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Original Research Article

Burden of Illness and Treatment Patterns for Patients with Fibromyalgia

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Abstract

Objective. This study was designed to describe burden of illness and treatment patterns, and to examine the patient, physician, and care factors associated with the treatment choices of individuals receiving new prescriptions for fibromyalgia (FM).

Design. This is a baseline assessment of the Real-World Examination of Fibromyalgia: Longitudinal Evaluation of Costs and Treatments (REFLECTIONS), a prospective observational study. Baseline data (including a physician survey, a patient visit form, and computer-assisted telephone interviews) were collected from July 2008 through May 2010 in 58 care settings in the United States, including Puerto Rico.

Results. Patients (N = 1,700) were mostly female (94.6%) and white (82.9%). Mean age was 50.4 years and mean duration of illness was 5.6 years. Mean Fibromyalgia Impact Questionnaire total score was 54.4 (range 0–80), and Brief Pain Inventory average pain severity level was 5.5 (range 0–10). Patients reported high annual health care use and numerous work limitations related to FM. Patients were taking 182 unique types of medications prescribed for FM, including duloxetine (26.8%), nonsteroidal anti-inflammatory drugs (26.6%), pregabalin (24.5%), opioids (24.2%), tramadol (15.3%), benzodiazepines (15.2%), cyclobenzaprine (12.9%), milnacipran (8.9%), and others. Most patients took more than one medication concurrently (77.8%). Type of current medications used was most strongly associated with medication history and physician specialty.

Conclusions. Burden of illness was high for patients with FM, and treatment patterns were highly variable. Importantly, the treatments with the most evidence to support their use were not always the most frequently chosen.

Key Words. Fibromyalgia; Observational; Duloxetine; Pregabalin; Milnacipran

Introduction

Fibromyalgia (FM) is characterized by chronic, widespread pain, and many associated symptoms such as mood,

sleep disturbances, and fatigue. It affects 0.5% to 5% of the general population [1], mostly women (90%) between the ages of 20 and 50 years [2,3]. The underlying pathophysiology of FM may also be shared with other disorders, such as a common disturbance in serotonin and norepinephrine neurotransmitter function [4–10]. Furthermore, FM can co-occur with other conditions that also share these symptoms, such as irritable bowel syndrome, painful bladder syndrome, headache, and sleep disorders [5–7]. The specific symptoms for a given individual can vary, often requiring more than one treatment to achieve an optimal effect.

Many treatments for FM have been studied, and evidence-based treatment guidelines have been established by organizations such as the American Pain Society (APS), the European League Against Rheumatism (EULAR), and the Association of the Scientific Medical Societies in Germany (AWMF). Each of these guidelines recommends multidisciplinary approaches to the treatment of FM, including combinations of nonpharmacologic and pharmacologic interventions [11]. However, there are some variations in these recommendations due to the complexity of treatment of patients with FM. The use of a multifaceted treatment approach involving a variety of medications and alternative or complementary treatments is well supported in the previous literature [12–16]. According to a recent review [11], the APS and AWMF assign the highest level of recommendation to aerobic exercise, cognitive-behavioral therapy (CBT), amitriptyline, and multicomponent treatment, while EULAR assigns the highest level of recommendation to a set of pharmacologic treatments (i.e., tramadol, amitriptyline, fluoxetine, duloxetine, milnacipran, moclobemide, pirlindole, tropisetron, pramipexole, and pregabalin). Although there is not enough evidence to support one of these treatment guidelines over another, in this article we focus on the guidelines written by the APS as the study reported here primarily involves a United States-based population.

The APS treatment guidelines were introduced in 2005 [17] and updated in 2007 [18] to include information about pharmacologic treatments. Among these treatments were pregabalin, duloxetine, and milnacipran, now the only medications approved for FM by the United States Food and Drug Administration (FDA). The APS guidelines recommend that opioid analgesics, aside from tramadol, be used with caution and only after all other therapeutic options have been exhausted [13–19]. Recommendations also include specialty referral, such as care provided by rheumatologists, physiatrists, psychiatrists, or pain management specialists.

Data from retrospective administrative claims in the United States have demonstrated that patients with FM use multiple medications and report high economic burden [20–22]. However, the reasons for select treatment decisions and the clinical outcomes associated with drug selection cannot be determined through claims. To our knowledge, no study has addressed the factors associated with treatment selection for FM. The Real-World Examination of Fibromyalgia: Longitudinal Evaluation of Costs and Treatments (REFLECTIONS) observational study was designed to address this gap. The primary objectives of this article were 1) to describe how FM is treated in "real world" patients from outpatient care settings; 2) to describe the burden of illness for FM patients; and 3) to examine patient, physician, and care factors that influence treatment choices. Thus, the purpose of the present article is to report the baseline findings of the REFLECTIONS study; longitudinal findings will be addressed in a separate communication.

Methods

Study Setting

Patients participating in this study were enrolled from July 2008 through May 2010 from 58 outpatient health care settings (including 91 participating physicians) in the United States, including Puerto Rico.

Sites included outpatient practices of rheumatology (56.0%), primary care (36.3%), as well as other specialty practices of neurology (2.2%), psychiatry (3.3%), pain specialists (3.3%), physical medicine (2.2%), obstetrics and gynecology (1.1%), and osteopathy (1.1%). The number of sites per specialty was monitored to attempt to be reflective of the types and rates of physicians seen in actual clinical practice. Sites were required to be practice settings, not research settings. They were identified based on their prior experience in observational or clinical research, their interest in FM based on publications in the literature, or referrals from other sites. Sites were further selected on the basis of the number of FM patients seen per month and whether they received good clinical practice training prior to the study entry visit of the patient. The protocol was approved by either a central or site-specific institutional review board. All patients provided written informed consent before participating in the study. As physicians had minimal study responsibilities beyond the baseline visit, compensation to physicians did not exceed what they would have normally received for a single regular patient office visit (approximately 1 hour).

Minimal inclusion and exclusion criteria were used to ensure this study remained noninterventional. Patients were identified by their care provider during routine office visits. The physicians' decisions regarding the proper treatment and care of patients were made in the course of normal clinical practice. Thus, patients were eligible for the study if they were at least 18 years of age, met criteria for FM in the opinion of the enrolling physician, were under the care of the participating physician, were cognitively able to understand and complete patient self-rated scales in English or Spanish via telephone interviews, and were available for 12 months to participate in the study. Patients also had to be initiating a new treatment for FM defined as being naïve to the treatment (over the last 6 months), starting the new therapy to replace a previously used therapy, or adding the new therapy to a previous therapy which was not discontinued. Individuals who were

investigators or site personnel directly affiliated with the study, and/or their immediate families, were excluded from the study.

Study Design

This was a baseline assessment of a prospective 12-month observational study. This study was designed to describe the burden of illness and treatment patterns of patients with FM, and to examine patient, physician, and care factors that influence treatment choices. All patient care by the enrolling physician occurred as part of the physician's routine clinical care.

Data were collected from three sources: a physician survey, a patient visit form, and computer-assisted telephone interviews (CATI). The physician survey was completed by the participating physician prior to enrolling patients into the study. Once informed consent was obtained, the patient visit form was completed during a standard office visit for which the physician was prescribing a new pharmacologic treatment (defined as any agent not used in the last 6 months). Physicians were asked to complete portions of the form related to the patients' medical history, physician's relationship with the patient, and a complete description of ongoing, discontinuing, and newly started pharmacologic and nonpharmacologic interventions for FM. The patients completed the portion of the form related to their demographic and medical history. No further study-specific office visits or physician information was required. All further data were collected with CATI, in which patients were asked to respond to various questions regarding their health status and care. Patients were assessed via telephone interviews in English or Spanish at five different time periods: baseline, and 1, 3, 6, and 12 months. Only the baseline information is included in this article. Each interview took approximately 30–45 minutes to complete. Baseline interviews had to be conducted within 14 days of the study entry visit. Patients were reimbursed for their time with a $25 gift card for each completed CATI.

Measures

Physician Characteristics

The physician survey included physician demographics, the physician's perception and experience treating FM, practice characteristics (e.g., number of years in practice, specialty), and beliefs and attitudes about FM, with item responses ranging from 1 completely disagree to 5 completely agree.

Patient Characteristics

Data included patient demographics, medical history, socioeconomic status, and work or disability status.

Disease Burden

Burden was assessed by measuring prior health care utilization and by domains deemed important to determine treatment success in studies of FM (by the Outcome Measures in Rheumatology Clinical Trial fibromyalgia steering committee). These domains included pain, fatigue, global functioning, sleep quality, health-related quality of life, physical function, depression, anxiety, and dyscognition [23]. Specific validated measures are as follows: the Fibromyalgia Impact Questionnaire (FIQ; total score range 0–80) [24] assesses physical functioning, number of days the patient felt well, number of days the patient felt unable to work due to FM symptoms, and patient ratings of work difficulty, pain intensity, fatigue, morning tiredness, stiffness, anxiety, and depression. General pain severity and functional impairment was measured by the Brief Pain Inventory (BPI) [25]. The average severity score (BPI-S) ranges from 0 (no pain) to 10 (pain as bad as you can imagine). The average interference score (BPI-I) measures the degree to which pain interferes with various functions, and has a range from 0 (does not interfere) to 10 (completely interferes). The Sheehan Disability Scale (SDS; range 0–30) [26] measures disability across three domains: work/school, social life, and family life/home responsibilities. The Patient Health Questionnaire (PHQ-15; range 0–30) [27,28] captures complaints of common physical symptoms seen in primary care settings. Each symptom was graded by the patient as 0 (bothered not at all), 1 (bothered a little), or 2 (bothered a lot). Anxiety symptoms were collected with the Generalized Anxiety Disorder (GAD-7; range 0–21) [29] (items were scored from 0 [not at all] to 3 [nearly every day]). The PHQ-8 [30,31] was used to measure depression severity (items were scored from 0 [not at all] to 3 [nearly every day]), with ranges from 0 to 15.

Individuals' perceptions of insomnia, including symptoms of sleep, fatigue, and cognition, were measured with the Insomnia Severity Index (ISI; range 0–28) [32]. The Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (MGH-CPFQ; range 7–42) [33] measures patients' cognitive and physical well-being, and the Multidimensional Fatigue Inventory (MFI) [34] measures five constructs related to fatigue, including general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. Each subscale ranges from 0 to 20. For all scales, higher scores indicate worse health status.

Treatment Characteristics

Treatment variables of interest included 1) type and number of pharmacologic treatments patients were currently taking (including new and continuing medications), 2) type of nonpharmacologic interventions used in the last 12 months as reported by the patient, and 3) treatment use patterns (including patients new to treatment, switching from, or augmenting with prior treatments). Pharmacologic treatment could include, but was not limited to, any medication for the management of FM, including antidepressants, pain medications, anticonvulsants, stimulants, sleep agents, or anxiolytics.

Statistical Analysis

Descriptive statistics were used to characterize current treatment patterns. Mean and standard deviation (SD) were calculated for continuous variables, and proportions were reported for categorical variables.

Analyses were also performed to determine which patient and physician characteristics were associated with specific FM treatments. Specifically, stepwise logistic regression models were run to determine factors independently associated with the use of the three medications with FDA approval for the treatment of FM (duloxetine, pregabalin, and milnacipran) vs all other medications. Models were also run to determine factors associated with duloxetine (vs no duloxetine), pregabalin (vs no pregabalin), and milnacipran (vs no milnacipran).

Variables of interest were allowed to enter the models at a 0.2-level and exit at a 0.1-level. These included the following:

- Patient characteristics: age over 65, gender, race, body mass index, socioeconomic status (whether the patient was comfortable, had just enough to pay the bills, or not enough to pay the bills), insurance coverage (yes or no), insurance type (private, public, or combination insurance), and region (whether the patient was receiving treatment in Puerto Rico vs other areas of the United States).
- Disease burden: BPI-I, BPI-S, FIQ, PHQ-8, GAD-7, PHQ-15, MFI general fatigue score, MFI physical fatigue score, MFI reduced activity score, MFI reduced motivation score, MFI mental fatigue score, MGH-CPFQ, ISI, SDS, and receipt of disability income in past 12 months.
- Physician characteristics: gender, specialty, and years of practice.
- Medication characteristics: use of opioids (excluding tramadol), use of nonsteroidal anti-inflammatory drugs (NSAIDs), number of medications currently taking, and medication status for FM (no treatment in the last 6 months, switching, augmenting).

All analyses were performed with SAS® Version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Patient and Physician Characteristics

A total of 2,115 patients were recruited into the study; 2,048 patients met the entry criteria and were eligible to participate in the study. Three hundred sixteen (15.4%) patients missed the baseline telephone interview, and 32 (1.6%) patients refused to participate. Out of the 2,048 eligible participants, there were 1,700 (83.0%) baseline participants. Patients were mostly female (94.6%) and white (82.9%), and had a mean age of 50.4 years (Table 1). Patients had a diagnosis of FM for 5.6 years, on average.

Table 1 Patient demographic characteristics at baseline

	Total N = 1,700
Age (years), mean (SD)	50.4 (11.9)
Over 65 years of age, N (%)	159 (9.4)
Women, N (%)	1,601 (94.6)
Race, N (%)	
White	1,391 (82.9)
Black	62 (3.7)
Asian	7 (0.4)
Native American	9 (0.5)
Hispanic	209 (12.5)
Region, N (%)	
United States (excluding Puerto Rico)	1,539 (90.5)
Puerto Rico	161 (9.5)
Body mass index, mean (SD)	31.3 (7.5)
Enough to pay the bills, N (%)	
Comfortable	633 (37.7)
Just enough	603 (35.9)
Not enough	442 (26.3)
Has insurance, N (%)	1,647 (96.9)
Insurance type, N (%)	
Public	321 (19.5)
Private	1,035 (63.0)
Combination	287 (17.5)

SD = standard deviation.

Of the 91 physicians in our study, 72.9% were male, and most were rheumatologists (59.3%) or primary care physicians (27.5%), followed by other specialties (14.2%). The mean (SD) number of years of practice in our sample was 15.6 (9.2). Most of the physicians were confident in diagnosing FM (mean = 4.4 on a scale of 1–5 [1 = completely disagree; 5 = completely agree]); agreed that psychological aspects of FM are important (mean = 4.5), and that the tender-point examination is important in diagnosing FM (mean = 4.2). Most did not agree with the statement that symptoms FM patients suffer are psychosomatic (mean = 2.2). Most of the physicians were more confident in treating FM with medications (mean = 4.3) than with alternative therapies (mean = 3.4), and most agreed with the statement that FM was more difficult to treat than other kinds of pain (mean = 3.8).

Disease Burden

On average, physicians reported that their patients with FM could be characterized with the following symptoms: widespread chronic pain (85.8%), mood symptoms (63.3%), sleep disorders (73.8%), and symptoms of fatigue (83.7%). Physicians reported that most of their patients had moderate to extremely severe symptom severity (91.6%) as well as moderate to severe disability (73.2%).

Table 2 Patient clinical characteristics at baseline

Health Status	Total N = 1,700 Mean (SD)
Concomitant diagnoses*	6.2 (2.9)
Brief Pain Index, severity	5.5 (1.8)
Brief Pain Index, interference	6.1 (2.2)
Fibromyalgia Impact Questionnaire, Total	54.4 (13.7)
Depression severity (PHQ-8)	13.0 (6.1)
Anxiety severity, (GAD-7)	10.8 (5.8)
Physical symptoms (PHQ-15)	13.7 (4.7)
Multidimensional Fatigue Inventory	
General fatigue	11.7 (2.4)
Physical fatigue	13.1 (2.3)
Reduced activity	12.6 (2.4)
Reduced motivation	11.0 (2.9)
Mental fatigue	11.5 (2.4)
MGH-CPFQ total score	26.4 (6.5)
Insomnia Severity Index	17.5 (6.0)
Sheehan Disability Scale	18.3 (7.6)
FM History	**Mean (SD)**
Time since first symptoms in months	120.1 (109.7)
Time since first FM diagnosis in months	67.4 (75.5)
No. of health care professionals seen for symptoms before FM diagnosis	3.6 (5.5)
No. of health care professionals currently involved in treatment of FM	1.6 (1.3)
Resource Utilization	
Any emergency room visit, N (%)	680 (40.2)
Any use of partial care (e.g., day care, day nursing home, observation), N (%)	171 (10.1)
Outpatient visits†, N (%)	1,405 (82.9)
Visits to specialty care, mean (SD)‡	7.9 (11.9)
Productivity Measures	
Family/friend(s) missed work due to your illness, N (%)	379 (22.3)
Cared for by an unpaid caregiver or relative, N (%)	622 (36.8)
Days of care by unpaid care giver, mean (SD)‡	88.5 (130.9)
Missed any work due to FM, N (%)	743 (47.4)
Days cut down on things for 1/2 day or more due to health, mean (SD)‡	100.7 (112.3)
Job effectiveness (0–100), mean (SD)	59.7 (27.3)
Received disability income benefits, N (%)	507 (29.9)
Months of disability income, mean (SD)‡	10.6 (3.1)

* *Concomitant diagnoses* included asthma, diabetes, heart disease, back pain, depression, arthritis, rheumatoid arthritis, sleep disorder, anxiety, chronic fatigue syndrome, irritable bowel syndrome, migraine, abdominal pain, hypertension, temporomandibular joint disorder, ulcer, emphysema, systemic lupus erythematosus, neurological disorder, chronic viral illness, liver disease, interstitial cystitis, renal disease, cancer, and substance abuse.

† *Outpatient visits* included visits to primary care physicians, specialty care, physical therapists, and nonphysician care providers (e.g., nurses, counselors).

‡ Means include only patients who experienced the event.

FM = fibromyalgia; GAD = Generalized Anxiety Disorder; MGH-CPFQ = Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire; PHQ = Patient Health Questionnaire; SD = standard deviation.

Patient clinical characteristics at baseline are presented in Table 2. Patients reported being diagnosed by a physician over the last 3 years with an average of six concomitant chronic medical conditions (range from 0 to 25 conditions). Of these 25 conditions, back pain (81.6%) was the most predominant condition reported. On average, over half of the patients in the sample reported prior diagnoses of depression (64.0%), arthritis (61.8%), sleep disorder

(58.5%), and anxiety (57.5%). Based on cut-points of validated measures, most patients also had moderate to severe rates of insomnia (71.3%; ISI score of 15 or greater), depression (69.3%; PHQ-8 score of 10 or greater), and anxiety (56.2%; GAD-7 score of 10 or greater). The mean (SD) FIQ total score was 54.4 (13.7) (total score ranges from 0 to 80, with higher scores indicating a more negative impact). Most patients claimed to have moderately/markedly diminished or absent ability to focus (57.1%), remember/recall information (63.2%), find words (52.6%), and experience sharpness/mental acuity (52.8%), as ascertained by items from the MGH-CPFQ. The most common events associated with the onset of FM were chronic stress (16.1%), physical trauma (12.8%), emotional trauma (7.1%), other (7.0%), and acute illness (6.2%).

Our findings of the annual health care resource utilization is presented as percentage followed by (mean [SD] for only those that used the service): 40.2% of patients visited emergency rooms (visits: 2.4 [2.6]) and 82.9% visited outpatient facilities (visits: primary care 7.0 [12.3], specialty care 7.9 [11.9], and physical therapy 5.8 [24.9]). Patients experienced a high number of work limitations related to FM: 47.4% missed work (mean [SD] days: 58.4 [102.8]); 29.9% received disability income (mean [SD] months on disability 10.6 [3.1]); and 21.6% were unemployed. Annually, patients spent 38.4 (68.7) days in bed, and 22.3% of caregivers missed paid work due to patients' illness (7.9 [17.5] days missed).

Treatment Patterns

A total of 182 unique medications were prescribed specifically for FM (as reported by physicians). Patients were currently taking an average of 2.6 medications for FM. Concomitant medication use occurred in 77.8% of patients (number of medications [percentage]: 2 [28.1%], 3 [22.4%], 4 [24.8%], 5 [2.4%], and 6 medications [0.2%]). For the 11% of patients who switched medications, the primary reasons were lack of efficacy (67.5%) and intolerance (16.5%).

As shown in Table 3, among 1,700 study patients, current medications prescribed for FM included the three FDA-approved drugs: duloxetine (26.8% of patients; approved July 2008), pregabalin (24.5%; approved June 2007), and milnacipran (8.9%; approved March 2009). Other drugs commonly used included NSAIDs (26.6%), opioids (24.2%), tramadol (15.3%), benzodiazepines (15.2%), and cyclobenzaprine (12.9%).

Nonpharmacologic treatment specifically for FM, as reported by physicians, was prescribed to 1,029 patients (60.5%) during the enrollment visit, and all patients (except seven who did not provide any response) previously had some form of nonpharmacologic treatment over the past 12 months. The most common nonpharmacologic treatments were rest (91.0%), exercise (89.5%), and heat modalities (75.5%) (Table 4).

Table 3 Current medication use for FM including newly initiated and continuing therapies

Type of Treatment, N (%)	N = 1,700
Duloxetine	456 (26.8)
NSAIDs	453 (26.6)
Pregabalin	416 (24.5)
Opioids (excluding tramadol)	412 (24.2)
Tramadol	260 (15.3)
Benzodiazepines	259 (15.2)
Selective serotonin reuptake inhibitors	223 (13.1)
Cyclobenzaprine	219 (12.9)
Nonbenzodiazepine sedative/hypnotics	219 (12.9)
Gabapentin	190 (11.2)
Milnacipran	152 (8.9)
Other antidepressants, not elsewhere classified*	132 (7.8)
Amitriptyline	92 (5.4)
Stimulants	88 (5.2)
Other medications, not elsewhere classified†	79 (4.6)
Other tricyclic antidepressants	69 (4.1)
Venlafaxine	69 (4.1)
Acetaminophen	58 (3.4)
Antivirals	52 (3.1)
Corticosteroids	46 (2.7)
Other anti-epileptics	41 (2.4)
Desvenlafaxine	38 (2.2)
Antipsychotics	29 (1.7)
Lidocaine	26 (1.5)
Nutritional supplements/vitamins	24 (1.4)
Nonergoline dopamine agonist	24 (1.4)
Medication Status	
Number of medications for FM, mean (SD)	2.58 (1.2)
Currently taking an opioid, N (%)	412 (24.2)
Currently taking NSAIDs, N (%)	453 (26.6)
Medication status at baseline, N (%)	
No treatment	247 (14.5)
Switching medications	187 (11.0)
Augmenting medications	1,266 (74.5)

* *Other antidepressants, not elsewhere classified* included bupropion, mirtazapine, trazadone, and buspirone (sometimes used off-label as an antidepressant).

† *Other medications, not elsewhere classified* included all remaining medications physicians reported prescribing to study patients that individually accounted for less than 1.4% of the total sample.

FM = fibromyalgia; NSAIDs = nonsteroidal anti-inflammatory drugs; SD = standard deviation.

Factors Associated with Treatment Selection: Multivariate Findings

Multivariate findings comparing the use of duloxetine, pregabalin, and milnacipran with any other medication are

Table 4 Nonpharmacologic interventions for FM during the past 12 months

	Total N = 1,700, N (%)
Rest	1,547 (91.0)
Exercise*	1,521 (89.5)
Heat modalities	1,284 (75.5)
Prayer/relaxation/meditation	1,279 (75.2)
Distraction	1,185 (69.7)
Cold therapy	714 (42.0)
Massage, reflexology	590 (34.7)
Counseling†	575 (33.8)
Trigger-point injections	466 (27.4)
Chiropractic manipulation	403 (23.7)
TENS unit	314 (18.5)
Acupuncture	149 (8.8)
Energy healing (Reiki)	85 (5.0)
Biofeedback	81 (4.8)
Cognitive-behavioral therapy	77 (4.5)
Spinal surgery	59 (3.5)
Hypnosis	18 (1.1)

* *Exercise* included gentle walking, aerobic, pilates, strength training, stretching, and pool therapy.
† *Counseling* included sessions with Master in Social Work, psychologists, psychiatric consult, and support groups.
FM = fibromyalgia; TENS = transcutaneous electrical nerve stimulation.

shown in Table 5. Medication history was one of the best predictors of the type of current medication patients were taking. Patients taking duloxetine (odds ratio [OR] = 0.475, 95% confidence interval [CI] = 0.337–0.670, $P < 0.001$), pregabalin (OR = 0.510, 95% CI = 0.357–0.728, $P < 0.001$), and milnacipran (OR = 0.460, 95% CI = 0.264–0.801, $P = 0.006$) were less likely to be on NSAIDs, whereas patients on other medications were significantly more likely to be on NSAIDs (OR = 0.447, 95% CI = 0.337–0.594, $P < 0.001$). Additionally, duloxetine was associated with less opioid use (OR = 0.576, 95% CI = 0.409–0.810, $P = 0.002$; excluding tramadol), and other medications were associated with more opioid use (OR = 0.667, 95% CI = 0.498–0.893, $P = 0.006$). Duloxetine (OR = 1.381, 95% CI = 1.220–1.563, $P < 0.001$) and pregabalin (OR = 1.800, 95% CI = 1.501–2.157, $P < 0.001$) use was associated with use of significantly more medications concomitantly, whereas use of other medications was associated with having fewer medications prescribed (OR = 1.394, 95% CI = 1.247–1.558, $P < 0.001$). Pregabalin also tended to be a first medication (of any kind) as opposed to an augmenting treatment (OR = 1.807, 95% CI = 1.004–3.253, $P = 0.049$).

Physician variables were also among the best predictors of the type of current medication patients were taking. Rheumatologists were more likely than primary care physicians to prescribe duloxetine (OR = 1.702, 95% CI = 1.090–2.657, $P = 0.019$), pregabalin (OR = 3.203, 95% CI = 1.980–5.182, $P < 0.001$), and milnacipran (OR = 2.154, 95% CI = 1.009–4.598, $P = 0.047$), and less likely to prescribe other medications (OR = 2.662, 95% CI = 1.864–3.802, $P < 0.001$). Other specialists were more likely to prescribe duloxetine (OR = 2.153, 95% CI = 1.324–3.499, $P = 0.002$) and milnacipran (OR = 4.915, 95% CI = 2.199–10.986, $P < 0.001$), and less likely to prescribe other medications (OR = 2.671, 95% CI = 1.758–4.06, $P < 0.001$) as compared with primary care physicians. Physicians prescribing duloxetine were more likely to be female (OR = 1.623, 95% CI = 1.081–2.437, $P = 0.020$), whereas physicians prescribing "other" medications were less likely to be female (OR = 1.665,

Table 5 Stepwise logistic regressions models of baseline medication use: duloxetine, pregabalin, or milnacipran (N = 634) vs any other medication (N = 641)

	OR	95% CI	*P* Value
Patient demographics*			
Age over 65	0.535	0.338–0.845	0.0074
Clinical variables†			
None significant			
Physician variables‡			
Female physician	1.665	1.192–2.325	0.0028
Rheumatology vs PCP	2.662	1.864–3.802	<0.0001
Other specialty vs PCP§	2.671	1.758–4.06	<0.0001
Medication variables¶			
Use of opioids	0.667	0.498–0.893	0.0064
Use of NSAIDs	0.447	0.337–0.594	<0.0001
No. of medications taking	1.394	1.247–1.558	<0.0001

* Age over 65, gender, race, body mass index, socioeconomic status, insurance status, insurance type, region (receiving treatment in Puerto Rico vs other areas of the United States).
† Brief Pain Inventory for average severity (BPI-S) and average interference (BPI-I) pain average score, Fibromyalgia Impact Questionnaire (FIQ) total score, Patient Health Questionnaire (PHQ)-8 total score, Generalized Anxiety Disorder (GAD)-7 total score, PHQ-15 total score, Multidimensional Fatigue Inventory (MFI) general fatigue score, MFI physical fatigue score, MFI reduced activity score, MFI reduced motivation score, MFI mental fatigue score, Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (MGH-CPFQ) total score, Insomnia Severity Index (ISI) total score, and Sheehan Disability Scale (SDS) total score, and receipt of disability income in the past 12 months.
‡ Gender, specialty, years of practice.
§ *Other specialties* included neurology, psychiatry, pain specialists, physical medicine, obstetrics and gynecology, and osteopathy.
¶ Use of opioids (excluding tramadol), use of NSAIDs, number of medications, medication status (no treatment, switching, augmenting).
OR = odds ratio; CI = confidence interval; PCP = primary care physician; NSAID = nonsteroidal anti-inflammatory drug.

95% CI = 1.192–2.325, $P = 0.003$). Physicians prescribing pregabalin were more likely to have fewer years of practice (OR = 0.958, 95% CI = 0.942–0.974, $P < 0.001$).

Additional variables associated with drug use varied by drug cohort. Current duloxetine use was associated with patients having private commercial insurance vs public insurance (such as Medicare, Medicaid, or Champus; OR = 1.710, 95% CI = 1.154–2.534, $P = 0.008$) and a reduced activity score on the MFI (OR = 1.068, 95% CI = 1.006–1.134, $P = 0.031$). Pregabalin use was associated with patients younger than 65 years of age (OR = 0.449, 95% CI = 0.228–0.881, $P = 0.020$), whereas other medication use was associated with patients 65 years of age or older (OR = 0.535, 95% CI = 0.338–0.845, $P = 0.007$). Pregabalin use was also associated with not having enough household income to be "comfortable" (OR = 0.669, 95% CI = 0.457–0.980, $P = 0.039$) or to "pay the bills" (OR = 0.547, 95% CI = 0.374–0.800, $P = 0.002$). Finally, pregabalin use was associated with lower (less functional impact of FM) FIQ scores (OR = 0.988, 95% CI = 0.977–0.999, $P = 0.032$). Milnacipran use was significantly associated with higher body mass indices (OR = 1.027, 95% CI = 1.001–1.053, $P = 0.039$), less severe cognitive and physical impairment according to the MGH-CPFQ (OR = 0.941, 95% CI = 0.910–0.973, $P < 0.001$), and higher rates of insomnia, according to the ISI (OR = 1.048, 95% CI = 1.009–1.089, $P = 0.016$).

Sensitivity analyses were performed to assess the fit and robustness of models. As logistic regression models only included 1,275 (75%) patients, a multiple imputation technique was used to impute missing predictors. A Markov Chain Monte Carlo approach was used to impute values for the missing data (a total of 685 patients [40%] have missing data points for one or more of the variables) and produce multiple data sets without missing values. Logistic regression analyses were run again with the imputed data. No substantial differences were observed. Models were also run with two definitions of opioid medication use (with and without tramadol included). Models reported in Table 5 exclude tramadol in the category of opioids in order to represent distinctions specified in the APS guidelines for FM. The results, including tramadol as an opioid, remained the same for models predicting use of duloxetine and milnacipran. When tramadol was added to the opioid class, pregabalin use was significantly and negatively associated with opioid use. Additionally, when tramadol was added to the opioid class, use of other medications was no longer associated with patients over 65 years of age, but it was associated with having a lower likelihood of being privately insured.

Discussion

The purpose of this report of the REFLECTIONS study baseline findings is to provide a cross-sectional description of real-world practice, including the burden of illness, treatment patterns, and factors associated with treatment choice, in a large sample of FM patients enrolled from both primary care and specialty settings.

Disease Burden

The burden of illness across a wide variety of measures was high for study patients. Most patients experienced clinically significant levels of disability, insomnia, depressive and anxiety symptoms, and cognitive problems as determined with standard cut-points for validated scales. Although patients with FM commonly report cognitive impairments [12], this is one of the first studies to document the severity of cognitive functioning in a naturalistic study. Most REFLECTIONS patients reported on the MGH-CPFQ an impaired ability to focus/concentrate, an impaired ability to recall information, word-finding difficulties, and reduced mental clarity.

Overall, the study findings were fairly consistent with demographic and outcome data from populations in France and Germany [35]. Compared with REFLECTIONS, the European study [35] reported an FIQ mean total score of 53.3 (vs 54.4) and a BPI-S mean score of 4.9 (vs 5.5, which represents moderate pain) [35].

In REFLECTIONS, patients experienced high annual work limitations related to FM: 47.4% missed work (mean [SD], 58.4 [102.8] days); 29.9% received disability income (mean [SD], 10.6 [3.1] months on disability); and 21.6% were unemployed. Health care resource utilization reported by patients was also consistent with previously reported retrospective claims data [20–22]. Annual health care use was high, with most patients visiting outpatient facilities. The rate of REFLECTIONS patients with emergency room visits was higher than those reported in retrospective insurance claims data (40.2% vs 19.7–23.3% in previous claims) [20,36].

Treatment Patterns

Multiple treatment approaches to FM were observed in this study. Physicians prescribed 182 different medications and most use included concomitant medications, with only 22% of patients taking only one medication. Although high use of various medications has been previously reported from insurance claims data [20–22,37,38], this study strengthens previous findings as it is the only study to provide an exhaustive list by physicians of all currently prescribed medications used to treat FM. In contrast, drug claims reported in FM populations cannot distinguish the indication for use when multiple conditions are present. The rate of concomitant medication use was higher than the rate found in previous literature using claims data [20,36], in which approximately one third of patients with FM, and over 40% of established patients with FM (i.e., those with consistent diagnoses for over 1 year), reported concomitant use of select medications [36]. Differences may be due to methods of collecting medication data or may be due to changing standards of practice.

The most commonly prescribed pharmacologic treatments in the REFLECTIONS study included the FDA-approved medications pregabalin, duloxetine, and milnacipran. This represents recent changes in treatment patterns when compared with the National Fibromyalgia Association's 2005 survey data, in which acetaminophen, ibuprofen, naproxen, cyclobenzaprine, amitriptyline, and aspirin were the most commonly used medications. Treatment patterns may reflect current changes in the environment with the entry of pregabalin in June 2007, duloxetine in June 2008 (just before the start of the study), and milnacipran in March 2009 (midway through the study enrollment period).

Opioids (excluding tramadol), NSAIDs, and benzodiazepines were also among the more frequently used medications in the REFLECTIONS study, despite there being little or inconclusive evidence to support the efficacy of these medications to treat FM. Despite the lack of evidence and the potential for side effects, the literature has reported that, among internet survey respondents with FM, opioids were among the highest ranking medications for perceived helpfulness [12]. Benzodiazepenes and nonbenzodiazepene sedatives may have been prescribed more for their roles in sleep disturbances rather than in FM specifically [13,18].

Nonpharmacologic treatments were prescribed to 60.5% of patients during the baseline visit, and all patients reported that they had received some form of nonpharmacologic treatment over the preceding 12 months. The most frequent therapies included exercise, rest, heat modalities, and cognitive strategies (e.g., prayer/relaxation/meditation and distraction). Again, these more frequently used therapies in the REFLECTIONS study were among those reported earlier by internet survey participants as being perceived to be the most effective treatments [12]. One exception was CBT. Despite strong evidence for its efficacy [18], CBT was administered to only 4.5% of patients over the preceding 12 months; whereas trigger-point injections, with less scientific evidence of efficacy in FM, were administered to 27.4% of patients. Less use of CBT may be related to its accessibility rather than to physician recommendations or patients' requests.

Factors Associated with Treatment Choice

Treatment patterns for duloxetine, pregabalin, and milnacipran tended to be associated with physician specialty, insurance type, and medication history. For example, rheumatologists and other specialists were more likely to prescribe approved medicines for FM than medicines for which there was little or no evidence base for efficacy in FM, perhaps reflecting greater evidence-based knowledge about FM treatment. Surprisingly, clinical characteristics of severity of pain, depression, anxiety, disability, cognition, sleep disturbances, and fatigue were not significantly related to the current medication patterns assessed at a single point in time. It was also of interest that, aside from age, patient demographics and socioeconomic status were not associated with treatment selection.

There are some limitations to these findings. First, patients may have initiated the new agent at any time in the management cycle for FM. For example, patients may have been naïve to treatment, switching from one medication to another, or adding the new medication to other medications. On average, patients reported living with FM for over 5 years. Although no significant differences were found across medication cohorts based on length of illness, these findings may not be generalizable to newly diagnosed patients, especially as new treatments have been made available. Previous research reported that the use of APS guideline medications tended to increase from prediagnosed and newly diagnosed to established patients with FM [36].

Second, patterns of care were found to be very diverse (use of nonpharmacologic treatments was universal, and polypharmacy was quite common), thus limiting the ability to assess any individual treatment as a stand-alone therapy. The rates of duloxetine and milnacipran use may be higher because these drugs were newly approved for FM; it is likely that patients had previously been prescribed other medications prior to this study. Use of the newer medications may also reflect changing trends in treatment of FM during and since the FDA approvals of medications for its management.

Third, the patients and physicians in this study may not have been nationally representative. Although the sample size was large and sites included offices in 26 states and several sites in Puerto Rico, participating physicians may have included those with greater knowledge of FM than other physicians treating FM patients. For example, participating physicians appeared knowledgeable about FM based on their consistent ratings of beliefs and understanding of FM that appeared consistent with the literature. However, the demographics and outcomes were consistent with other epidemiologic studies [12,35,39].

Fourth, REFLECTIONS did not capture all factors that might influence treatment selection, such as patient preference for medications, prior history of medication use beyond 12 months, and availability of select drugs within a health care system. While data from retrospective claims and randomized clinical trials offer much information, the reasons for select treatment decisions and the clinical outcomes associated with drug selection cannot be determined through either of these study methods. Further, randomized clinical trials may not represent patients in general practice where comorbid conditions and concomitant medications are common [40]. Thus, naturalistic studies may provide a different dimension of knowledge that allows a broad, inclusive, and more generalizable understanding of treatment for patients.

Conclusions

The prospective, observational design of the REFLECTIONS study makes it possible to address current gaps in a rapidly growing and evolving body of literature on FM. FM is a difficult condition to characterize and treat, and

this is a time of change in management of this disorder due to emergence of FDA-approved medications. Our study provides a snapshot of a sample of patients, each with multiple symptoms that vary greatly among individuals, who are being treated with a wide array of medications and nonpharmacologic therapies. We find that many of the treatments with the strongest evidence for their efficacy were among the most frequently used. Importantly, however, many of the 182 prescription medications and some of the nonpharmacologic treatments were not being used in accordance with supporting evidence. The longitudinal assessment of REFLECTIONS study patients may offer further insights into the treatment and outcomes of FM during the 12 months following this baseline analysis.

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