sleep disorders	0.151	0.326*	0.029*	0.313	0.322*
	Concurrent Medications				
Anticonvulsants	0.149	0.583*	0.937*	0.569	0.572
Benzodiazepines	0.197	0.524*	0.610*	0.514	0.517
Glucocorticoids	0.301	0.446*	-0.077*	0.433	0.442*
NSAIDS	0.413	0.550*	-0.237*	0.545	0.549
Muscle relaxants	0.290	0.674*	0.789*	0.675	0.667*
Hypnotics	0.132	0.381*	0.380*	0.364	0.375*
TCAs	0.048	0.197*	0.418*	0.184	0.192*
SSRIs	0.197	0.387*	0.126*	0.376	0.383*
SNRIs	0.078	0.318*	0.538*	0.293	0.311*
NDRIs	0.057	0.132*	0.024	0.127	0.130
SARIs	0.037	0.149*	0.271*	0.134	0.146*
Triptans	0.056	0.213*	0.575*	0.192	0.207*
Anti-migraine	0.027	0.106*	0.317*	0.093	0.102*
	Practitioner type				
Chiropractor	0.369	0.0	omitted-	0.073	0.087*
General surgery	0.004	0.0	1.209*	0.005	0.006
Emergency medicine	0.025	0.0	1.049*	0.022	0.025*
Family medicine	0.242	0.2	1.183*	0.290	0.282*
Internal medicine	0.141	0.1	1.161*	0.154	0.157
Orthopedic surgery	0.088	0.0	-0.858*	0.011	0.014*
Nurse practitioner	0.002	0.0	1.539*	0.004	0.004
Physician assistant	0.002	0.0	1.615*	0.004	0.004
Rheumatology	0.026	0.0	1.902*	0.087	0.095*
Neurology	0.033	0.0	0.578*	0.040	0.038*
Physical medicine	0.034	0.0	1.712*	0.098	0.092*
Anesthesiology	0.034	0.2	2.13*	0.212	0.197*

Table 8.2: Patient characteristics, before and after propensity score match (continued)

	State				
Alabama	0.007	0.012	0.324*	0.011	0.012
Arkansas	0.009	0.013	0.197*	0.014	0.013
Arizona	0.038	0.048	0.372*	0.048	0.048
California	0.048	0.030	0.005	0.029	0.030
Colorado	0.035	0.034	0.169*	0.035	0.034
Connecticut	0.006	0.005	0.019	0.005	0.005
District of Columbia	0.001	0.001	-0.679*	0.001	0.001
Delaware	0.001	0.001	-0.051	0.001	0.001
Florida	0.110	0.136	0.176*	0.141	0.136
Georgia	0.083	0.072	-0.088*	0.074	0.072
Iowa	0.009	0.008	0.211*	0.007	0.008
Idaho	0.003	0.003	0.264*	0.003	0.003
Illinois	0.028	0.019	-0.041	0.018	0.019
Indiana	0.016	0.021	0.393*	0.021	0.021
Kansas	0.010	0.009	0.180*	0.009	0.009
Kentucky	0.009	0.013	0.457*	0.013	0.013
Louisiana	0.016	0.017	-0.099*	0.016	0.017
Massachusetts	0.010	0.006	-0.140*	0.006	0.006
Maryland	0.018	0.021	0.195*	0.021	0.020
Maine	0.001	0.001	0.066	0.001	0.001
Michigan	0.008	0.008	0.284*	0.007	0.008
Minnesota	0.048	0.033	0.049	0.031	0.033
Missouri	0.038	0.030	0.010	0.030	0.030
Mississippi	0.007	0.011	0.283*	0.010	0.011
Montana	0.001	0.001	0.337*	0.001	0.001
North Carolina	0.034	0.044	0.280*	0.045	0.044
North Dakota	0.002	0.001	0.370*	0.001	0.001
Nebraska	0.008	0.006	-0.011	0.006	0.006
New Hampshire	0.002	0.001	-0.242	0.001	0.001
New Jersey	0.020	0.010	-0.270*	0.010	0.010
New Mexico	0.007	0.007	-0.001	0.007	0.007
Nevada	0.006	0.009	0.545*	0.010	0.009
New York	0.031	0.015	-0.281*	0.015	0.015
Ohio	0.058	0.073	0.300*	0.075	0.073
Oklahoma	0.010	0.012	0.277*	0.013	0.012
Oregon	0.006	0.009	0.570*	0.008	0.009
Pennsylvania	0.014	0.014	0.293*	0.015	0.015
Rhode Island	0.012	0.009	-0.152*	0.010	0.009
South Carolina	0.010	0.013	0.225*	0.012	0.013
South Dakota	0.002	0.001	0.193	0.001	0.001
Tennessee	0.020	0.031	0.468*	0.031	0.031
Texas	0.122	0.116	omitted	0.114	0.116
Utah	0.007	0.012	0.523*	0.011	0.011
Virginia	0.020	0.019	0.136*	0.018	0.019
Vermont	0.001	0.001	-0.447	0.001	0.001
Washington	0.011	0.010	0.159*	0.011	0.010
Wisconsin	0.036	0.032	0.166*	0.031	0.032
West Virginia	0.002	0.004	0.539*	0.004	0.004
Wyoming	0.001	0.001	0.181	0.001	0.001

Figure 8.1: Annualized medical charges, before and after propensity score match

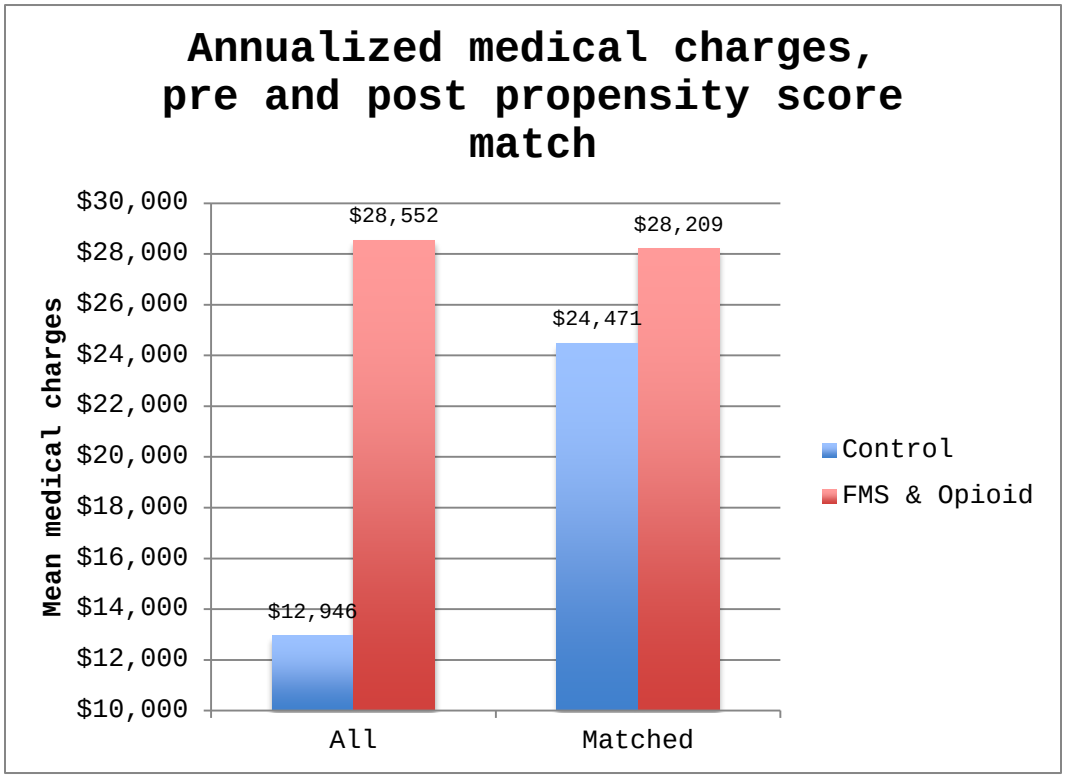
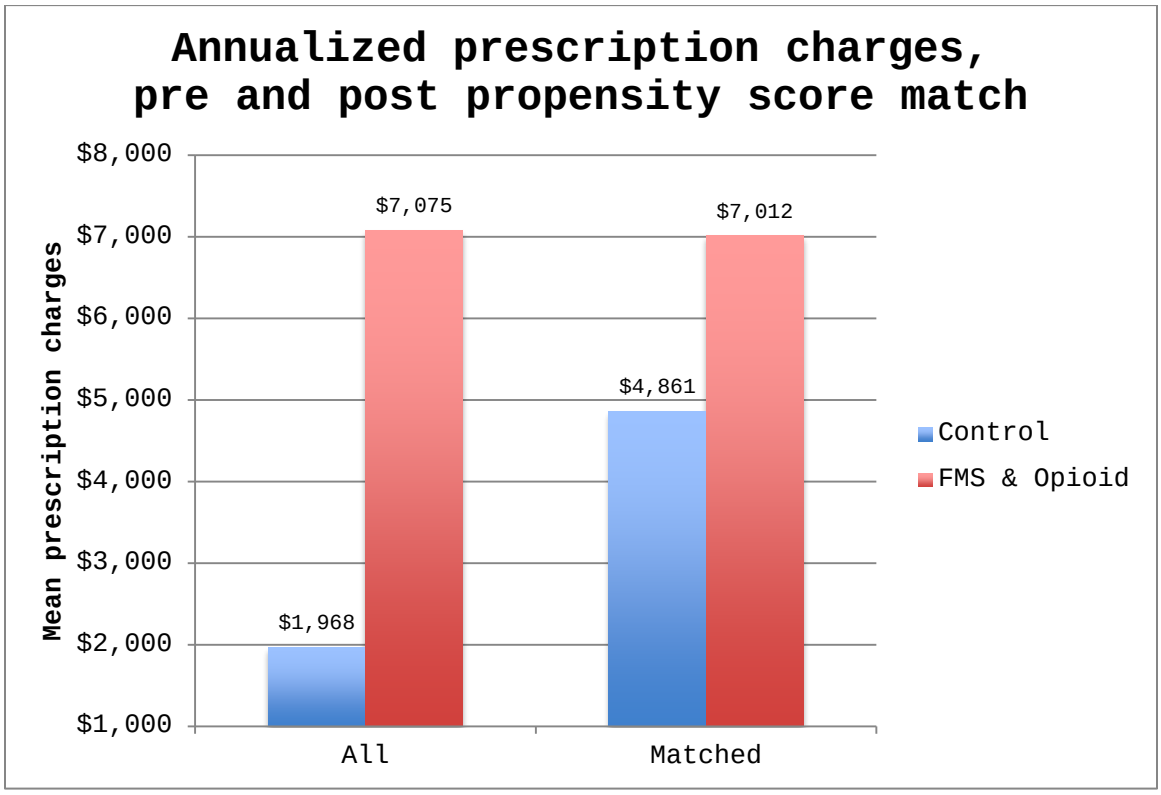


Figure 8.2: Annualized prescription charges, before and after propensity score match



Chapter 9: Conclusion, theory, and contribution to the literature

The treatment of chronic nonmalignant pain currently receives a large amount of attention in the literature. The most contentious issue is the use of opioids chronically in the management of this group of disorders. There is evidence in many chronic nonmalignant pain conditions that shows opioids are effective for symptomatic control. However, the primary clinical concern that divides the treatment of nonmalignant pain from malignant pain is the expected length of treatment course. Initiating a chronic nonmalignant pain patient on opioid therapy may result in the continuation of that treatment, including the inevitable dose increases to counter tolerance, over the lifetime of the patient. There are several reasons for this tendency, including clinical inertia as well as the physical and psychological dependence seen in many patients.

Chronic nonmalignant pain is a term that refers to a wide variety of conditions ranging from low back pain to headache. These conditions also range from purely organic conditions characterized by pain resulting from tissue damage to somatic disorders characterized by suffering and disability rather than specific tissue damage. Given the wide assortment of conditions that this term is applicable to, it is no surprise that the appropriateness of the use of chronic opioid therapy also varies.

Fibromyalgia syndrome is an example of a functional somatic syndrome characterized by abnormal central pain processing. Fibromyalgia is an ideal condition to study chronic opioid use

because, of the chronic nonmalignant pain conditions, fibromyalgia has one of the strongest theoretical cases against the use of opioids chronically. This case is built primarily on the pathophysiology of fibromyalgia patients, which may make them more susceptible to detriment from adverse effects such as opioid-induced hyperalgesia.

The research goals of this dissertation are to identify key characteristics at the structural-, practitioner-, and patient-levels associated with chronic opioid use in patients suffering from fibromyalgia syndrome and to elucidate outcomes associated with this treatment choice. My central hypothesis is that characteristics at the state-, practitioner-, and patient- levels are associated with chronic opioid use, and, independent of these characteristics, chronic opioid use will be correlated with poorer outcomes in fibromyalgia patients. This research track was undertaken for several reasons: (1) the increased use of opioids chronically in nonmalignant pain is troublesome given the individual and societal adverse effects associated with use, (2) fibromyalgia is an ideal condition for this research because of the strong theoretical case against chronic opioid therapy for treatment of this disorder, (3) the theoretical predilection of this patient population for adverse effects associated with chronic opioid use, and (4) the current gap of empirical evidence in the fibromyalgia literature surrounding this topic.

To test my central hypothesis and accomplish the objective of this dissertation the following specific aims were accomplished:

1. Identify characteristics at the state, practitioner, and patient level associated with chronic opioid use in fibromyalgia patients.
2. Determine outcomes associated with chronic opioid use in fibromyalgia patients.

Chapter 1 of this dissertation served as an introduction to fibromyalgia syndrome, chronic opioid use and the interaction of the two in clinical practice. A review of the literature surrounding the use of opioids chronically in fibromyalgia syndrome yields little in the way of empirical evidence. The bulk of the literature surrounding this topic consists of reviews and guidelines, which highlight the lack of evidence supporting the use of opioids in this disease state. Reviews published in *The Journal of the American Medical Association*, *The Journal of Pain*, and *International Journal of Rheumatic Diseases*, each point this out. Guidelines from the American Pain Society, the European League Against Rheumatism (EULAR), and the Association of Scientific Medical Societies (AWMF) each caution against the use of opioids chronically in fibromyalgia syndrome.

There are several reasons for this caution that are made apparent in the literature describing the pathophysiology and behavioral characteristics of fibromyalgia patients. The mechanism of action of opioid agonists only masks the pain

symptoms by treating the pain triggers rather than treating the central pain itself. Contrast this with other medications used in the treatment of fibromyalgia pain, including those approved by the Food and Drug Administration (pregabalin, duloxetine, and minalcipran), which act via central mechanisms to affect the action of afferent or efferent neurons resulting in lessened pain. Beyond the inefficacy of opioids in the treatment of fibromyalgia syndrome there is also concern pertaining to opioid-induced hyperalgesia. This disorder, which results in an independent pain condition separate from the pain the opioid was meant to treat, can occur as a result of opioid use in any pain disorder. However, the pathophysiology of fibromyalgia patients may result in an increased susceptibility to this condition. Each of these concerns shifts the risk-benefit ratio associated with the use of opioids chronically for the treatment of fibromyalgia syndrome away from use.

With a clear theoretical case against the use of opioids chronically in fibromyalgia syndrome, Chapters 2 through 6 set out to identify characteristics that were associated with the use of this treatment choice in patients. Chapters 2 and 3 identified structural characteristics associated with state-level variation in the level of chronic opioid use among patients suffering from fibromyalgia syndrome. The chapters use two different approaches to describe this variation. The first used a three-year cross section of data as a whole. The results of the study suggest that geographic variation in chronic opioid use among patients with

fibromyalgia syndrome is similar to that seen in the previous two studies of opioid use. Factors associated with chronic opioid use at the state-level were generally as predicted based on previous studies. Percentage of patients that were female and previous illicit opioid use rate each were associated with an increase in chronic opioid use among patients. Physician prevalence, state population, percent of the state population between 45 and 64 years of age were all negatively associated with chronic opioid use.

Chapter 3 uses the same data slice described in Chapter 2, but breaks the data into a panel separated by year. The level of variation is constant across the three years with a fivefold difference between states with low chronic opioid use in these patients and those with high use and a coefficient of variation of 36.5%. Using fixed-effects estimation techniques it was shown that within state variation is a significant source of variation overall for this dataset, meaning that identity as a certain state has an association with chronic opioid use in fibromyalgia patients.

The next chapters look at characteristics at higher levels of granularity: provider- and patient-level factors. Chapter 4 demonstrated that chronic opioid use in fibromyalgia patients was strongly correlated with diagnosing provider type. Patients diagnosed by specialists were more likely to be treated with chronic opioid therapy than those diagnosed by primary care practitioners including midlevel practitioners. One very

interesting finding is the very strong negative correlation chiropractic treatment had on chronic opioid therapy.

The following chapter examined patient-level characteristics including demographics such as age and sex, comorbid conditions, and concurrent medications. While age and female sex were both associated with increased chronic opioid use in patients, comorbid conditions and concurrent medications were more complicated. In general, those diseases associated with an independent pain condition are found to have large and positive marginal effects on chronic opioid use in this patient population, while disorders with little correlation with pain such as diseases of the respiratory, digestive, and circulatory system were found to have little association with chronic opioid use. Concurrent medication use was very high in this population with four-fifths receiving a medication other than an opioid in the data. Nearly three-fifths received an opioid prescription during their eligibility, a number significantly elevated over the general population, which generally sees rates of about 20% for annual opioid prescription receipt.

These chapters all built the case that characteristics aggregated at various levels each vary significantly and are associated with chronic opioid use in fibromyalgia patients. The fibromyalgia literature surrounding these characteristics is sparse, but even more troubling is the lack of outcomes studies in these patients. The lack of evidence in this area is the result of several contributing factors; one of the most important

of these is that the use of secondary databases to study fibromyalgia patients suffers from a significant weakness, the identification of a comparable control group. The next three chapters of this dissertation took the characteristics shown to be associated with chronic opioid use in fibromyalgia syndrome and used propensity score techniques to develop an appropriate control group for comparing outcomes.

Chapter 6 took patients with fibromyalgia syndrome and divided them according to their propensity to be chronic opioid users. Patients were stratified into deciles based on this propensity and compared within strata. A comparison of the two groups as wholes resulted in medical costs being 3-times higher for chronic opioid users and prescription costs being 6-times higher. However, inspection of individual strata showed that the relationship between costs and chronic opioid use was a heterogeneous one that varied according to propensity to use chronic opioids. While both medical and prescription costs remain elevated for all groups receiving chronic opioid therapy, as the propensity to receive this therapy increases, the differences seen in cost comparisons decreases.

While Chapter 6 focused on the effect of chronic opioid use within fibromyalgia syndrome, Chapter 7 focused on the cost effects of a fibromyalgia diagnosis. While there is literature previously available showing that fibromyalgia syndrome is associated with a significant disease burden the control groups in these studies are varied and generally lacking in

comparability. To improve on these previous studies, we used an extensive propensity score to match patients based on their propensity to be diagnosed with fibromyalgia syndrome. Matching on this propensity reduces the differences seen in medical and prescription costs by 90%, resulting in differences of 1% and 5% respectively. While the differences seen are still significant the use of a well-matched control population shows that the impact of a fibromyalgia diagnosis on costs is generally overstated.

Finally, Chapter 8 looks at the effect of the interaction of a fibromyalgia diagnosis with the receipt of chronic opioid therapy. Due to the unique theoretical predilection of these patients to have higher medical and prescription costs the difference-in-difference resulting from this interaction was examined. While Chapter 7 showed that a fibromyalgia diagnosis only resulted in a 1% increase in medical costs and a 5% increase in prescription costs, Chapter 8 highlights the large increase seen in costs over an above this increase. Even for well-matched individual balanced on a large set of observed variables, increases of 15% for medical costs and 44% for prescription costs are seen.

The findings of these final two chapters serve to show that although a fibromyalgia diagnosis may result in slightly increased costs for similar patients, the introduction of a treatment alternative that is has a strong theoretical case against use is severely detrimental to the patients receiving the

therapy. The utilization of chronic opioid therapy in the treatment of fibromyalgia syndrome is a practice based not on the evidence available to practitioners but on other variables, both observable and unobservable. The chapters of this dissertation help to fill the gap in the current literature regarding the identification of these characteristics, as well as describing the effects of this treatment choice on patient outcomes. Given the profound lack of evidence supporting the use of opioids in fibromyalgia, their prevalence as a treatment option is mysterious. Couple this lack of efficacy with the increasing armamentarium that does have evidence of safety and efficacy supporting use and with the clear societal and personal adverse effects of chronic use of opioids, and the prevalence of their use in fibromyalgia becomes very troubling. Beyond all of these concerns, which are common to the treatment of most chronic non-malignant pain conditions, the pathophysiology of fibromyalgia and the increased risk of opioid-induced hyperalgesia that results from this pathophysiology, make the use of opioids in this condition ill advised.

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Vita

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Born: March 16, 1984 in Paducah, Kentucky.

Education:

- Attended University of Kentucky
- Obtained Doctor of Pharmacy (Magna Cum Laude) in 2009
- Obtained Master of Business Administration (Summa Cum Laude) in 2009

Professional positions:

- Pharmacist, Sears Holding Corporation
- Teaching assistant, University of Kentucky
- Research assistant, University of Kentucky
- Outcomes researcher, Research and Data Management Center
- Regulatory affairs intern, Procter and Gamble
- Research technician, Radiopharmacy

Publications:

- Painter JT, Fink III JL. Educational innovations: Categories of bulletin board postings designed to increase awareness of contemporary pharmaceutical policy issues. Pharmacy Practice. 2010 8;4:255-259.
- Painter JT, Fink III JL. Using Bulletin Board Postings to Increase Students' Awareness of Pharmaceutical policy Issues. Abstract #180 J Am Pharm Assoc. 2009 (Mar-Apr);49:290.

Posters:

- Painter JT, Talbert J. Risk of Stroke Associated with Antipsychotic Use: A Retrospective Cohort Study. Presented: 2008 ASHP Midyear Clinical Meeting.
- Painter JT, Fink III JL. Using Bulletin Board Postings to Increase Students' Awareness of Pharmaceutical policy Issues. Presented: 2009 APhA Annual Meeting.
- Painter JT, Talbert J. Medication Utilization Patterns in Kentucky Medicaid Patients with Fibromyalgia Syndrome: A Retrospective Cohort Study. Presented: 2009 Academy Health Annual Research Meeting.
- Painter JT, Talbert J. Chronic Opioid Use in Kentucky Medicaid Patients with Fibromyalgia Syndrome. Presented: 2009 ASHP Midyear Clinical Meeting.
- Painter JT, Blumenschein KB. Consumer Willingness to Pay for Pharmacy Services:
- A Review of the Literature. Presented: 2010 International Society for Pharmacoeconomics and Outcomes Researchers.

- Painter JT, Talbert J. The effect of practitioner type on chronic opioid use in patients with fibromyalgia syndrome. Presented: 2010 Academy Health Annual Research Meeting.
- Painter JT. Effect of Prescription Monitoring Programs on Opioid Admission Rate: An HCUP Study. Presented: 2011 International Society for Pharmacoeconomics and Outcomes Researchers.

Presentations

- Clinical, Regulatory, and CMC Learnings from Review of 505(b)(2) Approved Drugs
- Global Risk Management: Understanding the Expectations of EMEA and FDA
- Inflammatory Bowel Disease: Current Therapeutic Landscape
- Introduction to Study Design
- Intoductory Biostatistics I & II
- Presentation of Korsakoff Syndrome
- Probiotics: A Market Overview
- Introduction to Pharmacoeconomics
- Measurement in Research

Honors and awards:

- Phi Lambda Sigma Leadership Honor Society
- Rho Chi 2009 Research Day 1st Place Poster
- Oscar C. Dilly Excellence in Pharmacy Administration Award

Applications submitted:

- Painter JT, Talbert J, & Crofford L. Economic and Clinical Implications of Opioid Use in Fibromyalgia Patients. AHRQ Individual Awards for Postdoctoral Fellows (F32), Submitted: June 2010.
- Crofford L, Painter JT & Talbert J. Medication utilization patterns in fibromyalgia syndrome patients: economic consequences of chronic opioid use. Investigator Initiated Grant, Forest Pharmaceuticals. Submitted: November 2010.

Organization memberships:

- International Society for Pharmacoeconomics and Outcomes Research
- American Society of Health-System Pharmacists
- The Phi Kappa Psi Fraternity
- Academy Health