THE IMPACT OF FIBROMYALGIA ON RESOURCE USE IN THE UK PRIMARY CARE SETTING

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Submitted to the faculty of the University Graduate School
in partial fulfillment of the requirements
for the degree
Master of Science
in the School of Health and Rehabilitation Sciences,
Indiana University

August 2008

Accepted by the Faculty of Indiana University, in partial
fulfillment of the requirements for the degree of Master of Science.

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CHAPTER ONE: THE PROBLEM

Introduction/Background

Fibromyalgia (FMS) is a complex, chronic condition involving persistent and widespread pain of unknown origin. FMS is sometimes mistaken as psychiatric in origin; however, the precise origin and cause of FMS is unknown (Klippel et al., 1998). Worldwide prevalence rates range from 0.18-12%, with 0.18% in the United Kingdom (UK) (Hughes et al., 2006), 2% in the United States (US) (Wolfe et al., 1997), and 12% in Spain (Carmona et al., 2001). In the UK, there is debate over the existence of FMS (Bohr, 1995), and the reluctance of a general practitioner (GP) to diagnose conditions that are poorly defined (Hughes et al., 2006).

Primary symptoms of FMS include generalized muscular pain, multiple tender points, sleep disruption and excessive fatigue. Additional symptoms include headaches, memory and concentration problems, dizziness, numbness/tingling, itching, fluid retention, abdominal cramps or pelvic pain and diarrhea (Hudson et al., 1992). Clearly, these symptoms may have an immense impact on daily life, limiting an individual's functioning and emotional well-being.

Statement of the Problem

Many FMS symptoms mimic those of other diseases; therefore, diagnosis is difficult. Clinical diagnosis of FMS should be based on the American College of Rheumatology (ACR) criteria for FMS. The ACR has developed criteria for FMS that physicians can use in diagnosing the condition. According to ACR criteria, a person is considered to have FMS if he or she reports widespread pain in all 4 quadrants of the body and more than 3 months of excessive tenderness in at least 11 of 18 specific tender point sites on the body (Burckhardt et al., 2005).

There are currently no laboratory tests available to diagnose FMS (National Horizon Scanning Centre, 2005). Even though the ACR criteria are widely accepted in the UK and there is a growing recognition of FMS as a distinct subgroup of chronic pain sufferers, (Fibromyalgia Association, 2004), a survey of occupational and physiotherapists in the UK found that a substantial proportion of therapists (30%) indicated that up to half of their patients, whom they considered to have FMS (based on the ACR criteria), are referred under other diagnostic labels. Therefore, different criteria may be used amongst physicians to diagnose FMS (Sim and Adams, 2003).

The diagnostic and treatment challenges of FMS make it a costly condition to manage. Because many patients affected by FMS are of prime working age, the condition may place a substantial economic burden on both private and public health care systems. Previous US studies have estimated the direct medical costs of FMS using self-reported data from small, community-based samples (Wolfe et al., 1997; White et al., 1999) and employer-based administrative data (Robinson et al., 2003, 2004), however there are no similar studies in the UK.

Purpose of the Study

FMS is associated with significant societal and health care costs. Patients with FMS may repeatedly present to the general practitioner with various symptoms before a definitive diagnosis of FMS is made. As a result, general practitioners may be more likely to diagnose FMS in patients who frequently present with symptoms related to FMS, while patients who meet the diagnostic criteria but who rarely present at the practice may be missed (Ehrlich, 2003). The condition is of unknown etiology, and this, together with the lack of verifiable diagnostic criteria (i.e. lab tests), has led some to speculate that the disease does not or is at best a surrogate marker for underlying psychosocial problems. As such, the very process of diagnosing a patient with FMS may exacerbate symptoms and lead to increased dependence on health care providers (Ehrlich, 2003). This study

examined the diagnoses of FMS made in "real-life" clinical practice and recorded by general practitioners in a large primary care population in the UK.

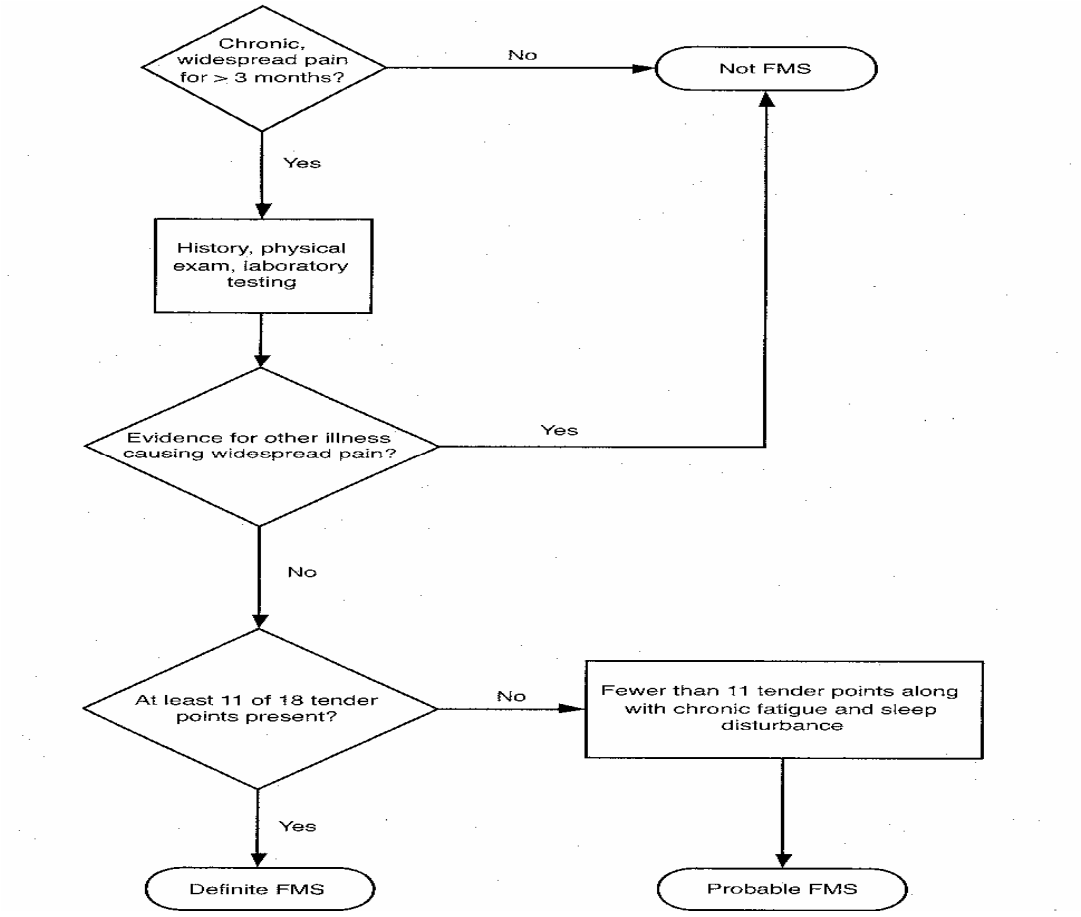
There were 8 US studies that evaluated the economic impact of FMS; however, only 1 study characterized resource use among FMS patients and no study was found in the literature that evaluated the direct cost of FMS in the UK. Due to the gap in the literature on the impact of FMS in the UK, the primary objectives of this study were to characterize patterns of medical and pharmacy resource utilization and associated costs for patients with FMS and compared levels of resource utilization before and after the FMS diagnosis. The secondary objective was to describe the characteristics of the patient population in terms of its epidemiology, demographics, and comorbidities. This pre-post study was designed to determine if a diagnosis of FMS will have a significant impact on the medical and pharmacy resource utilization of this patient population.

Rationale and Theoretical Frameworks

The assumption that FMS impacts medical and pharmacy costs was based on several theoretical frameworks: definition of FMS, clinical presentation, diagnosis, and treatment guidelines. FMS was defined as the presence of widespread chronic pain (for > 3 months) and the presence of excess tenderness to manual palpation of at least 11 of 18 specific muscle-tendon sites obtained through a manual tender point examination. The ACR created the criteria for the diagnosis of FMS. The criteria are: a history of widespread pain (i.e., bilateral, above and below the waist, and axial pain) and the presence of excessive tenderness on applying pressure (digital palpation with approximately 4 kg of force) at 11 or more of the following 18 specific bilateral tender point sites:

Bilateral Tender Point Sites
1. Occiput: bilateral, at the subocciptal muscle insertions
2. Low cervical: bilateral at the anterior aspects of the intertransverse spaces at C5-C7
3. Trapezius: bilateral, at the midpoint of the upper border
4. Supraspinatus: bilateral, at origins, above the scapula spine near the medical border
5. Second rib: bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces
6. Lateral epicondyle: bilateral, 2 cm distal to epicondyles
7. Gluteal: bilateral, in upper outer quadrants of buttocks in anterior fold of muscle
8. Greater trochanter: bilateral, posterior to the trochanteric prominence
9. Knee: bilateral, at the medial fat pad proximal to joint line

Figure 1: Algorithm used for the Assessment of Patients with Widespread Pain



Source: Burckhardt CS et al. Guideline for the management of FMS syndrome pain in adults and children. APS Clinical Practice Guidelines Series, No. 4. Glenview, IL: American Pain Society; 2005.

The ACR definition for FMS is widely accepted in the UK and a mandatory medical terminology coding system is used in primary care settings. Once a patient has been diagnosed with a FMS, the GP codes the diagnosis electronically using a Read/Oxford Medical Information System codes N248.00, N239.00, 7339F for "Fibromyalgia" or N241200 for "Fibromyositis, not otherwise specified". Each term of the Read code identifies a symptom, sign, or diagnosis. The Oxford Medical Information System (OXMIS) codes preceded Read codes and were used until the late 1990s. Read codes are based on codes in the International Classification of Diseases, 9th Revision (ICD-9) (Hughes et al., 2006).

The clinical features of FMS may include widespread pain with allodynia and hyperalgesia, persistent fatigue, feeling of weakness, sleep disturbances, morning stiffness, bowel and bladder irritability, mood disturbances, cognitive difficulties (e.g., memory, concentration), dyesthesia/paresthesia, chronic rhinitis, palpitations, auditory/vestibular/ocular complaints, regional pain (e.g., headache, atypical chest pain, pelvic pain, temporomandibular disorder, myofascial pain), and joint swelling (Hudson et al., 1992; Winfield et al., 1999; Geisser et al., 2003).

Many FMS symptoms are also associated with such syndromes as chronic fatigue syndrome (CFS), migraine and tension-type headaches, irritable bowel syndrome, or depression (Hudson et al., 1992). People with CFS and FMS have a wide range of symptom fluctuations and disability (from exercise intolerance to bed-bound confinement) as well as high levels of psychiatric morbidity (Leslie et al., 2000). The primary symptom of CFS is fatigue whereas pain is the primary symptom for FMS (Fukuda et al., 1994). CFS was defined as at least six months of persistent debilitating fatigue not attributable to any identifiable medical condition and at least four secondary symptoms such as post-exertional malaise, neurocognitive difficulties, sleep disturbance, multiple joint pains, or flu-like symptoms (Fukuda et al., 1994). Diagnosis for both of these syndromes is based primarily on patient-reported symptoms. However, using factor analysis of symptoms, it appears that CFS and FMS can be distinguished (Robbins et al., 1997). They also respond differently to the treatment interventions which may be another way to differentiate them.

Since FMS cannot be cured, the goal of treatment is to relieve symptoms and restore normal function. The treatment should initially focus on verifying the diagnosis of FMS, validating the symptoms, and involving the patient in disease management. It is also important to identify comorbid conditions and take them into account when creating a treatment regimen. A FMS treatment regimen should incorporate both pharmacological and non-pharmacological treatments. The most important non-pharmacologic treatment is education. Patients need to be educated about the disease, treatment options, and pain management. Referral to physical therapy or cognitive-behavioural therapy may be

appropriate for patients with persistent symptoms. Exercise, both aerobic and muscle-strengthening, is another non-pharmacologic treatment often prescribed to FMS patients (Burckhardt et al., 2005).

FMS is a complex syndrome associated with significant impairment on quality of life and function and substantial financial cost. Although its cause is not well understood, it is clear that interdisciplinary approaches to its management are probably the most beneficial. Therefore, once the diagnosis is made, providers should aim to increase patients' function and minimize their pain complaints. This can be accomplished through different non-pharmacological and pharmacological interventions.

Delineation of the Research Problem

Since FMS is so complex and no objective clinical markers exist to diagnose the condition, some practitioners may not recognize the syndrome or may view the condition as a psychiatric disorder or as simply not credible. As a result, patients are left feeling confused and frustrated and are often left to cope with symptoms and the related impact on their own. The majority of FMS patients have been found to reduce activities and spend at least one day in bed during a 2-week period because of health symptoms (Wolfe et al 1995). FMS patients in the US have self-reported disability rates between 6.3% and 23% (Wolfe, 1996). In the study by Bernard et al. (2000), they found that 53% of their sample stated that they were no longer working after a diagnosis of FMS. Of these respondents, 57% stated that their exit from the workforce was a direct result of FMS.

A 1993 study investigated the functional impact of FMS in a large number of UK patients. Seventy-two patients suffering from primary FMS syndrome were reviewed at a mean of 4 years following diagnosis. Levels of both anxiety and depression were high in most patients, as measured by the Hospital Anxiety and Depression Scale (HADS), but in general, patients had higher levels of anxiety than depression. Functional status, evaluated by the HADS and Steinbroker index, was impaired in many patients, evidenced

by 32% describing themselves as heavily dependent on disability and 50% had stopped working as a result of FMS. These results clearly showed that functional impairment still existed at a median of 4 years follow-up, and anxiety and depression were highly correlated with severity of FMS (Ledingham et al., 1993).

FMS is also associated with a high level of health care costs. A US study (Robinson et al., 2004) found that FMS claimants had 2.6 times more medical claims than the average beneficiary. In addition, 45% of the FMS claimants had at least one claim for other diseases of the 'musculoskeletal and connective tissue' compared to 16% in the sample of average beneficiaries and were more likely to use prescription medications. Approximately 76% of FMS claimants were seen a least once by a GP over a years time period.

Statement of Hypothesis

The primary hypothesis of this study was that FMS patients will have an increase in medical and pharmacy resource utilization and direct medical costs during the 12 month period after diagnosis. A study by Hughes et al. (2006) investigated the impact of a diagnosis of FMS in clinical practice on health care resource use in the UK. The study suggested that total clinical visits to a GP in primary care were found to be considerably higher in the FMS cases compared with matched controls for at least 10 years prior to diagnosis and rose sharply from 3 years prior to diagnosis, to 2,500 visits per 100 person-years. Overall rates of referrals were also significantly higher in FMS cases compared with controls and following FMS diagnosis, referral rates declined considerably. Referrals to rheumatologists dropped to near the control levels by 4 years following diagnosis.

Importance of the Study

The diagnostic and treatment challenges of FMS make it a costly condition to manage. Because many patients affected by FMS are of prime working age, the condition may place a substantial economic burden on both private and public health care systems. Previous US studies have estimated the direct medical costs of FMS using self-reported data from small, community-based samples (Wolfe et al., 1997; White et al., 1999) and employer-based administrative data (Robinson et al., 2003; 2004). In a 2006 UK study, researchers analyzed data from the General Practice Research Database (GPRD) and found that FMS patients had higher total clinical visits for at least 10 years prior to diagnosis compared to controls (Hughes et al., 2006).

Definition of Terms

Direct Medical Cost

Direct medical cost will be defined as the paid amount associated with the FMS diagnosis during the study period.

Direct Medical Visits

Direct medical visits will be defined as the number of medical utilizations associated with the FMS diagnosis.

Direct Pharmacy Cost

Direct pharmacy cost will be defined as the drug cost associated with the FMS diagnosis during the study period.

Discontinuation

Discontinuation will be defined as having > 60 day gap between exhaustion of previous fill supply and the end of the follow-up period: (follow-up period end date)-(last prescription fill date + day's supply) > 60 days.

Length of Therapy

Length of therapy will be defined as: (last medication prescription fill date + days' supply) - (first medication prescription fill date)

Scope of the Study

This study describes the characteristics of the FMS patient population in terms of its epidemiology, demographics, and comorbidities; characterized patterns of medical and pharmacy resource utilization and associated costs for patients with FMS; and compared levels of resource utilization among FMS patients 12 months before and 12 months after the initial diagnosis.

CHAPTER TWO: REVIEW OF RELATED LITERATURE

Overview

FMS patients present with numerous symptoms including widespread pain with allodynia and hyperalgesia, persistent fatigue, feeling of weakness, sleep disturbances, morning stiffness, bowel and bladder irritability, mood disturbances, cognitive difficulties, dyesthesia/paresthesia, chronic rhinitis, palpitations, auditory/vestibular/ocular complaints, regional pain and joint swelling (Hudson et al. 1992; Winfield, 1999; Geisser et al. 2003). Clinical diagnosis is based on ACR criteria of FMS.

The overall prevalence of FMS is 2.0% (between 1990 and 1995) in the United States. FMS is more prevalent in women than men (nearly 7-fold more common). The prevalence of FMS increases with age: for women from 2% in the age range 30-39 years to 7% in the age range of 70-79 years and for men 0.2% in the age range 30-39 years to 1.2% in the age range of 70-79 years (Wolfe et al., 1996; Wolfe et al., 1999).

Although ACR has clearly defined diagnosis criteria, in the United Kingdom (UK), there is still a debate over the classification of FMS as a physiological instead of a psychological condition (Bohr, 1995). As a result, UK prevalence estimates of FMS are lower than those for other countries. Hughes et al. (2006) estimated the overall prevalence of recorded FMS diagnoses to be 0.18% in a large primary care population in the UK.

Historic Background

FMS was first documented rigorously in the 1970s (Smythe, 1972). In 1990, the American College of Rheumatology (ACR) established classification criteria for FMS (Wolfe et al., 1990). These criteria are the basis for diagnosing and classifying FMS in the US, UK, Italy, Germany, Spain and Sweden. France's medical community differs from those of other countries for endorsing the 1992 Declaration of Copenhagen

approach to FMS diagnosis (Jacobsen et al., 1993). The Declaration recommends using the two criteria established by ACR for research purposes, but permitting clinical flexibility on the tender point requirement when patients exhibit other symptoms of FMS.

According to the World Health Organization (WHO) International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) (2005), the diagnostic code for FMS is 729.1 (myalgia and myositis, unspecified). Following the establishment of FMS as a distinct diagnosis in the 1992 Declaration of Copenhagen, FMS was incorporated in the WHO's 10th Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) (1994). FMS (with fibrositis) appears in ICD-10 as "M79-O Rheumatism, unspecified", one of the many soft-tissue disorders not specified elsewhere.

FMS is a syndrome of unknown etiology. Evidence shows that factors like stress and medical illness can be influential in the presentation of FMS' in some but not all patients. A variety of neurotransmitter and neuroendocrine changes accompany FMS. These changes include reduced levels of biogenic amines, increased concentrations of excitatory neurotransmitters, alterations of hypothalamic-pituitary-adrenal axis and autonomic nervous system activity (Mease et al., 2005).

Despite the lack of understanding of the causes of FMS, researchers are beginning to connect various theories that seek to explain the symptomatology of the condition. In recent years, research has focused on the neuroendocrine axis and its involvement in FMS. Altered patterns of basal and stimulated activity of several neuroendocrine axes have been discovered in FMS patients (Neeck et al., 2000). Researchers have noted that many FMS symptoms overlap with symptoms associated with neuroendocrine hormone deficiencies such as adult growth hormone deficiency and hypothyroidism (Burckhardt et al., 2005).

Substance P is a neurotransmitter of pain, specifically type C pain fibers which are associated with slow or chronic pain. Researchers found that FMS patients have

approximately threefold higher concentrations of substance P when compared to healthy people (Russel 1994). In FMS patients it is suspected that substance P promotes the spread of slow pain and increases pain transmission (Lash et al., 2003). Decreased levels of norepinephrine have been found in FMS patients and therefore it is also implicated in the etiology of FMS.

A dysfunction in the neurotransmitter, serotonin, is also among the possible etiologies of FMS. Tryptophan is serotonin's precursor and together they ease pain and induce sleep. Studies have shown that levels of serotonin and tryptophan are low in FMS patients (Lash et al., 2003).

Because the prevalence of FMS is higher in women, there has been speculation that sex steroid hormones may play a role in its etiology. However, no data suggests that altered ovarian hormone levels are a causative factor. In one study, pituitary and ovarian hormone levels and secretory patterns were measured in menstruating women with FMS during the follicular phase and were found to be normal (Korszun et al., 2000).

Review of Similar or Related Studies

Epidemiology

It is important to have established criteria for FMS in epidemiological research. Consensus criteria for FMS were developed in 1990 (Wolfe et al., 1990). Prior to 1990, the signs and symptoms of FMS were classified and reclassified several times under various diagnostic labels (including fibrositis, psychogenic rheumatism, myogelosis, and muscle pain syndrome). As a result, epidemiological research was hampered. Since 1990, the criteria for FMS have become more standardized and epidemiological studies using the ACR criteria have been initiated (Linaker et al., 1999). There is only one large scale epidemiological survey (Wolfe et al., 1995) study and 2 administrative database studies (Robinson et al., 2003; Robinson et al., 2004) of FMS in the US. Based on Wolfe's mail survey of 3,000 adults the overall prevalence of FMS is 2.0% in the US.

Table 1: Prevalence Estimates of Fibromyalgia in the United States

Reference	Population	Prevalence	Study design
Wolfe et al., 1995	• Random sample of 3,006 Witchita, KS residents	• FMS overall prevalence was 2.0% • FMS prevalence for men estimated at 0.5% and women 3.4%	• Survey with some in-person examination • Estimates based on the ACR criteria for FMS
Robinson et al., 2003	Database of a Fortune 100 manufacturer excluding employees over the age of 65 and those enrolled in HMOs	• 2.8% in the database • 61% of FMS claimants were female • Average age 46 years	• Administrative claims database • Patients identified by ICD-9 codes
Robinson et al., 2004	Database of a Fortune 100 manufacturer excluding employees over the age of 65 and those enrolled in HMOs	• 2.8% in the database • 9.2% of FMS patients had a claim for depression **(note much smaller than anticipated)** • 59% of FMS claimants were female • 72% of FMS + depression claimants were women	• Administrative claims database • Patients identified by ICD-9 codes

In Europe, a number of studies were identified that provided epidemiological data on the prevalence of FMS. The results of these studies are summarized in Table 2. The prevalence of FMS in the general population from all the studies ranged from 0.18% to 7.42%, with an average estimate of 2.42%. Although there are prevalence data for FMS for the European countries, the criteria defining FMS and the characteristics of samples, such as age and gender requirements vary, making direct comparison of prevalence across studies difficult.

Table 2: Summary of the Prevalence of Fibromyalgia

Country	Study Population	Sample Size	Prevalence	Study
France	Non-institutionalized adults (>15 years)	N = 1,018	7.42% Women: 9.5% Men: 3.86%	Myon and Taieb, 2004
Germany	General population- female residents aged 35 to 74 years.	N = 653	5.5%	Schochat et al., 2003
Italy	General population – aged ≥ 18 years	N = 3,662	2.22%	Salaffi et al., 2005
Spain	General population– subjects aged ≥ 20 years	N = 2,998	Overall: 2.4% Age bands: 20-29: - 30-39: 1.6% 40-49: 4.9% 50-59: 3.7% 60-69: 2.9% 70-79: 2.9% Women: 4.2% Men: 0.2%	Carmona et al., 2001a
	Rheumatology outpatient offices	N = 1,134	Overall: 12% Women: 15.5 Men: 2.2%	Gamero Ruiz et al., 2005
	Patients in a health clinic	N = 685	Overall: 7.75%	Ganuza et al., 2002
UK	Patients in a large primary care population	Sample represents ~4.6% of the UK population	0.18%	Hughes et al., 2006

Treatment

Currently, FMS cannot be cured. Therefore, the goal of FMS treatment is to relieve symptoms and restore function. FMS is considered a chronic disease and therefore must be controlled using an approach of lifelong management (Clauw et al., 2003). The goal of

FMS treatment is to develop an individualized treatment approach that takes into account the nature of the patient's FMS symptoms and their severity, the level of function and stressors, and the presence of medical and psychiatric co-morbidity (Arnold, 2006).

Treatment should initially focus on verifying the diagnosis of FMS, validating the symptoms, and involving the patient in disease management. It is important to confirm diagnosis and educate the patient regarding the disease and its symptoms because education facilitates patient adherence to treatment and validates the disease. It is also important to identify comorbid conditions and take them into account when creating a treatment regimen. A FMS treatment regimen should incorporate multiple strategies and include both pharmacologic and non-pharmacologic therapies. For example, an appropriate treatment regimen may include basic education about FMS, low-dose antidepressants for sleep, an exercise program, non-pharmacologic strategies for pain and stress management (Karin et al., 2002).

A variety of pharmacologic treatments have been used to alleviate FMS symptoms. The following are the American Pain Society's recommendations for the pharmacologic treatment of FMS patients (Burckhardt et al., 2005).

American Pain Society's Recommendations For The Pharmacologic Treatment Of FMS
1. For initial treatment of FMS, prescribe tricyclic antidepressants (TCA) or cyclobenzaprine for sleep at bedtime.
2. For pain relief, use selective serotonin reuptake inhibitors (SSRIs) alone or in combination with tricyclics.
3. Non-steroidal anti-inflammatory (NSAIDs) should not be used as the primary pain medication for people with FMS.
4. Tramadol (atypical opioid) for pain relief. Tramadol can be used alone or in combination with acetaminophen. The dose should be increased slowly over time and should be tapered gradually when discontinued.
5. Opioids should be used only after all other pharmacological and non-

pharmacological therapies have been exhausted.
6. For sleep disturbances, sleep and anti-anxiety medications such as trazodone, benzodiazepines, nonbenzodiazepine sedatives, or L-dopa and carbidopa are recommended.

Lyrica is currently the only drug that is licensed for the treatment of FMS in the US and no drug(s) are licensed for treatment of FMS in the UK; however, there are a large number of drug classes that are used off-label to manage the condition. These include opioids, TCAs, SSRIs, and opiate receptor agonists. Patients with FMS tend to be sensitive and/or relatively intolerant to medications; therefore, it is advisable to begin with low doses and with the least number of side effects. All medications should be reviewed at regular intervals to monitor their efficacy (Fibromyalgia Association UK, 2004).

A study by Hughes et al. (2006) examined prescribing practice for patients who had been diagnosed with FMS in the UK. All patients with a recorded diagnosis of FMS were identified. A non-FMS control group (with 10 controls per case) was generated by matching subjects for index date, practice, sex, and year of birth. Overall rates of prescriptions were significantly higher in FMS cases compared to controls (at 6 months prior to diagnosis, 1,100 prescriptions per 100 person-years in FMS cases compared with 450 prescriptions per 100 person-years in controls).

In the one year prior to FMS diagnosis, rates of prescription for TCAs rose sharply and peaked at 35 prescriptions per 100 person-years at diagnosis (compared with two prescriptions per 100 person-years in controls). Thereafter, prescriptions for TCAs declined sharply to control levels. Prescription patterns for SSRIs were similar but less pronounced. Rates of prescriptions for NSAIDs rose steadily from 10 years prior to FMS diagnosis, and following a brief dip, continued to rise (to 250 prescriptions per 100 person-years) by 4 years after FMS diagnosis (Hughes et al., 2006).

The Fibromyalgia Association UK (2004) also suggests that a combination of non-pharmacological and pharmacological treatments are more helpful in managing FMS symptoms and daily functioning, than pharmacological treatment alone (Fibromyalgia Association UK, 2004). The non-pharmacological treatments recommended are presented in Table 3.

Table 3: Examples of Non-pharmacological Treatments for Fibromyalgia in the UK

Treatment	Notes
Cognitive Behavioral Therapy (CBT)	This helps patients to understand their pain and develop coping strategies; this has been shown to be effective.
Body conditioning and exercise management	A physiotherapist with an understanding of fibromyalgia will advise patients on different types of exercise.
Activity scheduling, activity/rest cycling and goal setting	This manages activity in a way that uses energy wisely by prioritizing, planning, and pacing activity.
Alternative Therapies ▪ Osteopathy ▪ Acupuncture ▪ Massage therapy ▪ Herbal remedies	There is limited empirical research to substantiate the use of alternative therapies; however, more focused research is beginning to recognize physiological and emotional benefits of these interventions.

Source: Fibromyalgia Association UK, 2004.

Quality of Life

Since women comprise the majority of the FMS patient population, most of the literature focuses on the impact that FMS has on women's lives, especially with regard to issues such as employment and family life (Reisine et al., 2003). Evidence of physician-patient discordance exists across both genders, and male FMS patients commonly report delaying treatment for fear of not being believed or taken seriously (Paulson et al., 2002). Moreover, there is conflicting evidence of symptom severity as experienced by male patients versus female patients (Reisine et al., 2003; Wolfe et al., 1995).

Patients with FMS often experience a negative impact on quality of life (QoL) issues such as personal relationships, career (Reisine et al., 2003), mental health (Bernard et al., 2000), daily activities (Martinez et al.,1995), bodily pain and vitality (Bernard et, al., 2000). Treatments that entail physical training are purported to bring about improvements in QoL in spite of the difficulties presented by chronic pain in maintaining a high level of physical fitness (Valim et al., 2003). FMS impacts all aspects of daily physical functioning; however, the most pressing issues for FMS patients appear to be the impact of chronic pain on their emotional health and social functioning (Bernard et, al., 2000). For instance, FMS patients often experience acute anxiety and depression, and their pain is exacerbated by fatigue (Affleck et al., 1996). Additionally, patients typically experience a loss of social support networks because their efforts to maintain them are hampered by the loss of vitality caused by chronic pain (Bernard et, al., 2000; Soderberg et al., 2002). Because FMS causes are poorly understood and there is no known cure, FMS patients also suffer the effects of medical and social isolation (Cudney et al., 2002).

Cost of illness

Data on the direct costs associated with the management of FMS were not available for the UK. Although the literature search identified no articles or Internet resources that provided direct cost estimates of FMS in UK, there were 8 US cost studies. The results of the US costs studies are summarized in Table 4 with the total estimated US annual direct medical costs for FMS per patient range from $2,274-$4,393 and indirect costs range from $1,394-$3,411. It is important to note that only one study provided an estimate for annual direct non-medical costs of $724. When the cost of the comorbidity of depression was added, the estimated annual direct medical costs range from $7,328 - $8,686 and indirect costs range from $3,212 - $7,328. In general, based on an analysis by Greenberg et al. (2003) almost half the economic loss associated with FMS is due to work loss. The rate of absenteeism amongst patients with FMS is 1.9 times greater than that of the average employee in their study. For employees with both FMS and depression, the rate of absenteeism is 3.4 times higher. Since the 2003 study by Greenberg et al. (2003) did not include the costs associated with presenteeism, it is likely that the total burden of disease to US employers is much higher than that found in their study. In Robinson et al.

(2004) study, employees in the plan were significantly more likely to file a disability claim for any reason (45% vs 22%) compared to the average employee.

It is also worth noting that the majority of disability claims and medical costs are not directly related to FMS but are related to comorbid diseases or other conditions. Robinson found that only 1% of FMS employees filed a claim related to FMS and only 2% of the employers total costs were tied to a FMS diagnosis (Robinson et al., 2004). In Robinson's follow-up study which examined comorbid depression the total costs of treating FMS patients with major depressive disorder (MDD) were estimated at $11,899 in 1998 (Greenberg et al. 2003). In Wolfe et al. (2004) study, rheumatoid arthritis (RA) with comborbid FMS was more expensive than RA alone ($6,447 versus $4,687). Wolfe et al. (1997) confirm the findings that comorbid conditions contribute significantly to costs. His multivariate regression found 3 significant factors that were associated with total costs: the number of comorbidities, disability as measured by the Health Assessment Questionnaire (HAQ) and global disease severity.

Resource utilization of FMS patients is higher than typical insurance beneficiaries. Robinson et al. (2004) found that FMS claimants had 2.6 times more medical claims than the average beneficiary. Moreover, 45% of the FMS claimants had at least one claim for other diseases of the 'musculoskeletal and connective tissue' compared to 16% in the sample of average beneficiaries and were more likely to use prescription medications. Approximately 76% of FMS claimants were seen a least once by a general practitioner over a years time period. In contrast, Wolfe et al. (1997) found a much higher level of resource use: an average of 9.8 physician visits per year. The difference in these estimates is that Wolfe's study was potentially better at capturing these estimates as it did not rely on claims data.

Table 4: Cost of Illness Studies in Fibromyalgia Patients

Reference	Population	Cost (direct, indirect)
Greenberg et al., 2003	Company employees under the age of 65 who are enrolled in a company sponsored fee for service health plan and are eligible for disability benefits	• Total medical costs (work loss cost): ➢ 10% sample of average employees = $2,346.10 ($1,698.90) ➢ FMS only = $3,148.80 ($3,411.20) ➢ FMS + Depression = $7,328 ($7,328)
Robinson et al., 2003	Database of a Fortune 100 manufacturer excluding employees over the age of 65 and those enrolled in HMOs	• Total annual medical costs (disability/ absenteeism cost): ➢ Average employees = $1,934 ($330.64/$221.25) ➢ FMS only = $4,393.36 ($1,016.56/$535.05)
Robinson et al., 2004	Database of a Fortune 100 manufacturer excluding employees over the age of 65 and those enrolled in HMOs	• Total annual medical costs (workplace cost): • Average employees = $1,939.08 ($546.92) • FMS only = $3,768.99 ($1,394.01) • FMS + Major Depression = $8,686.27 ($3,212.73)
Wolfe et al., 1997	538 patients (mean age =49, 89% female, 86% white)	• Annual costs ➢ $882 = hospitalization ➢ $731 = drugs ➢ $340 = outpatient visits ➢ $320 = other • Total direct medical = $2,274
Wolfe and Michaud, 2004	2,078 RA patients with FMS (mean age =59, 84.5% female, 88% white)	• Cost per 6 months in FMS + RA ➢ $1,324 = hospitalization ➢ $3,776 = drugs ➢ $1,377 = outpatient • $6,477 = total costs
Wassem and Hendrix, 2003	102 FMS patients attending a FMS support group meeting (mean age 54 years, 83% female)	• Annual costs ➢ $2,943 = Direct medical ➢ $724 = Direct non-medical ➢ $1,833 = Indirect
Bombardier and Buchwald, 1996	402 patients (147 Chronic Fatigue syndrome, 28	• For FMS patients only: ➢ Mean number of medical visits a year =25.7

Reference	Population	Cost (direct, indirect)
	FMS and 68 Chronic Fatigue Syndrome and FMS (mean age 39 years, 75% female)	➢ Mean number of diagnosis = 1.7 ➢ 32% saw a chiropractor ➢ 39% saw a psychiatrist ➢ 25% saw a naturopath/homeopath ➢ 21% saw an acupuncturist
Bigatti and Cronana, 2002	135 male spouses of FMS patients matched to an equal number of spouses of women with no FMS	• Annual Direct medical cost of spouses whose wife has FMS = $1,108 • Annual Direct medical cost of spouses whose wife does not have FMS = $1,424

CHAPTER THREE: METHODOLOGY

Description of Approach

The approach of this study built upon the work of Hughes et al. (2006) by providing a detailed examination of resource utilization among FMS patients in the UK. This study was classified into 2 different analyses: comparison of resource utilization 12 months before and after the FMS diagnosis; and the characteristics of the patient population in terms of its epidemiology, demographics, and comorbidities, in the UK. The results of this study provided a comprehensive characterization of FMS, its treatments, and associated costs.

Research Design

This study was a pre-post retrospective database analysis of FMS patients. Among patients with FMS during the study period, an analysis was conducted to compare levels of medical resource utilization, pharmacy utilization, and associated costs incurred during the period 12-month prior to the first observed (index) diagnosis with those incurred during the period 12-month following the index diagnosis.

Selection of Subjects

For patients in the study cohort, an index date was defined as the date of the first observed FMS diagnosis that took place between January 1, 1999, and December 31, 2005. The study cohort was deemed acceptable as defined by the data quality criteria in the General Practice Research Database (GPRD). The patients' index date was also be an incident FMS diagnosis (no prior record of FMS), and patients also had a minimum registration duration of 12 months pre-index date.

Sample/Population of Interest

Construction of the study sample for this analysis began with the selection of patients from the GPRD. The study cohort included all patients with any diagnosis of FMS between January 1, 1999, and December 31, 2005. Patients with FMS were identified based on the following Read/Oxford Medical Information System codes: N248.00, N239.00, 7339F (Fibromyalgia), and N241200 (Fibromyositis, not otherwise specified).

Outcome Measures

The primary outcomes that were analyzed in this study included demographic characteristics; medical resource utilization, including GP visits and referrals to secondary-care specialists and hospitals; utilization patterns for specific pharmacotherapies; and overall prevalence of comorbidities. The targeted comorbidities and referrals were established by an initial investigation of the data.

Pharmacotherapy resource utilization was examined in 10 pharmacotherapy categories identified a priori as relevant to patients with FMS based on the literature; these included anticonvulsants, benzodiazepines, centrally acting analgesics, muscle relaxants, nonbenzodiazepine sleep medications, NSAIDs, SNRIs, SSRIs, systemic corticosteroids, and TCAs (Goldenberg et al., 2004).

This study also used UK costing data based on the medical and pharmacotherapy resource utilization data to calculate the cost of FMS in the 12-month prior to and following the FMS diagnosis. Results of these analyses provided a comprehensive characterization of medical and pharmacotherapy treatment for FMS, as well as the costs associated with FMS among UK primary care patients.

Procedures

Demographic characteristics that were analyzed included age (continuous and categorical), gender, and geographic location of the patient's GP. A visit to the GP was assumed for each unique date indicating a clinical event. Results on GP utilization was stratified by visits for all causes as well as by visits related to the specific comorbidities of interest. The overall number and percentage of patients with at least one referral to a hospital or to a secondary-care specialist was estimated and reported. Results on referrals to secondary-care specialists were further stratified by specialty type (e.g., rheumatology, mental health, gastroenterology, orthopaedics or other specialties).

The overall number and percentage of patients that use any prescription pharmacotherapies was estimated and reported. Patterns of pharmacotherapy use (e.g., average of number of pharmacotherapy, duration, discontinuation, and concomitant use) were quantified for the specific drug classes that have been identified as relevant to FMS in the literature. The observed total costs will also be summarized for FMS patients pre- and post-index date.

Data Analysis

The statistical approaches that were implemented to address the study objectives described above were summarized in this section. Descriptive analyses entailed the tabular display of mean values of continuous variables of interest. Descriptive analyses of categorical variables entailed the tabular display of frequency distributions. The statistical significance of descriptive differences in the outcomes of interest between the pre- and post-diagnosis time periods within the study cohort was measured using t-tests and χ^2 tests, with results reported as *P* values (significance level < 0.05).

Institutional Review Boards (IRBs)

The GPRD data was provided by Research Triangle Institute (RTI). RTI holds a Federal-Wide Assurance (FWA) from the Department of Health and Human Services' Office for Human Research Protections (FWA #3331) that allows them to review and approve human subject protocols through their internal Institutional Review Boards (IRBs). RTI's FWA requires IRB review for all studies that involve human patients, regardless of the funding source. The GPRD data was ruled as exempt from IRB review by an IRB chair and designated IRB member on August 2, 2006. RTI currently has three IRB committees and these IRBs have been reviewed by the FDA and are fully compliant with applicable regulatory requirements. The committee assigned a given research study reviews the study protocol and consent documents to ensure both are in compliance with the 21 CFR 50 Federal regulations that govern human subjects research. The committee can approve, approve with modifications, or disapprove any research protocol based on the compliance of the protocol and consent procedures with these regulations.

Hypothesis

The primary hypothesis of this pre-post study was that FMS patients will have an increase in medication resource utilization after the initial FMS diagnosis compared to the 12 months prior to the FMS diagnosis.

CHAPTER FOUR: RESULTS

Demographics

The pre-post analysis was performed on a subset of patients from the FMS cohort (n = 5,444) and the analyses assessed within-patient differences for 12 months prior to compared with 12 months after the date of the first observed FMS diagnosis (index date). The average age of FMS patients included in the pre-post analysis was 48.5 years. More than 60% of patients were over age 45 years. More than 83% of patients were women. By design, all patients had a total of 2 years of follow-up, 12 months prior to the index date (pre-index period) and 12 months following the index date (post-index period). Table 5 summarizes the demographics.

Table 5: Demographics

Parameter	Fibromyalgia
Gender	
Female	4,529 (83.2%)
Male	915 (16.8%)
Age at index date	
Mean (SD*)	48.5 (13.3)
Median	49
Range	7.0 - 90.0
Age group at index date	
0 to 17	56 (1.0%)
18 to 24	137 (2.5%)
25 to 34	571 (10.5%)
35 to 44	1,310 (24.1%)
45 to 54	1,649 (30.3%)
55 to 64	1,100 (20.2%)
65 or Higher	621 (11.4%)

*SD = standard deviation.

Comorbidities

Table 6 presents the comorbidities and comorbidity classes that occurred in ≥ 5% of patients with FMS. The most common class of comorbidities were Musculoskeletal & Connective Tissue Disorders. Within this class, there were a higher number of patients with arthralgia (17.3% vs. 10.7%), back pain (12.6% vs. 10.3%), neck pain (7.2% vs. 6.0%), pain in limb (6.4% vs. 5.4%) and myalgia (5.7% vs. 2.7%) in the pre-index period compared to the post-index period.

Table 6: Comorbidities (Occurring in ≥ 5% of Patients in the Pre-Period) in the 12 Months Prior to and After FMS Index Period

Comorbidities	Pre–Index Period	Post–Index Period	*P* Value
Musculoskeletal and connective tissue disorders	1,273 (23.38%)	898 (16.50%)	<0.001
Arthralgia	943 (17.32%)	584 (10.73%)	<0.001
Back pain	687 (12.62%)	562 (10.32%)	<0.001
Neck pain	392 (7.20%)	325 (5.97%)	0.012
Pain in limb	349 (6.41%)	295 (5.42%)	0.033
Myalgia	308 (5.66%)	147 (2.70%)	<0.001
General disorders and administration site conditions	1,077 (19.78%)	999 (18.35%)	0.086
Pain NOS	580 (10.65%)	401 (7.37%)	<0.001
Fatigue	375 (6.89%)	239 (4.39%)	<0.001
Pre-existing condition improved	299 (5.49%)	424 (7.79%)	<0.001
Chest pain	310 (5.69%)	282 (5.18%)	0.249
Drug hypersensitivity	234 (4.30%)	307 (5.64%)	0.001
Respiratory, thoracic and mediastinal disorders	833 (15.30%)	1,000 (18.37%)	<0.001
Cough	404 (7.42%)	494 (9.07%)	0.002
Upper respiratory tract infection NOS	307 (5.64%)	359 (6.59%)	0.043
Lower respiratory tract infection NOS	260 (4.78%)	308 (5.66%)	0.044

Comorbidities	Pre–Index Period	Post–Index Period	*P* Value
Pharyngitis	284 (5.22%)	294 (5.40%)	0.677
Surgical and medical procedures	685 (12.58%)	755 (13.87%)	0.065
Hormone replacement therapy	256 (4.70%)	220 (4.04%)	0.098
Contraception NOS	174 (3.20%)	142 (2.61%)	0.071
Gastrointestinal disorders	755 (13.87%)	912 (16.75%)	<0.001
Abdominal pain NOS	336 (6.17%)	373 (6.85%)	0.164
Dyspepsia	260 (4.78%)	280 (5.14%)	0.389
Psychiatric disorders	673 (12.36%)	842 (15.47%)	<0.001
Depression	339 (6.23%)	404 (7.42%)	0.017
Anxiety	205 (3.77%)	219 (4.02%)	0.496
Nervous system disorders	665 (12.22%)	753 (13.83%)	0.019
Headache	219 (4.02%)	221 (4.06%)	0.924
Vascular disorders	613 (11.26%)	719 (13.21%)	0.003
Immune system disorders	575 (10.56%)	662 (12.16%)	0.013
Drug hypersensitivity	234 (4.30%)	307 (5.64%)	0.001
Skin and subcutaneous tissue disorders	523 (9.61%)	636 (11.68%)	<0.001
Reproductive system and breast disorders	463 (8.50%)	543 (9.97%)	0.011

Comorbidities	Pre–Index Period	Post–Index Period	*P* Value
Metabolism and nutrition disorders	352 (6.47%)	462 (8.49%)	<0.001
Cardiac disorders	289 (5.31%)	388 (7.13%)	<0.001
Injury, poisoning and procedural complications	278 (5.11%)	265 (4.87%)	0.576

NOS = not otherwise specified

GP Visits and Referrals

The mean number of GP visits for arthralgia was slightly higher in the post–index date period (1.76) compared with the pre–index date period (1.69). Similarly, patients who had a visit for back pain in the pre–index date period had 1.77 visits on average compared to 1.84 visits in the post-index period.

Table 7 presents the number and percentage of patients with a referral to each of the 30 most common specialties (occurring in ≥ 0.3% of FMS patients in the pre-period). In the pre–index period, 53.1% of patients had a specialist referral, with an average of 2.11 referrals compared to 53.3% of patients and 2.09 referrals in the post-index period (difference not statistically significant). Rheumatology referrals were the most common, with 17.2% of patients in the pre–index date period and 10% of patients in the post–index date period receiving a referral ($P < 0.001$).

In addition, the rate of hospital referrals was low in both the pre– and post–index date periods (2.0% and 2.4%, respectively, difference not statistically significant).

Table 7: Health Care Utilization (Specialist Referrals) 12 Months Prior to and After Index Period

Reason for Utilization	Pre–Index Period (N = 5,444)			Post–Index Period (N = 5,444)		
	N (%)	Mean Referrals	Total Referrals	N (%)	Mean Referrals	Total Referrals
ALL	2,892 (53.1%)	2.11	6,094	2,902 (53.3%)	2.04	5,915
Rheumatology	939 (17.2%)	1.09	1,028	545 (10.0%)	1.1	597
Other	444 (8.2%)	1.27	562	514 (9.4%)	1.24	638
Diagnostic test and investigations	404 (7.4%)	2.25	910	322 (5.9%)	2.28	735
General medicine	382 (7.0%)	1.13	432	366 (6.7%)	1.17	428
Radiology	330 (6.1%)	1.19	394	322 (5.9%)	1.28	411
General surgical	326 (6.0%)	1.12	364	398 (7.3%)	1.08	430
Trauma and orthopaedics	288 (5.3%)	1.08	310	284 (5.2%)	1.1	313
Physiotherapy	274 (5.0%)	1.12	308	325 (6.0%)	1.1	356
Gynecology	216 (4.0%)	1.14	246	251 (4.6%)	1.08	270
Ear, nose, and throat	169 (3.1%)	1.11	188	170 (3.1%)	1.06	181
Dermatology	138 (2.5%)	1.09	150	103 (1.9%)	1.1	113
Ophthalmology	136 (2.5%)	1.02	139	145 (2.7%)	1.04	151
Neurology	89 (1.6%)	1.06	94	101 (1.9%)	1.14	115
Accident and emergency	71 (1.3%)	1.24	88	53 (1.0%)	1.19	63
Chemical pathology	69 (1.3%)	1.51	104	63 (1.2%)	2.05	129
Gastroenterology	65 (1.2%)	1.14	74	76 (1.4%)	1.09	83
Adult psychiatry	59 (1.1%)	1.1	65	72 (1.3%)	1.11	80
Cardiology	57 (1.0%)	1.04	59	71 (1.3%)	1.1	78
Anaesthetics	46 (0.8%)	1.07	49	85 (1.6%)	1.22	104

Reason for Utilization	Pre–Index Period (N = 5,444)			Post–Index Period (N = 5,444)		
	N (%)	Mean Referrals	Total Referrals	N (%)	Mean Referrals	Total Referrals
Urology	39 (0.7%)	1.08	42	49 (0.9%)	1.04	51
Rehabilitation	33 (0.6%)	1.12	37	40 (0.7%)	1.13	45
Mental illness	32 (0.6%)	1.06	34	46 (0.8%)	1.13	52
Dietetics	26 (0.5%)	1	26	32 (0.6%)	1.06	34
Non-referral report	26 (0.5%)	1.92	50	35 (0.6%)	2.06	72
Chiropody	24 (0.4%)	1	24	42 (0.8%)	1.02	43
Clinical psychology	24 (0.4%)	1.04	25	14 (0.3%)	1.21	17
Obstetrics	21 (0.4%)	1.1	23	27 (0.5%)	1.07	29
Haematology	20 (0.4%)	1.2	24	18 (0.3%)	1.5	27
Plastic surgery	16 (0.3%)	1.06	17	28 (0.5%)	1.04	29
Psychotherapy	15 (0.3%)	1	15	27 (0.5%)	1.04	28

*The *P* value tests the probability that the mean difference equals 0.

N (%) is calculated on patients experiencing at least one event.

Mean visits are calculated for patients experiencing at least one event in the specified category.

Mean per-patient difference is calculated by taking the mean of each patient's post-pre difference.

Pharmacotherapy Utilization

In the pre–index period, 93.3% of patients were prescribed a pharmacotherapy from one of the 10 selected pharmacotherapy categories; in the post–index period, 97.7% of patients were prescribed a pharmacotherapy from one of these categories ($P < 0.001$). Table 8 presents the percentage of patients with at least one prescription for a pharmacotherapy in each of the 10 selected pharmacotherapy categories in the pre– and post–index periods; these data also are presented for specific drugs prescribed by ≥ 5% of patients in the pre–index period.

Nonsteroidal anti-inflammatory drugs (NSAIDs) were the most commonly prescribed pharmacotherapy. More FMS patients were prescribed NSAIDs in the post-index period compared to the pre-index period (19.0% vs. 13.5% p-value < 0.001). The second most commonly prescribed pharmacotherapy category was systemic corticosteroids. There was also a significant increase in the number of FMS patients with a prescription for systemic corticosteroid in post–index period compared to the pre-index period (14.8% vs. 10.9%, p-value < 0.001).

Table 8: Pharmacotherapy Used by ≥ 5% of Patients with FMS

Drug Class	Pre–Index Period N (%)	Post–Index Period N (%)	P Value
NSAIDS	734 (13.5%)	1,032 (19.0%)	<0.001
Systemic corticosteroids	592 (10.9%)	805 (14.8%)	<0.001
Centrally acting analgesics	472 (8.7%)	695 (12.8%)	<0.001
TCAs	300 (5.5%)	1,648 (30.3%)	<0.001
SSRIs	353 (6.5%)	612 (11.2%)	<0.001
Benzodiazepines	301 (5.5%)	358 (6.6%)	0.026
Nonbenzodiazepine sleep medications	165 (3.0%)	214 (3.9%)	0.011
SNRIs	95 (1.7%)	154 (2.8%)	<0.001
Anticonvulsants	59 (1.1%)	181 (3.3%)	<0.001
Muscle relaxants	55 (1.0%)	95 (1.7%)	0.001

NSAID = nonsteroidal anti-inflammatory drug

SNRI = serotonin and norepinephrine reuptake inhibitor

SSRI – selective serotonin reuptake inhibitor

TCA = tricyclic antidepressants.

Pharmacotherapy Utilization Patterns

Table 9 shows the number and percentage of patients with FMS who used multiple categories of drugs from the selected pharmacotherapy list in the pre- and post-index periods. On average, FMS patients used fewer different drug categories in the pre–index date period compared with the post–index date period (2.2 vs. 2.7) and fewer unique medications (3.0 vs. 3.6). Table 9 also lists the number and percentage of patients who used the selected drug categories concurrently. FMS patients used more medications concurrently in the post-index period than in the pre-index period. Approximately 20% of FMS patients used two or more drug classes concurrently in the post-index period compared with 6.4% in the pre–index date period ($P < 0.001$). Compared to the pre-index period, more FMS patients had a concurrent prescription for three or more drug classes in the post-index period (13.8% vs. 5.4%, p-value < 0.001).

Table 9: Multiple Drug Use

Drug Category	Pre–Index Period	Post–Index Period	P Value
Multiple medication use			
From 0 of the drug categories	652 (12.0%)	156 (2.9%)	<0.001
From 1 of the drug categories	838 (15.4%)	599 (11.0%)	<0.001
From 2 of the drug categories	845 (15.5%)	906 (16.6%)	0.144
From 3 of the drug categories	669 (12.3%)	923 (17.0%)	<0.001
From 4 of the drug categories	448 (8.2%)	647 (11.9%)	<0.001
From 5 of the drug categories	215 (3.9%)	354 (6.5%)	<0.001
From 6 of the drug categories	94 (1.7%)	146 (2.7%)	<0.001
From 7 of the drug categories	23 (0.4%)	47 (0.9%)	0.004
From 8 of the drug categories	7 (0.1%)	9 (0.2%)	0.617
From 9 of the drug categories	0 (0.0%)	4 (0.1%)	0.045
From 10 of the drug categories	652 (12.0%)	156 (2.9%)	<0.001
Concurrent medication use			
From ≥2 of the drug categories	351 (6.4%)	1,106 (20.3%)	<0.001
From ≥3 of the drug categories	294 (5.4%)	752 (13.8%)	<0.001

Duration of Therapy

For FMS patients who received pharmacological treatment in both the pre- and post-index periods, the average duration of therapy was highest for the serotonin and norepinephrine reuptake inhibitor (SNRI) drug class (241.1 and 264.4 days in the pre– and post–index periods, respectively: $P < 0.001$). The average duration of therapy was slightly lower for the selective serotonin reuptake inhibitor (SSRI) class, with 218.0 and 233.1 days in the pre– and post–index periods respectively ($P = 0.001$).

The mean duration of therapy across all patients was the highest for NSAIDs (70.2 and 87.0 days in the pre– and post–index periods, respectively; $P < 0.001$). Muscle relaxants had the lowest therapy duration across all patients (1.7 and 2.6 days in the pre– and post–index periods, respectively; $P < 0.001$).

Table 10 presents the number and percentage of patients who discontinued therapy with the selected pharmacotherapy categories at various time points following the index date. For example, among the 2,023 patients that used TCAs in the post–index period, 65.4% discontinued therapy at some point over the 12 months following the index date and 34.6% did not discontinue therapy. The discontinuation rate was the highest between 31-60 days (22.5%). Overall discontinuation rate was the highest for NSAIDs (71.6%) and lowest for anticonvulsants (41.1%). Patients who discontinued pharmacotherapy had a > 60 day gap between exhaustion of previous pharmacotherapy and the end of the 12-month post-index period; therefore, FMS patients did not restart pharmacotherapy later in the year after discontinuing pharmacotherapy.

Table 10: Frequency Distribution of Post–Index Discontinuation of Prescription Therapy

Drug Class at Index Date	N*	1-30 Days	31-60 Days	61-90 Days	91-180 Days	181-305 Days	Total Discontinued
TCAs	2,023	275 (13.59%)	455 (22.49%)	165 (8.16%)	260 (12.85%)	168 (8.30%)	1,323 (65.40%)
NSAIDS	1,952	521 (26.69%)	367 (18.80%)	121 (6.20%)	223 (11.42%)	165 (8.45%)	1,397 (71.57%)
Centrally acting analgesics	1,157	236 (20.40%)	139 (12.01%)	66 (5.70%)	109 (9.42%)	94 (8.12%)	644 (55.66%)
Systemic corticosteroids	849	183 (21.55%)	159 (18.73%)	51 (6.01%)	124 (14.61%)	78 (9.19%)	595 (70.08%)
SSRIs	753	99 (13.15%)	72 (9.56%)	47 (6.24%)	93 (12.35%)	81 (10.76%)	392 (52.06%)
Benzodiazepines	386	57 (14.77%)	37 (9.59%)	12 (3.11%)	32 (8.29%)	22 (5.70%)	160 (41.45%)
Nonbenzodiazepine sleep medications	171	41 (23.98%)	17 (9.94%)	13 (7.60%)	15 (8.77%)	6 (3.51%)	92 (53.80%)
Anticonvulsants	129	15 (11.63%)	16 (12.40%)	2 (1.55%)	12 (9.30%)	8 (6.20%)	53 (41.09%)
SNRIs	113	12 (10.62%)	13 (11.50%)	5 (4.42%)	10 (8.85%)	8 (7.08%)	48 (42.48%)
Muscle relaxants	55	22 (40.00%)	7 (12.73%)	4 (7.27%)	3 (5.45%)	3 (5.45%)	39 (70.91%)

* N = number of patients receiving the specified treatment on the index day

Medical and Pharmacotherapy Costs

Table 11 and Table 12 present patient costs for the pre– and post–index periods. Because the timeframe for analysis is 12 months in the pre– and post–index periods, these costs represent annualized estimates. FMS patients had a 20.3% increase in GP visit costs in the post-index period compared to the pre-index period (£346.84 vs. £288.41, p-value < 0.001).

In addition, the annual per-patient pharmacotherapy cost was £88.15 in the pre–index period compared with £118.62 (increased by 34.6%) in the post–index period. TCAs had the highest percentage change between the pre– and post–index periods (increased by 80.5%), followed by anticonvulsants (77.6% increase).

After controlling for age, gender, and geographic region, patients incurred £75 more per year in GP visits and pharmacotherapy costs in the post–index period compared with the pre–index period ($P < 0.001$). These patients incurred £22 more in pharmacotherapy expenses and £53 more in GP visits in the post–index period compared with the pre–index period. After controlling for demographic characteristics, centrally acting analgesics had the largest pre-to-post difference among all of the drug categories. Among GP visit reasons, arthralgia had the largest difference (reduction in £2.5 annually).

Table 11: Annualized Patient Costs for General Practitioner Visit (With an Annualized Cost ≥ £1 for Patients in the Pre–Index Period)

General Practitioner Visit Reason	Mean Per-Patient Cost				
	Pre–Index Period	Post–Index Period	Difference	Percentage Change	*P* Value*
All	£288.41	£346.84	£58.43	20.30%	<0.001
Arthralgia	£10.30	£6.93	–£3.38	–32.80%	<0.001
Back pain	£7.71	£6.28	–£1.43	–18.50%	<0.001
Pain NOS	£5.30	£3.97	–£1.33	–25.10%	<0.001
Cough	£4.10	£4.70	£0.61	14.80%	0.016
Depression	£3.92	£4.46	£0.55	14.00%	0.044
Hormone replacement therapy	£3.69	£3.56	–£0.12	–3.40%	0.5
Neck pain	£3.38	£2.71	–£0.67	–19.80%	0.002
Abdominal pain NOS	£3.13	£3.36	£0.23	7.30%	0.321
Chest pain	£2.85	£2.35	–£0.50	–17.40%	0.012
Fatigue	£2.71	£1.71	–£1.00	–36.80%	<0.001
Contraception NOS	£2.67	£2.53	–£0.14	–5.30%	0.363
Pre-existing condition improved	£2.65	£3.41	£0.76	28.80%	<0.001
Pain in limb	£2.61	£2.09	–£0.52	–19.90%	0.004
Lower respiratory tract infection NOS	£2.33	£2.82	£0.48	20.70%	0.006
Myalgia	£2.27	£1.09	–£1.18	–52.00%	<0.001
Pharyngitis	£2.10	£2.08	–£0.02	–0.90%	0.907
Dyspepsia	£2.09	£2.21	£0.12	5.90%	0.451
Anxiety	£2.03	£2.07	£0.04	2.00%	0.813
Physiotherapy	£1.99	£2.10	£0.11	5.50%	0.614
Upper respiratory tract infection NOS	£1.96	£2.31	£0.35	18.00%	0.017
Headache	£1.85	£1.59	–£0.25	–13.70%	0.105
Insomnia	£1.63	£1.74	£0.11	6.50%	0.493
Drug hypersensitivity	£1.51	£1.89	£0.38	25.20%	0.004
Urinary tract infection NOS	£1.47	£1.39	–£0.08	–5.60%	0.532

General Practitioner Visit Reason	Mean Per-Patient Cost				
	Pre–Index Period	Post–Index Period	Difference	Percentage Change	*P* Value*
Osteoarthritis NOS	£1.25	£1.06	–£0.19	–15.40%	0.144
General symptom NOS	£1.22	£1.18	–£0.05	–3.80%	0.699
Sinusitis acute NOS	£1.22	£1.40	£0.18	14.70%	0.127
Asthma NOS	£1.19	£1.32	£0.13	10.80%	0.315
Constipation	£1.17	£1.52	£0.35	29.80%	0.016
Diarrhea NOS	£1.17	£1.38	£0.22	18.50%	0.098
Dyspnea NOS	£1.08	£1.30	£0.22	20.30%	0.078
Migraine NOS	£1.04	£1.06	£0.02	2.20%	0.833
Acupuncture	£1.03	£1.83	£0.80	77.70%	<0.001

* The *P* values test the probability that the mean per-patient difference equals 0.

The percentage change is calculated with the pre–index date period as a reference.

Hospitalizations and referrals are not included in the costing, as further details on these are not recorded.

NOS = not otherwise specified

Table 12: Annualized Patient Pharmacotherapy Costs

Pharmacotherapy Category	Mean Per-Patient Cost				
	Pre–Index Date	Post–Index Date	Difference	Percentage Change	*P* Value*
All	£88.15	£118.62	£30.48	34.60%	<0.001
Systemic corticosteroids	£27.52	£33.64	£6.12	22.30%	0.247
NSAIDS	£21.93	£29.09	£7.16	32.70%	<0.001
Centrally acting analgesics	£14.60	£20.73	£6.13	42.00%	<0.001
SNRIs	£6.94	£9.03	£2.09	30.20%	<0.001
TCAs	£5.41	£9.76	£4.35	80.50%	<0.001
SSRIs	£4.99	£6.59	£1.61	32.30%	<0.001
Anticonvulsants	£2.65	£4.71	£2.06	77.60%	<0.001
Benzodiazepines	£2.65	£3.06	£0.41	15.70%	0.045
Nonbenzodiazepine sleep medications	£0.96	£1.29	£0.32	33.30%	<0.001
Muscle relaxants	£0.51	£0.72	£0.21	40.70%	0.078

* The *P* values test the probability that the mean per-patient difference equals 0.

CHAPTER FIVE: DISCUSSION

This study supports findings from previous studies indicating that FMS predominantly affects women (de Girolamo, 1991; Hughes et al., 2006), and tends to emerge in middle-aged individuals (Kahn, 2003; Hughes et al., 2006). Not unexpectedly, given that FMS is often accompanied by comorbidities (Wolfe et al., 1990) and is diagnosed based on the presence of widespread pain (particularly in designated tender points) (Wolfe et al., 1990), patients with FMS had significantly lower rates of musculoskeletal and connective tissue disorders (such as arthralgia, back pain, neck pain, chest pain, pain in limb, and myalgia) after being diagnosed and treated for FMS compared to the 12 months prior to being diagnosed. Furthermore, this study also found that patients had a higher rate of depression and anxiety after being diagnosed with FMS than prior to the diagnosis. This finding is consistent with studies that have linked FMS with abnormalities in the neurotransmitters serotonin and norepinephrine (Russell et al., 1992a, Russell et al., 1992b; Schwarz et al., 1999; Yunus et al., 1992).

With respect to medical resource utilization, this study found that patients with FMS had an average of 12.1 GP visits in the 12-month period prior to the FMS diagnosis and 13.9 visits in the 12-month period after the diagnosis, which may reflect increased visits for pharmacological treatment following diagnosis. GP visits for specific conditions were also higher after being diagnosed with FMS than in the 12-month prior period. Similar to the finding with respect to comorbidities, patients with FMS had significantly higher rates of GP visits for a variety of pain-related conditions (including arthralgia, back pain, pain NOS, neck pain, chest pain, pain in limb, abdominal pain NOS), as well as anxiety and depression.

Like this study, Hughes et al. (2006) found that pain-related conditions (including chest pain and headache), as well as anxiety and depression, were among the most common reasons that patients with FMS visited the GP. Sleep disturbance, dizziness, and irritable bowel syndrome also were among the most common reasons of those considered by Hughes et al. (2006) that patients with FMS visited GPs. However, one limitation to

Hughes et al. (2006) study was that it examined GP visits only for specific clinical symptoms identified a priori, which limits comparisons between the two studies.

There were no statistically significant differences in the rate of hospital referrals between the pre– and post–index date periods. In addition, the rates of specialist referrals in the pre– and post–index periods were similar. Similarly, Hughes et al. (2006) found that specialist referrals were significantly higher among patients with FMS relative to control patients (at 6 months prior to diagnosis: 130 referrals per 100 person-years for patients with FMS, vs. 57 referrals per 100 person-years for control patients). Rheumatology was the most common specialist referral for patients with FMS in this study as well as in the Hughes et al. (2006) study. As was the case with the GP visit rates, the lower referral rates found in this study relative to the Hughes et al. (2006) study can be attributed to the differences in the periods examined in each study. Hughes et al. (2006) examined referral rates in 6-month intervals. Similar to US studies in FMS (Greenberg et al., 2003; Robinson et al., 2003; Robinson et al., 2004; Wolfe et a., 1997; Wassem et al., 2003; Bombardier and Buchwald, 1996) this study was conducted for 12-month interval, which is a common timeframe for resource utilization studies.

With respect to the pharmacologic management of patients with FMS, this study found that significantly more patients with FMS were prescribed pharmacotherapy from one of the 10 selected categories during the 12-month period after being diagnosed (after index date) with FMS (97.7%) than during the period prior to the diagnosis (93.3%) ($P < 0.001$), suggesting that pharmacotherapy with one or more of the 10 selected pharmacotherapy categories is an accepted treatment approach given a diagnosis of FMS. Analysis also found that patients with FMS were prescribed more pharmacotherapies in multiple categories after being diagnosed with FMS than in the period before diagnosis. In the post–index period relative to the pre–index period, more patients used two or more pharmacotherapies concurrently (66.2% vs. 52.3%; $P < 0.001$) and three or more pharmacotherapies concurrently (33.9% vs. 25.5%; $P < 0.001$). These findings are consistent with the profile of FMS as a chronic condition characterized by a variety of symptoms, including widespread body pain and muscle tenderness, fatigue, headaches,

and sleep disturbances (Wolfe et al., 1990), with an unclear etiology (Russell et al., 1992a, Russell et al., 1992b; Schwarz et al., 1999; Yunus et al., 1992).
Of the 10 selected pharmacotherapy categories in this study, NSAIDs, systemic corticosteroids, and TCAs were the most commonly prescribed pharmacotherapies and the utilization rates were higher after the FMS diagnosis than in the 12-month prior period. Although Hughes et al. (2006) analyzed pharmacotherapy utilization for only three pharmacotherapy classes (TCAs, SSRIs, and NSAIDs), that study also found that prescriptions for these three pharmacotherapy classes were higher among patients with FMS than among control patients (Hughes et al., 2006).

In this study (as in the study by Hughes et al. [2006]), these pharmacotherapies may have been prescribed to patients with FMS prior to or following a FMS diagnosis, and may have been related to comorbid conditions rather than FMS. Nevertheless, the high rates of NSAID and systemic corticosteroid prescribing in this study are noteworthy, given that evidence-based guidelines have indicated there is no evidence to support the efficacy of these pharmacotherapies (Goldenberg et al., 2004). In particular, systemic corticosteroids are associated with a variety of concerning adverse effects, including weight gain; fluid and electrolyte disturbances (such as hypertension and increased calcium excretion, creating a risk for osteoporosis); musculoskeletal effects (such as muscle weakness); dermatological effects (such as impaired wound healing); endocrine effects (such as manifestation of latent diabetes mellitus); cardiovascular effects (such as myocardial rupture following recent myocardial infarction); as well as gastrointestinal, neurological, and metabolic effects (electronic Medicines Compendium, 2007).

Using UK-specific sources to derive cost estimates (Curtis et al., 2007; BNF, 2006; NHS, 2007), this study found the annual cost for FMS patients was £377 (£288 for GP visits and £88 for pharmacotherapies) in the 12-month prior period and £465 (£347 for GP visits and £119 for pharmacotherapies) in the 12-month period after FMS diagnosis. Similarly, in a study conducted in the United States using administrative claims data, Robinson et al. (2003) found that the total annual cost for FMS claimants was nearly twice that for typical beneficiaries ($5,945 vs. $2,486; $P < 0.0001$).

Limitations of the Study

This study used the General Practice Research Database (GPRD) that is managed by the Medicines and Healthcare product Regulatory Agency and contains data for 8.9 million patients, with approximately 3 million active patients and over 35 million patient-years of data from more than 350 practices in the UK. It is the world's largest source of primary care data taken from a single country's health care system and covers the full cross section of the UK population. The GPRD contains longitudinal data from real-life clinical practices, with information on diagnoses, comorbidities, prescribing (including off-label use), co-prescribing, health outcomes, and demographic and lifestyle factors.

The results of this study should be interpreted in the context of the limitations of the study design. First, because the study is restricted to patients who had a FMS diagnosis recorded by the GP, some patients may have met the ACR diagnostic criteria but remained undiagnosed because they consulted the GP less frequently than those who were diagnosed; therefore, the results of this study may not be generalizeable to other populations. Second, the use of primary care data precludes the use of patient assessments; as a result, the analysis cannot examine quality of life, functioning, or any clinical outcomes. Clinical investigations were also not available including visits for muscle pain, stiffness, or tender points, which may be the most common symptoms on which the diagnosis was based, and possibly those most affected by the diagnosis. Third, this database study does not capture over the counter medication. Finally, the analyses focused exclusively on medical and pharmacy resource utilization associated with a diagnosis of FMS; therefore, it does not include any other potentially important costs, such as productivity costs, cost of other medical interventions (such as physiotherapy), national cost of illness and disability benefits.

CHAPTER SIX: CONCLUSION

FMS is a chronic and often debilitating condition. Treatment of FMS requires a comprehensive approach, including pharmacotherapy, cognitive-behavioral therapy, and physical exercise (Goldenberg et al., 2004). No pharmacotherapy is currently licensed for the treatment of FMS in the UK; however, there are a range of pharmacotherapies that may be used off label to manage FMS. Tricyclic antidepressants (TCAs) (e.g., amitriptyline) and muscle relaxants (e.g., cyclobenzaprine) have strong evidence of efficacy. Centrally acting analgesics (e.g., tramadol), selective serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine), serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g., duloxetine), and anticonvulsants (e.g., pregabalin) have modest evidence of efficacy. Although systemic corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), benzodiazepines, and nonbenzodiazepine sleep medications have no evidence of efficacy (Goldenberg et al., 2004), they may be prescribed to treat the symptoms of FMS before and after patients receive a definitive diagnosis.

Because many patients affected by FMS are of prime working age, the condition may place a substantial economic burden on both private and public health care systems. In a 2006 UK study (Hughes et al., 2006), researchers analyzed data from the General Practice Research Database (GPRD) and found that health care utilization declined in the short term after diagnosis, suggesting that resolution to a formal diagnosis helps patients cope with some of their symptoms. However, in the long term, resource utilization was found to increase, reverting back to the levels observed before diagnosis.

This study examined levels of resource utilization and corresponding costs associated with FMS among primary care patients in the UK, both in the 12 months prior to and following a FMS diagnosis. The study assessed medical resource utilization in terms of general practitioner (GP) visits, specialist referrals, and inpatient hospital referrals. Pharmacotherapy resource utilization was examined in 10 pharmacotherapy categories identified a priori as relevant to patients with FMS based on the literature; these included anticonvulsants, benzodiazepines, centrally acting analgesics, muscle relaxants,

nonbenzodiazepine sleep medications, NSAIDs, SNRIs, SSRIs, systemic corticosteroids, and TCAs (Goldenberg et al., 2004).

This study's finding indicated that patients with FMS have greater GP-specific medical resource utilization, as well as greater pharmacotherapy resource utilization, in the 12-month following an FMS diagnosis than in the 12-month prior to an FMS diagnosis. This increased resource utilization is reflected in higher associated costs following an FMS diagnosis relative to prior to the diagnosis. Results of these analyses provided a comprehensive characterization of medical and pharmacotherapy treatment for FMS, as well as the costs associated with FMS among UK primary care patients.

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CURRICULUM VITAE

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Education

MS, Indiana University-Purdue University Indianapolis, August 2008
- MS Therapeutic Outcomes Research

MPH, University of South Carolina, June 2000
- Masters of Public Health, May 2000
- Emphasis in Health Promotion and Epidemiology

BS, University of Maryland, December 1997
- Bachelor of Science in Biology
- Major in Biology
- Minor in Biochemistry

Experience

Current
- Nov 2003: Health Outcomes Scientist – Indianapolis, IN (Eli Lilly & Company)

Previous
- Mar 2001: Research Associate/Project Leader - Bridgewater, NJ (Merck-Medco)
- May 2000: Health Research Associate - Philadelphia, PA (Independence Blue Cross)
- Aug 1998: Research Assistant (Science & Tech) - Columbia, SC (Center for Health Services)

Conferences Attended

- Amy S Chappell, Kar Wong, James M Russell, Misha Backonja, Deborah D'Souza, **Trong K Le**. Duloxetine In The Treatment Of Diabetic Peripheral Neuropathic Pain: Evaluation of Functional Outcomes. American Podiatric Medical Association 2005 Annual Scientific Meeting, August 2005; Orlando, Florida
- **Le Trong**, Able Stephen, Lage Maureen. Resource Use Among Diabetes Mellitus Patients With And Without The Complications Of Diabetic Neuropathy Or Depression. *Diabetes*; Suppl June 2005. Ref ID: 2103-PO
- Wu EQ, Birnbaum HG, Mareva MN, **Le TK**, Robinson R, Rosen A, Corey-Lisle P. Cost-Effectiveness of Duloxetine Versus Routine Treatment for Painful Diabetic Neuropathy in a Randomized Trial From a Societal Prospective. ISPOR 9th Annual International Meeting, May 2004; Arlington, Virginia USA
- **T Kim Le**, Holly Yu. A Cost Consequence on Concomitant Drug Use During HCV Therapy in Managed Care Patients in the United States. International Society for Pharmacoeconomics and Outcomes Research 6th Annual European Congress, November 2003; Barcelona, Spain

- **T Kim Le**, J Wogen. Evaluation of Hepatitis C Genotype Testing in Newly Diagnosed Hepatitis C Managed Care Patients. The American Association for the Study of Liver Disease 54th Annual Meeting, October 2003: Boston, Massachusetts USA
- AL Robin, **TK Le**, J Wogen, SJ Boccuzzi. Adjunctive Medication Use Associated with Travoprost, Bimatoprost, and Latanoprost Therapy. American Glaucoma Society 2003 Annual Meeting, March 2003; San Francisco, California USA
- Boccuzzi S.J., Wogen J.L., **Le T.K**. Improved Medication Adherence With Metformin Extended Release (Metformin XR) Versus Standard Metformin. ASHP Midyear Clinical Meeting, December 2002; Atlanta, Georgia USA
- Boccuzzi SJ, **Le TK**, Wogen J, Williamson T. Utilization Patterns And Economic Factors Associated With Detrol Versus Oxybutynin In The Management Of Overactive Bladder (OAB). ISPOR Seventh Annual International Meeting, May 2002; Arlington, Virginia USA
- **Le TK**, Wogen J, Boccuzzi S. Use Of Antipsychotic Agents And The Association Of Diabetes Mellitus Diagnosis. 15th Annual U.S. Psychiatric And Mental Health Congress, October 2002; Las Vegas, Nevada USA
- Stephen J. Boccuzzi, **Kim Le**, Jenifer Wogen, Gail Wygant, Pankaj Patel, Ole Hauch. Warfarin Therapy And Concomitant Use Of Agents Effecting INR. 4TH Scientific Forum On Quality Of Care And Outcomes Research In Cardiovascular Disease And Stroke, October 2002; Washington DC USA

Publications

- S.M. Beard, L. McCrink, **T.K. Le**, A. Garcia-Cebrian, B. Monz , R.A. Malik. Cost Effectiveness of Duloxetine in the Treatment of Diabetic Peripheral Neuropathic Pain (DPNP) in the UK. *Current Medical Research and Opinion* 2008; 24 (2);385-99
- EQ Wu, J Borton, G Said, **TK Le**, B Monz, M Rosilio, S Avoinet. Estimated prevalence of peripheral neuropathy and associated pain in adults with diabetes in France. *Current Medical Research and Opinion* 2007; 23(9): 2035-42
- Amy M. Barrett, Melanie A. Lucero, **Trong L**e, Rebecca L. Robinson, Robert H. Dworkin, Amy Chappell. Epidemiology, Public Health Burden, and Treatment of Diabetic Peripheral Neuropathic Pain: A Review. *Pain Medicine* 2007; 8 (2): S50–S62
- Armstrong, A.S. Chappell, **T.K. Le**, D.K. Kajdasz, M. Backonja, D.N. D'Souza, J.M. Russell. Duloxetine In The Treatment Of Diabetic Peripheral Neuropathic Pain: Evaluation of Functional Outcomes. *Pain Medicine* 2007; 8(5): 410-418
- Anju Parthan, Christopher J. Evans, **Kim Le**. Chronic low back pain: epidemiology, economic burden and patient reported outcomes in the USA. *Expert Review of Pharmacoeconomics and Outcomes Research* 2006; 6(3): 359-369

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- Joachim F. Wernicke, Joel Raskin, Amy Rosen,Yili L. Pritchett, Deborah N. D'Souza, Smriti Iyengar, Kelly Knopp, **Trong K. Le**. Duloxetine in the Long-Term Management of Diabetic Peripheral Neuropathic Pain: An Open-Label, 52-Week Extension of a Randomized Clinical Trial. *Current Therapeutic Research* 2006; 67(5): 1-22,
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