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Longitudinal Observation of Treatment Patterns and Outcomes for Patients with Fibromyalgia: 12-Month Findings from the REFLECTIONS* Study

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*Real World Examination of Fibromyalgia: Longitudinal Evaluation of Costs and Treatments.

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Abstract

Objective. To describe 12-month treatment patterns and outcomes for patients starting a new medication for fibromyalgia in routine clinical practice.

Design and Outcome Measures. Data from 1,700 patients were collected at baseline and 1, 3, 6, and 12 months. Repeated measures and Poisson regression models controlling for demographic, clinical, and baseline outcomes were used to assess changes in health outcomes (Brief Pain Inventory severity and interference, Sheehan Disability Scale, Fibromyalgia Impact Questionnaire), satisfaction, and economic factors for patients who initiated on pregabalin (214, 12.6%), duloxetine (264, 15.5%), milnacipran (134, 7.9%), or tricyclic antidepressants (66, 3.9%). Sensitivity analyses were run using propensity-matched cohorts.

Results. Patients started on 145 unique drugs for fibromyalgia, and over 75% of patients took two or

more medications concurrently for fibromyalgia at each time point assessed. Overall, patients showed improvement on the four health outcomes, with few differences across medication cohorts. At baseline, patients reported annual averages of 20.3 visits for outpatient care, 27.7 missed days of work, and 32.6 days of care by an unpaid caregiver. The duloxetine and milnacipran (vs pregabalin or tricyclic antidepressant) cohorts had fewer outpatient visits during the 12-month study. Patients reported satisfaction with overall treatment and their fibromyalgia medication (46.0% and 42.8%, respectively).

Conclusions. In this real-world setting, patients with fibromyalgia reported modest improvements, high resource, and medication use, and were satisfied with the care they received. Cohort differences were difficult to discern because of the high rates of drug discontinuation and concomitant medication use over the 12-month study period.

Key Words. Fibromyalgia; Treatment; Observational; Longitudinal; Pharmacotherapy; Outcomes

Introduction

Fibromyalgia (FM) is a painful chronic condition associated with high levels of long-term social and economic burden [1]. Patients experience a wide range of symptoms with varying intensities that can wax and wane over time [2]. Only one study was found to measure health outcomes over time (without assessment of treatment) in large clinical practice settings [3]. In that study, 1,555 patients identified through the National Data Bank for Rheumatic Diseases were surveyed in 6-month intervals for a mean duration of 4 years and were found to have generally high levels of symptoms and distress over time, with modest improvement noted over the period of observation. Because of the chronic nature of FM, patients experience long-term illness-related burdens, including reduced daily functioning and interference with work (including absenteeism and productivity loss while at work), as well as disability assistance claims and economic difficulties [4,5]. In one 6-month study of 91 working women with FM, 25% received disability assistance or retired because of FM, and over 50% missed some work because of the condition (approximately 4 weeks annually) [4]. Patients with FM may experience substantial losses in quality of life [6] while incurring great costs for health care services [5].

Poor economic outcomes have been associated with the presence of symptoms common in FM, including chronic pain, depressive symptoms, sleep disturbances, fatigue, back pain, and anxiety [7–12]. Further, family members and caregivers of patients with FM experience caregiver-related burdens as well as economic hardships [13].

Among the goals of treatment for FM are pain reduction, restoration of physical function, and reduction in the utilization of expensive health care resources [14]. Deciding on the appropriate treatment may be complicated by the overlap of FM with symptoms of other health conditions, such as other pain or mood disorders, sleep disturbances, and fatigue [15–17]. It is believed that medications targeting more than one symptomatic domain (i.e., those with unique underlying biochemical and neurophysiologic abnormalities) may allow for more successful individualization of therapy [14].

Currently, there are three US Food and Drug Administration (FDA)–approved medications for the management of FM: pregabalin, which is an α-2-delta modulator, and the serotonin and norepinephrine reuptake inhibitors (SNRIs) duloxetine and milnacipran. FDA approvals for the management of FM were granted in June 2007 for pregabalin, June 2008 for duloxetine, and January 2009 for milnacipran. In addition, various other drug classes, such as tricyclic antidepressants (TCAs), are used off-label to treat FM and are often recommended as first-line therapy [18–20].

Most research examining medication treatment patterns for patients with FM have used retrospective insurance claims data [21–25]. These studies report extensive use of prescription medications and other health care resources in patients with FM. Earlier work identified that total direct and indirect costs for claimants with FM were twice the total cost of overall claimants, with the indirect costs three times higher [21]. However, only 6% of these costs were attributable to FM-specific claims [21]. Recent studies highlight that the choice of treatment may be influenced by patient demographics or the presence of select comorbidities [26]. For example, patients with FM who were prescribed duloxetine vs other medications were more likely to have a history of rheumatoid arthritis or sleep disorders [26]. The most effective treatments reported by self-selected respondents to an Internet survey were rest, heat, pain medications, antidepressants, and hypnotics [27]. The medications perceived to be the most effective were hydrocodone preparations, alprazolam, oxycodone preparations, zolpidem, cyclobenzaprine, and clonazepam [27]. The results of this survey and claims data guided the development of the current study, ensuring the full representation of specific medications, symptoms, and comorbid conditions identified for study.

To our knowledge, no study has addressed the long-term treatment patterns and effect of various therapies on outcomes for patients receiving care for FM in actual clinical practice [28]. Randomized clinical trials may not be representative of patients in general practice, where comorbid conditions and concomitant medications are common [29]. Data from insurance claims cannot determine clinical outcomes associated with medication use, nor can claims distinguish the indication for use when multiple conditions are present.

This observational study, which we identified as the REFLECTIONS (Real World Examination of Fibromyalgia: Longitudinal Evaluation of Costs and Treatments) study, was designed to prospectively evaluate long-term treatment patterns, health outcomes, and economic

outcomes in actual clinical practice among patients who were newly prescribed a medication for FM and followed for 12 months. Baseline findings from REFLECTIONS previously reported high levels of burden of illness and much variability in treatment patterns for patients with FM [28]. At baseline, most patients experienced moderate to severe symptoms of pain, disability, insomnia, depression, and anxiety. Almost all patients had multiple visits to outpatient facilities and almost half missed work due to FM. Caregivers also have work limitations due to the patient's FM. On average, patients had experienced FM for 5 years. Patients were taking a variety of medications and alternative or complementary treatment modalities. Multiple treatment approaches were observed, with physicians prescribing 182 different medications to treat patients with FM. The majority of patients (78%) was taking more than one medication for FM and was also prescribed nonpharmacologic interventions (60.5%) at study entry. The treatments with the most evidence to support their use were not always the most frequently chosen. Common medications included the FDA-approved medications duloxetine (26.8%), pregabalin (24.5%), and milnacipran (8.9%). Nonsteroidal anti-inflammatory drugs (26.6%), opioids (24.2%), and benzodiazepines (15.2%) were also among the more frequently used medications despite little or inconclusive evidence to support the efficacy of these medications to treat FM.

Treatment selection of branded medications vs all other drugs was most strongly associated with physician specialty, insurance type, and medication history and not significantly related to current medication patterns or severity of pain and other FM-related symptoms [28]. In multivariate models, duloxetine initiators were more likely to have private insurance; sustain greater reductions in activities; have physicians who were female, rheumatologists, or other specialists; and take more FM medications [28]. They were less likely to be using opioids or nonsteroidal anti-inflammatory drugs (NSAIDs) [28]. Pregabalin initiators were more likely to be <65 years of age, have "not enough" income, have lower Fibromyalgia Impact Questionnaire (FIQ) total scores, have physicians who were younger and rheumatologists [28], and take more FM medications. They were less likely to be using NSAIDs. Milnacipran initiators were more likely to have higher body mass indexes (BMIs), better (lower) scores on cognitive and physical functioning, more severe insomnia, and physicians who were rheumatologists or other specialists. They were less likely to use NSAIDs. "Other" medication initiators were more likely to be ≥65 years of age and use opioids/NSAIDs, were less likely to have physicians who were males and primary care physicians, and took a lower mean number of medications.

For this longitudinal assessment of REFLECTIONS, the objectives were 1) to describe the 12-month treatment patterns for patients who are "newly prescribed" pharmacologic treatments for FM; 2) to examine illness-related burdens considered key to quality of life patients with FM [30] including pain severity and interference (Brief Pain Inventory [BPI]) [31], disability (Sheehan Disability Scale [SDS]) [32], function (FIQ) [33], and economic factors associated with work loss and health care resource utilization; and 3) to examine patients' satisfaction with their overall medical care and with their medication.

Methods

Study Setting

The study methodology is fully described by Robinson et al. [28] and summarized here as it pertains to this report. Study participants were enrolled from 58 health care settings (including 91 participating physicians) in the United States and Puerto Rico. Study sites included outpatient practices of rheumatology (59.3%), primary care (37.4%), neurology (2.2%), psychiatry (3.3%), pain specialists (3.3%), physical medicine (2.2%), obstetrics, and gynecology (1.1%), and osteopathy (1.1%). Sites were selected on the basis of reported number of patients seen per month, experience in observational or clinical research, and whether they received good clinical practice training prior to being included in the study. 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.

Eligible patients were at least 18 years of age, had been determined to have FM by the enrolling physician, were under the care of the enrolling physician, were cognitively able to understand and complete patient self-rated scales in English or Spanish via telephone interviews, and agreed to participate in the study for 12 months. Patients also had to be initiating a "new" treatment for FM, defined as being naive to the treatment (over the last 6 months), starting a new therapy to replace a previously used therapy (switching treatment), or adding a new therapy to their current FM treatment regimen (augmenting treatment). Study site personnel and/or their immediate families were excluded from the study.

Study Design and Measures

This was a prospective 12-month observational study designed to determine the treatment patterns and health outcomes (including symptom severity, functionality, and economic impact) of patients with FM. Measures included in REFLECTIONS were in part those deemed important for determining treatment success in other studies by the Outcome Measures in Rheumatology Clinical Trial fibromyalgia steering committee [30]. The domains included pain, fatigue, global functioning, sleep quality, health-related quality of life, physical functioning, depression, anxiety, and dyscognition. All patient care by the enrolling physician occurred as part of the physician's routine clinical care. Treatment pattern and treatment initiation or changes were solely at the discretion of the physician and the patient. Patients could initiate a "new" pharmacologic agent at any time in their management cycle for FM.

Data were collected using a physician survey, a patient visit form, and computer-assisted telephone interviews

(CATI). Prior to enrolling patients into the study, the physician completed a physician survey to identify his or her demographic and practice characteristics (such as number of years in practice and specialty) and beliefs and attitudes about FM. Patients were invited to participate in the study during a patient visit in which the patient was prescribed a new pharmacologic treatment for management of FM. Unlike previous studies or claims assessments, the REFLECTIONS study used a list of unique medications that included any treatment that physicians reported specifically for the treatment of FM. Each medication reported by the physician was uniformly coded, as defined using the World Health Organization Drug Dictionary classification for unique medicinal products at the generic name level [34] (e.g., pregabalin, duloxetine, milnacipran, gabapentin, acetaminophen, amitriptyline, tramadol, cyclobenzaprine). For descriptive purposes, drugs were later categorized using this classification system at the class (e.g., selective serotonin reuptake inhibitor [SSRI]) or therapeutic level (e.g., antidepressants). A patient form was completed at this time to assess patient demographics, medical history with enriched items on FM history, baseline treatment patterns, and the physician's assessment of the patient. There were no additional study-specific office visits nor additional input from physicians required for the remainder of the study. All further data were collected using CATI, in which patients were asked to respond to various questions regarding their health status and care. Patients were assessed via 30 to 45-minute telephone interviews in English or Spanish at baseline, and 1, 3, 6, and 12 months post-baseline. Baseline interviews were conducted within 14 days of the study entry. Patients were reimbursed for their time with a $25 gift card for each completed CATI.

Treatment patterns were assessed at each data collection wave from baseline to 12 months; information collected included 1) type of medications used, 2) the medication possession ratio (MPR; number of days that supply of medication was used/number of days in the 12-month study) for selected drugs, 3) number of unique concurrent medications at each visit, 4) cumulative number of unique medications over time, and 5) rate of treatment discontinuation and reasons for discontinuation (multiple responses were allowed, including "felt better," "didn't help," "adverse events," "too costly," and "other").

The CATI included the outcome measures of BPI, SDS, and FIQ, as well as economic outcome measures. The BPI [31] includes four pain severity items that assess worst, least, and average pain in the prior week, as well as pain right now, on a scale from 0 (no pain) to 10 (pain as bad as you can imagine). These four items were averaged for a mean rating or what is referred to in this article as a "pain severity average score" (possible range, 0 to 10). In addition, there are 7 BPI interference items assessing pain-related interference with daily functioning (e.g., work, physical, and social activity) on a scale from 0 (does not interfere) to 10 (completely interferes); these items were averaged for a mean rating referred to in this report as a "pain interference average score" (possible range, 0 to 10). The SDS [32] assesses disability across three domains: work/school, social life, and family life/home responsibilities. The total score ranges from 0 to 30, with higher scores indicating greater disability. The FIQ [33] 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. The FIQ total score for the version used ranges from 0 to 80, with a higher score indicating a more negative impact. Economic measures included individual patient-rated items to assess the effect of FM on work or disability status and health care utilization. Another outcome was the level of disability due to the patient's FM, which was captured using seven variables (in days): family member missed paid work, had an unpaid caregiver, hired a paid caregiver, missed work due to FM, stayed in bed, cut down on activities, and received disability income. Resource utilization over the 12 months included number of visits to outpatient facilities overall, emergency room visits, partial day care, and partial night care. CATI items also inquired about patients' satisfaction with their medical care. Patients were asked to rate "the treatment of your fibromyalgia overall" as well as "the medication you were prescribed" from 1 (excellent) to 5 (poor).

Measures that were included in the CATI and were used to control for differences across patient cohorts included the Patient Health Questionnaire (PHQ)–15 [35,36], which captures complaints of common physical symptoms seen in primary care settings; the Generalized Anxiety Disorder (GAD)–7 measure [37], which measures severity of GAD; the PHQ–8 [38,39], which assesses depression severity; the Insomnia Severity Index (ISI) [40], which measures individuals' perceptions of insomnia including symptoms of sleep and fatigue; and the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (MGH-CPFQ) [41], which measures patients' cognitive and physical well-being.

Patients initiated on 145 unique types of medication; therefore, this study condensed the analysis to only the three FDA-approved medications and the predominantly recommended first-line therapy for the treatment of FM. Thus, the four mutually exclusive medication cohorts, defined based on medications initiated at baseline, were: 1) pregabalin, 2) duloxetine, 3) milnacipran, and 4) TCAs. The specific TCAs included in this analysis (i.e., amitriptyline, clomipramine, desipramine, dosulepin hydrochloride, doxepin, imipramine, lofepramine, nortriptyline, and trimipramine) were chosen because they are considered a first line of therapy in many guidelines and have been evaluated in the highest number of clinical studies [19]. Patients who initiated on a combination of any of these four groups and the remaining patients who had initiated on other medications were not included in the medication cohort comparative analyses but are included in the description of the overall sample.

Statistical Analysis

Treatment patterns were summarized using 1) percentage of patients who used medications from baseline to 12 months, 2) the MPR (number of days that supply of medication used/number of days in the 12-month study), 3) number of unique concurrent medications at each visit and cumulative number of unique medications over time from baseline to 12 months, and 4) time to treatment discontinuation estimated by Kaplan–Meier survival analysis, as well as reasons for discontinuation.

Descriptive statistics were used to characterize patients' demographic and baseline clinical characteristics, physician characteristics, treatment patterns, baseline outcome measures, annual use of health care resources recalled by patients at baseline and use of health care resources reported by patients post-baseline. Summary statistics were calculated for the overall sample, for all enrolled patients (N = 1,700), and for patients in each of the four cohorts. The four groups were first compared using chi-square tests for categorical variables and *F* test (analysis of variance) for continuous variables. For variables with significant differences at the $P < 0.05$ level, a second step, using pairwise comparisons, was used to further identify distinctions among the groups.

Repeated-measures regression models for each of the health outcomes were done to understand the association of the outcome over time with the initiated medication. Poisson regression analyses, with a scale parameter to allow for over-dispersion and length of follow-up as an offset factor, were done to examine the association of economic outcomes (including resource utilization) with the initiated medication. The covariates for the model were chosen prior to conducting the analysis and included demographic variables (age, sex, race, region [whether the patient was receiving treatment in Puerto Rico or the United States]), baseline clinical variables (BPI pain severity average score, BPI pain interference, PHQ-8 total score [used in Poisson regression model for resource utilization]); physician specialty, baseline resource utilization variables (any emergency room visits, any outpatient visits, any primary care visits [used in repeated measures models for outcome measures]), baseline opioid use (YES/NO), and baseline medication status (no treatment in the last 6 months, switching, augmenting).

Because of the nonrandomized nature of these data, multiple sensitivity analyses were conducted to assess the robustness of the regression bias adjustment. Sensitivity analysis included propensity score matching, which is a commonly used tool in observational research for reducing bias in analyses involving comparisons between cohorts. Propensity score matching corrects for cohort differences in measured covariates, avoids the need to make assumptions regarding the relationships between covariates and the outcome variables as is necessary in regression modeling, and can incorporate more variables in the propensity adjustment model [42,43]. Propensity score matched samples were created for three pairwise cohort comparisons: duloxetine vs pregabalin, duloxetine vs milnacipran, and duloxetine vs TCA. The variables used in propensity score logistic regression model included all the variables listed above plus these additional variables: demographic variables (BMI; insurance type [none, public insurance (such as Medicare, Medicaid, Champus), private insurance (such as Omnicare, Aetna, WellPoint, Kaiser, etc), or a combination of public and private insurance (such as Medicare and supplemental private insurance)]; socioeconomic status in terms of whether the patient was comfortable, had just enough to pay the bills, or did not have enough to pay the bills); baseline clinical variables (time since first FM symptoms and each total score for the FIQ, GAD-7, PHQ-15, MGH-CPFQ, ISI, SDS); physician variables (sex, years of practice); and baseline resource utilization variables (any physical therapy visits, any care by unpaid caregiver, days cut down on activities, use of NSAIDs, and use of tramadol).

For the propensity score matched cohort comparisons, a propensity score for each patient was estimated using the above model, then a greedy 1:1 matching algorithm was used to form propensity score-matched samples. The 1:1 greedy matching algorithm used in this research sequentially matches each patient in the smaller treatment group (without replacement) to the patient in the other cohort with whom the absolute differences in the propensity score are smallest. Standardized differences were computed to confirm appropriate balance between cohorts for the above covariates, and the propensity matching process was finalized prior to initiating the outcome analysis. Pairwise cohort differences in each outcome measure were then examined using repeated-measures models on the matched samples, with cohort and visit as covariates.

To provide an additional sensitivity analysis that used the full patient sample, entropy balancing was also utilized. Entropy balancing is a recently proposed technique that controls biases due to measured baseline covariates in observational research comparisons [44]. Similar to weighting by the inverse of the propensity score, this approach finds the weight for each patient that leads to balance between cohorts for the baseline covariates. It potentially improves on propensity score methods by directly balancing the covariates such that the means and the variances of all baseline covariates will be similar between any number of cohorts. Propensity score matching is designed for two cohorts and simply matches on the propensity score, which does not guarantee that each matched pair has similar baseline values for each covariate.

Results

Participant Baseline Characteristics

A total of 2,115 patients were recruited into the study, and 1,700 were successfully enrolled into the study. Of the baseline patients, 1,205 (70.9%) completed the 12-month assessment, and 1,073 (63.1%) completed all of the

assessments; Figure 1 shows the number of patients who completed the CATI at each assessment.

Participants (N = 1,700) were mostly female (94.6%) and White (82.9%). Mean (standard deviation [SD]) age was 50.4 (11.9) years, duration of FM diagnosis was 5.6 (6.3) years, BPI severity was 5.5 (1.8), and BPI interference was 6.1 (2.2). Descriptive baseline information on the overall sample is fully described by Robinson et al. [28]. Patients who were not successfully enrolled in the study due to a missed telephone interview at baseline (n = 316) were younger than those who enrolled (n = 1,700) (mean age 46.8 vs 50.4 years, $P < 0.001$); no differences were noted in sex, race, region, BMI, years since first FM symptom, or baseline medication status. Patients who completed the study (N = 1,205) were compared with those who did not complete the study (N = 495); those who completed the study were older (mean age 51.5 vs 47.8 years, $P < 0.001$) and had experienced FM symptoms for a longer mean period of time (10.5 vs 8.7 years, $P < 0.001$); in addition, a greater percentage were using NSAID medication at baseline (28.7% vs 22.0%, $P = 0.005$). No other statistically significant ($P \leq 0.005$) differences emerged.

Table 1 contains the demographic and baseline characteristics of patients in each of the four medication cohorts. Of the overall sample (N = 1,700), 678 patients were divided into each of the following four cohorts based on the type of drug initiated at baseline: pregabalin (214/1,700, 12.6%), duloxetine (264/1,700, 15.5%), milnacipran (134/1,700, 7.9%), and TCAs (66/1,700, 3.9%). Six patients were initiated on a combination of duloxetine, milnacipran, pregabalin, or TCA and were excluded from the four cohorts. Statistical evaluation of baseline characteristics among these cohorts revealed overall significant differences between the groups in the following variables: race, region, medication status, physician gender, number of years physician was in practice, and physician specialty. Most patients in the pregabalin, duloxetine, milnacipran, and TCA cohorts enrolled into the study in the United States (94.9%, 87.9%, 97.0%, and 95.5%, respectively). Overall, the physicians in this study had been in practice

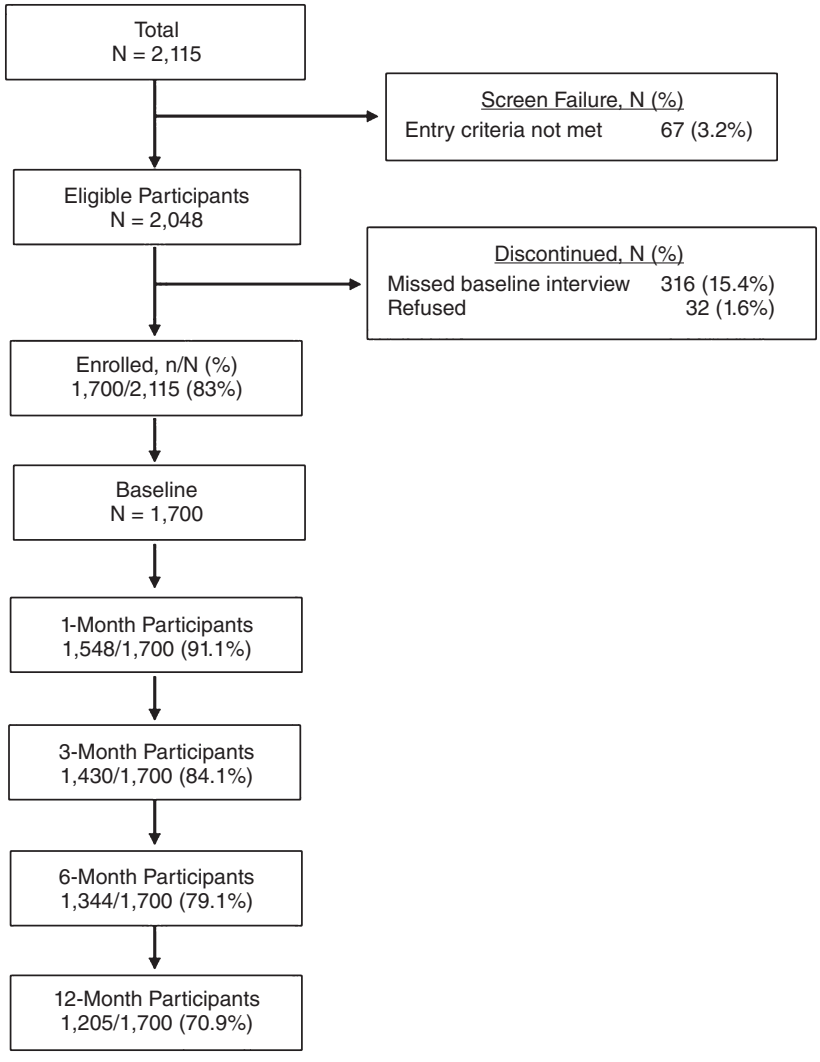

Figure 1 REFLECTIONS study enrollment and disposition.

Table 1 Baseline characteristics for medication cohorts

		Medication Cohorts					
		Pregabalin N = 214	Duloxetine N = 264	Milnacipran N = 134	TCA N = 66	*P* value†	Pairwise Comparison of Variables with $P < 0.05$ in Group Comparisons*
Demographics							
Age, mean (SD)		49.3 (11.6)	50.1 (11.4)	49.2 (11.6)	49.7 (13.3)	0.867	
Gender, n (%)	Female	203 (96.7)	251 (95.8)	130 (97.0)	60 (90.9)	0.184	
Race, n (%)						<0.001	P v D, D v M
	White	185 (89.8)	207 (79.3)	124 (93.9)	54 (84.4)		
	Hispanic	13 (6.3)	43 (16.5)	4 (3.0)	3 (4.7)		
	Other	8 (3.9)	11 (4.2)	4 (3.0)	7 (10.9)		
Region, n (%)						0.002	P v D, D v M
	Puerto Rico	11 (5.1)	32 (12.1)	4 (3.0)	3 (4.5)		
	US	203 (94.9)	232 (87.9)	130 (97.0)	63 (95.5)		
BMI, mean (SD)		31.9 (7.7)	31.1 (7.2)	32.6 (8.1)	32.2 (8.1)	0.324	
Insurance, n (%)						0.523	
	Private/combination (public + private)	171 (79.9)	219 (83.3)	114 (85.1)	52 (78.8)		
	Public/no insurance	43 (20.1)	44 (16.7)	20 (14.9)	14 (21.2)		
Income level, n (%)						0.912	
	Just enough/not enough to pay bills	125 (59.5)	159 (60.9)	77 (59.2)	41 (64.1)		
	Comfortable	85 (40.5)	102 (39.1)	53 (40.8)	23 (35.9)		
Illness and medical characteristics							
Years since first symptom, mean (SD)		9.7 (9.1)	8.6 (7.6)	10.7 (9.1)	9.6 (9.2)	0.181	
Medication status, n (%)						0.003	P v M, D v M
	No treatment	41 (19.2)	55 (20.8)	13 (9.7)	18 (27.3)		
	Switching medications	19 (8.9)	44 (16.7)	24 (17.9)	5 (7.6)		
	Augmenting medications	154 (72.0)	165 (62.5)	97 (72.4)	43 (65.2)		
Concurrent opioid use, Yes, n (%)		43 (20.1)	52 (19.7)	41 (30.6)	15 (22.7)	0.073	
Concurrent tramadol use, Yes, n (%)		28 (13.1)	33 (12.5)	10 (7.5)	8 (12.1)	0.406	
Concurrent NSAID use Yes, n (%)		38 (17.8)	35 (13.3)	16 (11.9)	10 (15.2)	0.412	
Physician characteristics							
Doctor gender, n (%)	Female	28 (15.9)	36 (15.7)	19 (16.1)	1 (1.6)	0.029	P v T, D v T, M v T
Doctor practice years, mean (SD)		15.7 (8.5)	16.8 (8.3)	15.1 (9.7)	21.9 (0.3)	<0.001	P v T, D v T, M v T
Doctor specialty, n (%)						<0.001	P v D, P v M, D v T, M v T
	Primary care	13 (6.1)	24 (9.1)	8 (6.0)	8 (12.1)		
	Rheumatologist	172 (80.4)	180 (68.2)	88 (65.7)	54 (81.8)		
	Other specialty‡	29 (13.6)	60 (22.7)	38 (28.4)	4 (6.1)		

* $P < 0.05$ in group comparisons: P v D, P v M, P v T, D v M, D v T, M v T.

† After propensity-score matching no statistically significant differences ($P < 0.05$) existed among the cohorts based on chi-square and F test (analysis of variance).

‡ Other specialties (and percentage of patients seen in the 4 treatment cohorts) included neurology (4.6%), psychiatry (7.7%), physical medicine (5.2%), pain specialist (2.2%), obstetrics and gynecology (0.7%), and osteopathy (0.7%).

BMI = body mass index; D = duloxetine; FM = fibromyalgia; M = milnacipran; NSAID = nonsteroidal anti-inflammatory drug; P = pregabalin; SD = standard deviation; TCA = tricyclic antidepressant.

an average of 16 (SD = 8.8) years, and most were male (84.7%) and identified their specialty as rheumatology (66.5%). Pairwise comparisons between the four medication cohorts revealed differences in several variables including patient characteristics (race, region, medication status) and physician characteristics (gender, years in practice, specialty) (Table 1).

Longitudinal Treatment Patterns

Patients in the overall sample took prescription medications for fibromyalgia 98.6% of the days during the 12-month study. The percentage of days during the 12-month study that patients in the overall sample were taking one, two, three, four, or at least five medications was 20.9%, 26.3%, 24.1%, 16.6%, and 10.7%, respectively. Over three fourths of patients were taking two or more medications at each time interval assessed (77.8% at baseline, 75.3% at 1 month, 79.5% at 3 months, 78.4% at 6 months, and 78.9% at 12 months). Similar mean (SD) cumulative number of medications for FM used by patients in each of the medication cohorts who completed all study visits over 12 months were found: pregabalin, 5.0 (2.0); duloxetine, 4.9 (2.0); milnacipran, 5.3 (1.7); and TCA, 4.7 (1.7) (pairwise comparison $P > 0.05$).

Because multiple medications were used over the 12 months, the data shown in Table 2 for each cohort are the percentage of medication use (among the 12 most common types) any time during the study and the mean length of time for each of these drugs using the MPR [45,46]. Categories of opioid and NSAID use were high among the selected medication cohorts with 36.5% (n = 621) and 36.6% (n = 622) of the overall sample, respectively, using these medications any time during the 12 months. Use of opioids in each medication cohort included pregabalin (n = 69), 32.2%; duloxetine (N = 78), 29.5%; milnacipran (N = 62), 46.3%; and TCA (N = 21), 31.8%. Of the overall sample, 411 (24.2%) patients took any form of gabapentinoid (i.e., pregabalin or gabapentin) and any type of SNRI (i.e., duloxetine, milnacipran, or venlafaxine) either concurrently or sequentially during the study. Concurrent or sequential use of duloxetine and pregabalin was reported by 227 (13.4%) patients, and 67 (3.9%) patients took milnacipran and pregabalin concurrently or sequentially during the course of the study.

The mean (SD) MPR for the patients in each of the four medication cohorts on their initiated medications were pregabalin, 0.61 (0.38); duloxetine, 0.61 (0.39); milnacipran, 0.39 (0.41); and TCA, 0.56 (0.42). For the overall sample, opioids had the highest mean MPR at 0.27 (0.41). Among patients in the medication cohorts who had any opioid use (36.5%), the MPR was 0.72 (0.34).

Few medication use differences were found between the four cohorts (Table 2). Patients in the milnacipran cohort were more likely to take opioids (46.3%) than patients in the pregabalin (32.2%) or duloxetine (29.5%) cohort and were likely to use opioids more (MPR 0.37 [0.45]) than the other three cohorts (MPR: pregabalin 0.21 [0.37], duloxetine 0.21 [0.38], TCA 0.23 [0.39]). Patients in the TCA cohort were less likely to take pregabalin (10.6%) and had a lower mean MPR (0.06 [0.20]) for pregabalin than the duloxetine (29.9%, 0.21 [0.37]).

From the observed data, the percentage of patients in the pregabalin, duloxetine, milnacipran, and TCA cohorts who discontinued their medication at 12 months was 47.7%, 42.4%, 35.1%, and 39.4%. The percentage of patients in the pregabalin, duloxetine, milnacipran, and TCA cohorts for whom it was "unknown" whether they discontinued their medication at 12 months was 21.5%, 29.5%, 48.5%, and 34.8%, respectively. To account for "unknown" patients, Kaplan–Meier survival analysis was performed to estimate medication discontinuation rates. Estimated time to drug discontinuation is presented in Figure 2. Discontinuation was common during the first month of treatment as well as during the first 3 months of treatment, and this pattern was especially evident for the milnacipran group. The estimates of 3-month (90-day) discontinuation rates from Kaplan–Meier survival analysis in the four medication cohorts were pregabalin, 32.2% (standard error [SE] = 3.4%); duloxetine, 31.2% (SE = 3.1%); milnacipran, 43.7% (SE = 5.3%); and TCA, 33.2% (SE = 6.6%). At 12 months, the estimated drug discontinuation rates based on the survival model were pregabalin, 56.9% (SE = 3.8%); duloxetine, 54.2% (SE = 3.6%); milnacipran, 57.1% (SE = 5.9%); and TCA, 54.9% (SE = 7.5%).

Patients could identify multiple reasons for discontinuation (as many as applied) and were allowed to remain in the study regardless of whether they discontinued the medication. Among those with available data, there were 287 affirmative responses; the most commonly reported reason for discontinuation for patients in all four of the medication cohorts was adverse events (N = 182, 63.4%), followed by lack of efficacy ("did not help," N = 87, 30.3%). Additional reasons included the cost of treatment ("too costly," N = 20, 7.0%), the patient felt better (N = 3, 1.0%), and "other" reasons (N = 43, 15.0%). Finally, in several cases, there was no reason given (N = 13, 4.5%).

Outcome Measures

Pooling across the four medication cohorts, patients reported statistically significant improvements in the BPI pain severity, BPI pain interference, SDS, and FIQ from baseline to each follow-up visit where the measure was included throughout the 12 months (all $P < 0.001$ visit compared with baseline). The mean BPI pain severity average score and pain interference average score at each visit for patients in the four medication cohorts are presented in Figure 3a and b, respectively. Pairwise comparisons between medication cohorts revealed only one significant overall between-group differences. Patients in the duloxetine cohort reported a greater reduction in pain severity compared with patients in the milnacipran cohort (adjusted means estimate [SE] = –0.28 [0.14], $P = 0.048$). No other significant differences emerged on the BPI pain

Table 2 Longitudinal use of medications for FM

Medications over 12 Months		Overall Sample N = 1,700†	Medication Cohorts: Pregabalin N = 214	Duloxetine N = 264	Milnacipran N = 134	TCA N = 66	*P* value	Pairwise Comparison of Variables with $P < 0.05$ in Group Comparisons*
Opioids	Any use (%)	621 (36.5)	69 (32.2)	78 (29.5)	62 (46.3)	21 (31.8)	0.008	P v M, D v M
	MPR, mean (SD)		0.21 (0.37)	0.21 (0.38)	0.37 (0.45)	0.23 (0.39)	0.001	P v M, D v M, M v T
NSAIDs	Any use (%)	622 (36.6)	58 (27.1)	63 (23.9)	33 (24.6)	18 (27.3)	0.844	
	MPR, mean (SD)		0.12 (0.29)	0.12 (0.29)	0.13 (0.30)	0.19 (0.36)	0.409	
Duloxetine	Any use (%)	619 (36.4)	57 (26.6)	264 (100)	29 (21.6)	11 (16.7)	<0.001	
	MPR, mean (SD)		0.15 (0.32)	0.61 (0.39)	0.12 (0.28)	0.12 (0.32)	<0.001	
Pregabalin	Any use (%)	584 (34.4)	214 (100)	79 (29.9)	29 (21.6)	7 (10.6)	<0.001	D v T
	MPR, mean (SD)		0.61 (0.38)	0.21 (0.37)	0.15 (0.32)	0.06 (0.20)	<0.001	D v T, M v T
Benzodiazepines	Any use (%)	426 (25.1)	48 (22.4)	60 (22.7)	31 (23.1)	11 (16.7)	0.732	
	MPR, mean (SD)		0.18 (0.36)	0.16 (0.34)	0.16 (0.33)	0.10 (0.27)	0.408	
Tramadol	Any use (%)	423 (24.9)	48 (22.4)	57 (21.6)	23 (17.2)	13 (19.7)	0.666	
	MPR, mean (SD)		0.16 (0.33)	0.17 (0.35)	0.14 (0.32)	0.12 (0.30)	0.658	
Nonbenzodiazepine Sedative/hypnotics	Any use (%)	372 (21.9)	39 (18.2)	57 (21.6)	26 (19.4)	11 (16.7)	0.733	
	MPR, mean (SD)		0.12 (0.31)	0.16 (0.34)	0.14 (0.32)	0.12 (0.31)	0.682	
SSRI	Any use (%)	366 (21.5)	48 (22.4)	42 (15.9)	27 (20.1)	15 (22.7)	0.282	
	MPR, mean (SD)		0.17 (0.35)	0.09 (0.24)	0.13 (0.30)	0.17 (0.36)	0.021	P v D
Cyclobenzaprine	Any use (%)	353 (20.8)	38 (17.8)	44 (16.7)	19 (14.2)	9 (13.6)	0.766	
	MPR, mean (SD)		0.12 (0.31)	0.13 (0.31)	0.12 (0.31)	0.11 (0.29)	0.978	
Gabapentin	Any use (%)	331 (19.5)	26 (12.1)	36 (13.6)	23 (17.2)	4 (6.1)	0.169	M v T
	MPR, mean (SD)		0.05 (0.18)	0.08 (0.26)	0.15 (0.33)	0.05 (0.22)	0.009	P v M, M v T
TCAs	Any use (%)	237 (13.9)	22 (10.3)	21 (8.0)	13 (9.7)	66 (100.0)	<0.001	
	MPR, mean (SD)		0.06 (0.22)	0.06 (0.21)	0.08 (0.26)	0.56 (0.42)	<0.001	
Milnacipran	Any use (%)	224 (13.2)	12 (5.6)	12 (4.5)	134 (100)	3 (4.5)	<0.001	
	MPR, mean (SD)		0.02 (0.11)	0.02 (0.12)	0.39 (0.41)	0.02 (0.11)	<0.001	

* $P < 0.05$ in group comparisons: P v D, P v M, P v T, D v M, D v T, M v T.

Sample sizes were decreased for the MPR calculation because these means required at least 1 follow-up visit. Sample size for these comparisons included: pregabalin (N = 202), duloxetine (N = 243), milnacipran (N = 125), and TCAs (N = 61). *P* values for "any use" were generated from chi-square tests, and *P* values for MPR were generated from *F* test (analysis of variance).

† The overall sample is reported for descriptive purposes only and includes the 4 cohorts plus study patients taking all other medications.

D = duloxetine; FM = fibromyalgia; M = milnacipran; MPR = medication possession ratio (total supply days/total number of days in the 12-month study); NSAID = nonsteroidal anti-inflammatory drug; P = pregabalin; SD = standard deviation; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

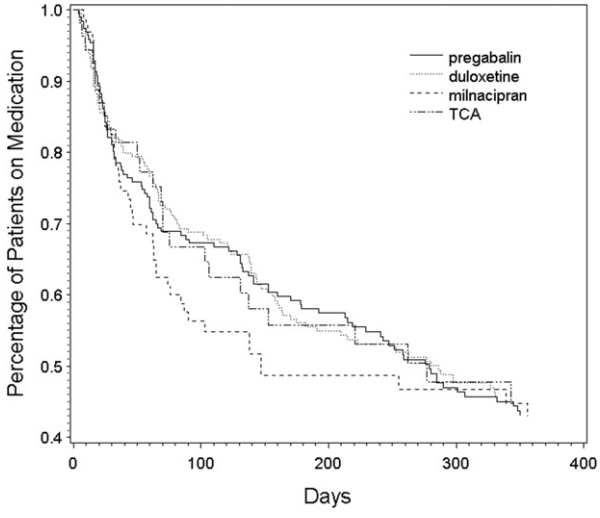

Figure 2 Time to drug discontinuation (baseline to 12 months). TCA = tricyclic antidepressant.

severity measures. On the BPI interference score, there were no significant overall differences between the patient cohorts.

The mean FIQ total score and the mean SDS total score at each visit for patients in the four medication cohorts is presented in Figure 3c and d, respectively. Adjusted pairwise comparisons between medication cohorts revealed no significant between-treatment differences on the FIQ or the SDS.

Sensitivity analyses were conducted using multiple methods. For the pairwise comparisons following the propensity score matching procedure, the number of patients in each of the matched samples was pregabalin vs duloxetine, 162; duloxetine vs milnacipran, 117; and duloxetine vs TCA, 57. There were no statistically significant differences in baseline characteristics between the cohorts after the propensity matching procedure. Results on the matched samples confirmed the initial findings; significant

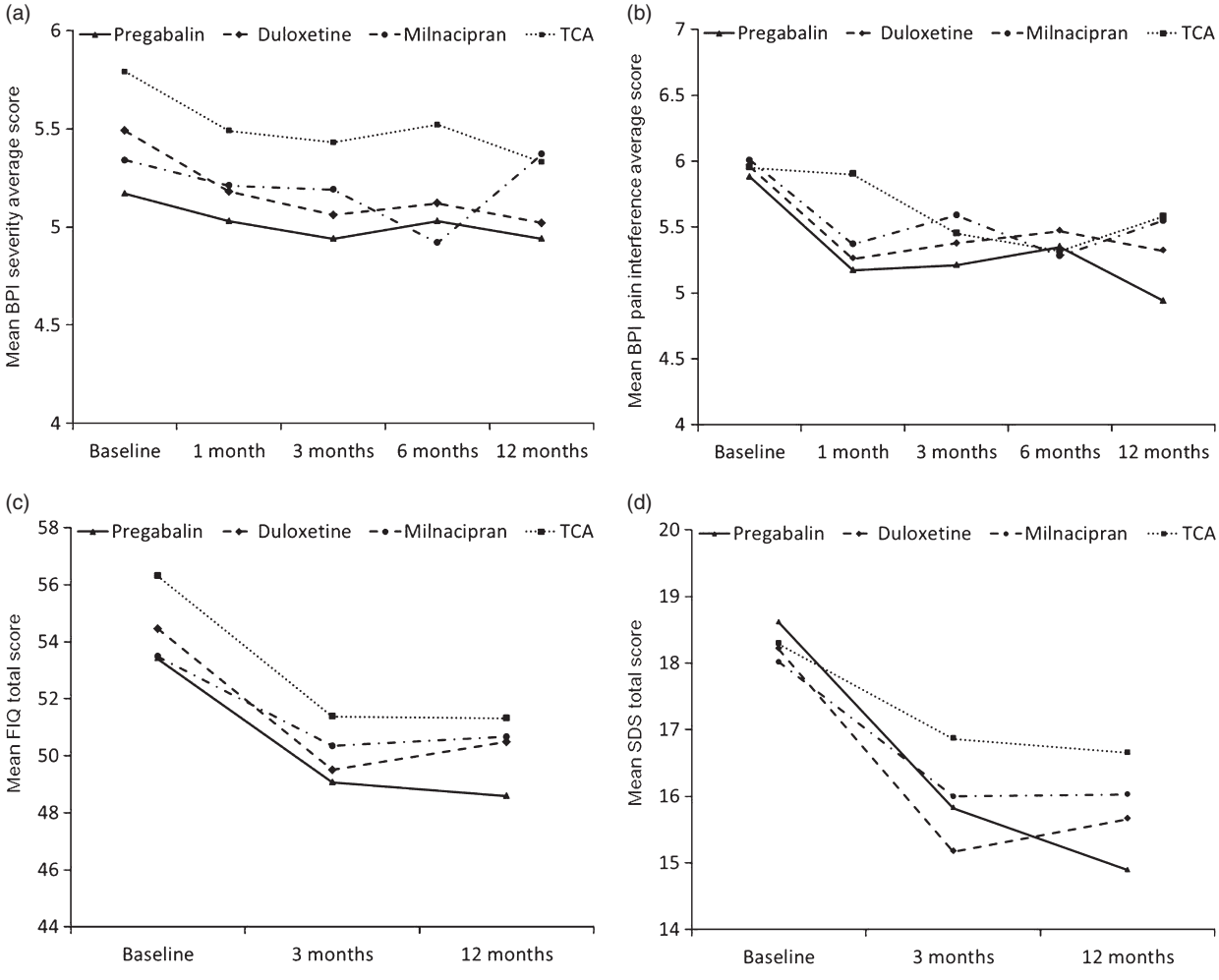

Figure 3 Mean changes from baseline to 12 months on outcome measures. BPI = Brief Pain Inventory; FIQ = Fibromyalgia Impact Questionnaire; SDS = Sheehan Disability Scale; TCA = tricyclic antidepressant.

differences emerged only on the BPI pain severity average score, with patients in the duloxetine cohort reporting greater pain reduction compared with patients in the milnacipran cohort (estimate –0.35 [0.15], $P = 0.026$).

Economic Factors

Information on resource utilization and other economic measures over the course of the study, for the overall sample as well as for each of the medication cohorts, is presented in Table 3. For the overall sample, patients reported approximately 20 visits annually for outpatient care (20.3 at baseline, 21.2 over 12 months). Compared with the 12 months prior to the beginning of the study, there were patient-reported reductions in the number of days of missed work due to FM (27.7 to 25.0) and in the days that patients cut down their activity by at least half (100.7 to 86.5), yet the number of days in bed and days patients received disability income increased (38.4 to 40.6 days; 96.6 to 98.2 days, respectively).

Pairwise comparisons using Poisson regression among the medication cohorts revealed multiple statistically significant differences in resource utilization (Table 3). Over the 12-month study period, patients in the duloxetine cohort reported fewer outpatient visits compared with patients in the pregabalin ($P = 0.005$) or TCA ($P = 0.003$) cohorts; likewise, patients in the milnacipran cohort reported fewer outpatient visits than those in the pregabalin ($P = 0.022$) or TCA ($P = 0.008$) cohorts. As summarized in the table, there were also cohort differences in number of days that a family member missed paid work due to the patient's FM as well as the number of days that either a paid or unpaid caregiver was required. Sensitivity analyses using the propensity matched samples tended to show fewer statistically significant pairwise differences than the regression analyses, in part due to the smaller sample sizes, though results were directionally consistent.

Satisfaction with Medical Care

Most patients rated their satisfaction with overall treatment and their fibromyalgia medication as "very good" or "excellent" (46.0% and 42.8%, respectively). The percentage of patients reporting a level of satisfaction (with overall treatment and with medication) that was either "very good" or "excellent" for each of the four medication cohorts is presented in Figure 4. Across all study time points, there were no statistically significant differences between the medication cohorts in patients' level of satisfaction with their overall care. However, patients in the pregabalin, duloxetine, and milnacipran cohorts, respectively, were significantly more likely to report satisfaction with their medication than were patients in the TCA cohort (odds ratio [confidence interval] = 1.97 [1.12, 3.48], $P = 0.018$, for pregabalin; 1.83 [1.05, 3.18], $P = 0.033$, for duloxetine; and 1.91 [1.04, 3.50], $P = 0.037$, for milnacipran).

Discussion

The REFLECTIONS study was designed to describe treatment patterns and outcomes for patients with FM in a naturalistic setting. The longitudinal study results indicate that patients with FM used multiple pain medications over 12 months to treat their FM. Augmenting current therapy was common, as was discontinuing from medications early in the study period. Patients displayed some improvements in health outcomes and function. Satisfaction with overall treatment and with the current medication was high for the majority of patients.

Longitudinal Treatment Patterns

Similar to the baseline REFLECTIONS findings [28], treatment patterns continued to be complex over the 12 months of the study. Although patients were taking at least one medication for FM on the vast majority of days (98.6%), length of time on any individual drug was less than optimal based on the standard MPR cutoff point of 0.80 for an adequate time on medication [47]. MPR rates in the REFLECTIONS study were 0.61 for pregabalin and duloxetine, 0.56 for TCAs, and 0.39 for milnacipran. These MPR results are slightly lower than those reported in retrospective insurance claims of patients with FM in which cohorts were matched on demographics, pre-drug initiation clinical and economic characteristics, and pre-drug initiation treatment patterns; results found 12-month MPRs of 0.50 for pregabalin and 0.70 for duloxetine [25]. Similar to the baseline findings where drugs with less evidence based on treatment guidelines were frequently used, NSAIDs and opioids continued to be used throughout the 12-month study [28]. Nonadherence in the use of prescribed medications has been previously reported to be common in FM patients and was associated with factors such as the therapeutic relationship between the physician and patient as well as other psychosocial characteristics [48]. With patients initiating on 145 unique medications and averaging five unique medications over the course of 12 months, our study may imply that patients continue to search for effective treatment of ongoing symptoms. Patients may be satisfied with a medication for the short time they take it, but they continually adjust their regimens. In this study, reasons for discontinuation were primarily adverse events and lack of efficacy. However, observation of discontinuation rates reported a good portion of "unknowns," which should be considered in the interpretation of these findings.

High rates of therapy switching, augmentation, and discontinuation are not unique to patients with FM. In a recent study of patients with osteoarthritis who were newly prescribed pain medications in a real-world setting, 90% of patients had switched, augmented, or discontinued their therapies within 6 months [49]. Intolerability to medications and suboptimal pain relief were suggested as the primary reasons for changes in osteoarthritis pain therapy.

Table 3 Cohort comparisons of 12-month post-baseline utilization of health care resources*

			Medication Cohorts				
		Overall N = 1,700 Mean (SD)†	Pregabalin N = 214 Mean (SD)	Duloxetine N = 264 Mean (SD)	Milnacipran N = 134 Mean (SD)	TCA N = 66 Mean (SD)	Pairwise Comparison of Relative Risk $P < 0.05$ [RR (95% CI)]§¶
Number of outpatient visits‡	Pre-study	20.3 (34.1)	18.2 (27.4)	17.9 (27.4)	24.3 (28.8)	19.5 (19.7)	D v P 0.78 (0.65, 0.93)
	Post-study	21.2 (28.6)	22.3 (26.2)	19.4 (30.2)	20.8 (29.8)	27.8 (41.9)	D v T 0.68 (0.53, 0.87)
							P v M 1.28 (1.04, 1.57)
							M v T 0.68 (0.52, 0.90)
Number of ER visits	Pre-study	1.0 (2.0)	0.8 (2.1)	0.8 (1.3)	1.0 (2.0)	1.4 (1.9)	
	Post-study	0.9 (2.5)	0.8 (2.2)	0.8 (1.6)	0.9 (2.2)	1.1 (1.7)	
Number of days:							
Partial day care	Pre-study	1.0 (13.7)	0.7 (4.3)	0.2 (1.1)	4.1 (31.9)	0.4 (1.5)	D v P 0.63 (0.42, 0.93)
	Post-study	1.2 (8.1)	1.6 (8.1)	0.9 (4.8)	2.3 (18.9)	0.9 (3.3)	D v M 2.06 (1.15, 3.68)
							P v M 3.29 (1.87, 5.80)
Partial night care	Pre-study	0.8 (12.7)	0.6 (4.1)	0.2 (1.0)	3.8 (31.9)	0.2 (1.1)	
	Post-study	0.6 (3.9)	1.0 (6.3)	0.7 (4.2)	0.5 (2.0)	0.9 (3.2)	
Family missed paid work	Pre-study	1.8 (8.9)	2.4 (15.8)	1.8 (11.2)	1.9 (5.3)	2.1 (5.6)	D v P 1.47 (1.05, 2.06)
	Post-study	2.7 (12.2)	2.3 (9.6)	4.3 (20.2)	1.9 (6.9)	2.7 (6.9)	D v M 1.85 (1.20, 2.86)
Had unpaid caregiver	Pre-study	32.6 (90.1)	20.2 (67.1)	30.1 (82.1)	26.7 (77.1)	29.8 (85.7)	D v M 1.70 (1.14, 2.54)
	Post-study	36.4 (76.6)	28.1 (64.4)	33.8 (72.7)	27.8 (71.1)	53.4 (90.4)	D v T 0.60 (0.42, 0.86)
							P v M 1.66 (1.09, 2.53)
							P v T 0.58 (0.40, 0.85)
							M v T 0.35 (0.22, 0.57)
Hired paid caregiver	Pre-study	2.1 (17.8)	0.5 (3.5)	0.7 (6.6)	5.0 (34.0)	0.7 (4.0)	D v M 0.44 (0.27, 0.72)
	Post-study	2.7 (17.6)	2.4 (13.0)	2.2 (17.6)	5.6 (30.4)	1.3 (8.5)	P v M 0.38 (0.22, 0.66)
							M v T 3.58 (1.41, 9.06)
Missed work due to FM	Pre-study	27.7 (76.5)	29.0 (68.3)	24.3 (64.9)	21.0 (71.3)	40.8 (89.9)	
	Post-study	25.0 (56.1)	24.5 (51.1)	23.4 (55.2)	24.2 (46.3)	31.9 (68.2)	
Stayed in bed	Pre-study	38.4 (68.7)	31.9 (57.1)	35.8 (65.5)	36.9 (54.6)	43.7 (77.2)	
	Post-study	40.6 (58.2)	38.8 (57.7)	39.1 (53.5)	34.3 (50.2)	44.2 (54.9)	
Cut down activity by at least half	Pre-study	100.7 (112.3)	110.0 (113.8)	94.3 (106.4)	120.2 (119.7)	109.2 (121.0)	P v T 0.74 (0.60, 0.92)
	Post-study	86.5 (76.3)	81.8 (77.0)	83.0 (74.9)	88.6 (77.2)	99.9 (86.0)	
Received disability income	Pre-study	96.6 (157.1)	109.7 (163.7)	71.7 (140.6)	92.4 (156.2)	94.0 (160.8)	
	Post-study	98.2 (148.3)	111.6 (155.0)	79.4 (138.4)	97.7 (148.1)	101.1 (153.1)	

* Resource utilization variables were aggregated over the 12 months and prorated if patients dropped out of the study before the 12-month visit.
† The overall sample is reported for descriptive purposes only and includes the four cohorts plus study patients taking all other medications.
‡ Outpatient visits included any visits to primary care physicians, specialists, physical or occupational therapists, and nonphysician caregivers like nurses or counselors.
§ Only the significant relative risks and the associated 95% CIs were calculated using Poisson regression model with 12-month post-baseline resource utilization variables as outcome of interest.
¶ Only the significant associations are presented here for each resource utilization outcome for the following six pairwise comparisons: D v P, P v M, P v T, D v M, D v T, and M v T.
CI = confidence interval; D = duloxetine; FM = fibromyalgia; M = milnacipran; P = pregabalin; RR = relative risk ratio; SD = standard deviation; T and TCA = tricyclic antidepressant; v = versus.

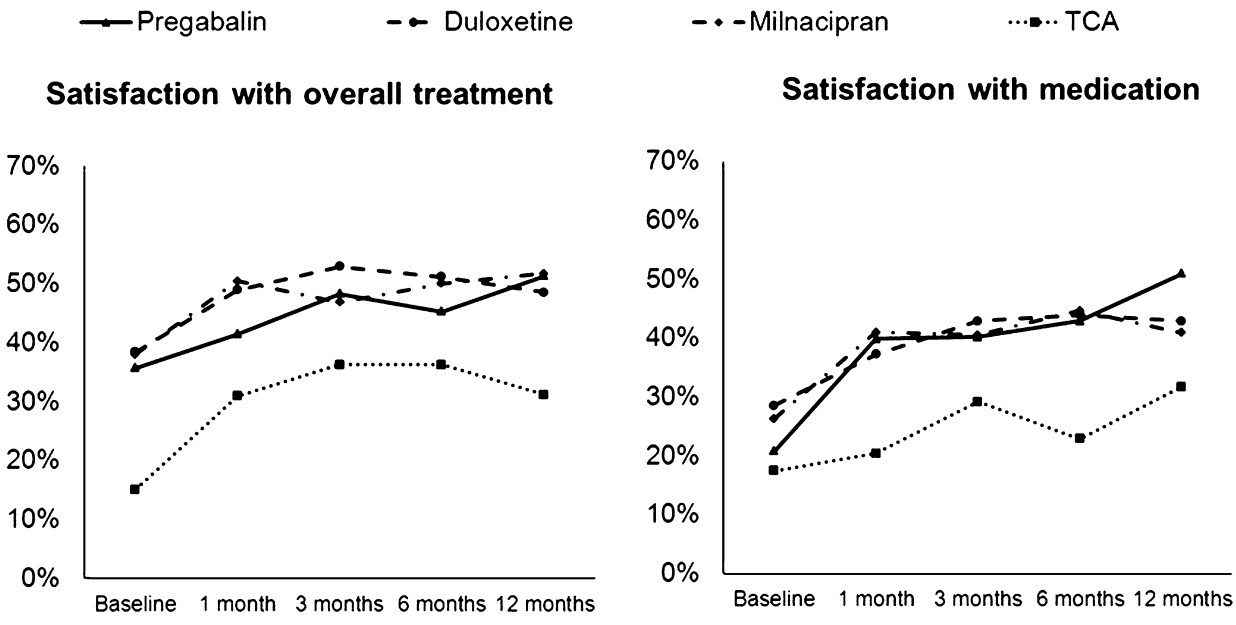

Figure 4 Percentage of patients rating their satisfaction with care as "excellent" or "very good" during the study (baseline to 12 months). TCA = tricyclic antidepressant.

Health Outcomes

Health outcome measures of pain severity, pain interference, disability, and the impact of FM improved throughout the 12 months of the study. Comparisons across the four medication cohorts found few differences across measures of pain severity and interference with pain and no differences in disability or the impact of FM. The modest differences between medication cohorts may be due to the ability of physicians to appropriately match patients to medications because, prior to propensity matching, there were significant differences between the groups on factors such as race, region where treated (Puerto Rico or United States), medication history, and prescribing physician characteristics. From the baseline assessment, current medication use was most strongly associated with medication history and physician specialty instead of clinical characteristics, where patients seen by specialists (vs primary care) not taking opioids or NSAIDs were more likely to be currently taking the three medications with regulatory approved indications for FM vs all other medications [28]. Based on these findings, we adjusted for these variables in a propensity score model to attempt to attenuate this bias. Differences may also be difficult to glean because of the use of concurrent medications and the high rate of discontinuation for initiated medications over the 12 months. For example, approximately 13% of the sample was taking both pregabalin and duloxetine at some time during the 12 months. Roughly half of patients discontinued their initial medications sometime during the 12 months of the REFLECTIONS study. However, Walitt et al. [3] also reported modest improvements in outcomes over an average of 4 years among rheumatology patients who met American College of Rheumatology 2010 diagnostic criteria for FM. The current study expands the generalizability of these findings; patients were enrolled from multiple physician specialties, and diagnosis was based on the enrolling physician's opinion. Additionally, the patients had a lower mean pain severity score at baseline, yet modest improvements were still reported.

High satisfaction was reported by study patients with their overall care and with their medication regimens. Satisfaction was highest in patients initiating on pregabalin, duloxetine, or milnacipran and lower in patients initiating on TCAs. The rates of high satisfaction are somewhat inconsistent with modest improvements in symptom severity and the variability in treatment patterns. Satisfaction may depend upon increased physician interactions [50] or patient expectations during ongoing experimenting with therapies for the management of FM [51].

Economic Outcomes

To our knowledge, this is the first longitudinal prospective observational study of FM patients with new drug initiation that also assessed resource use, measures of productivity, and caregiver burden. The current study corroborates previous retrospective claims studies finding that patients with FM are heavy users of health care resources and that FM is associated with lower level of work productivity [5,23]. Overall, patients reported high annual mean rates of outpatient visits with approximately 20 visits for outpatient care. The number of outpatient visits increased over time for all drug cohorts except for milnacipran, which had the highest average pre-study rate of outpatient visits; this rate generally tended to reduce over time to rates seen for

the other drug cohorts. More intensive care measures (number of ER visits and partial day and night care) tended to reduce or remain at low rates or stable rates over time. This may be an indicator that symptoms become more manageable over time. However, reliance on others rose over time as measured by the number of days family members hired paid caregivers, days of unpaid or paid caregivers, and days receiving disability payment regardless of the drug initiated. Being cognizant of these effects on families may be useful as disease management programs target social support during long-term care. Variability was found across economic outcomes: initiators on duloxetine and milnacipran (vs pregabalin or TCAs) had fewer outpatient visits post-study. However, between-drug comparisons of other economic indicators such as missed work or the need for paid or unpaid caregivers varied by drug. Continued modifications in medications may contribute to the modest changes in the pre-study health care use patterns compared with health care use during the 12 months of the study. In general, patients initiating on TCAs reported fewer declines across most of the measures of health care resources. These findings may be attributable to the cohort differences rather than drug differences. TCAs are generic medications that are relatively inexpensive, and unlike branded medications, they are typically available on most insurance formularies without any restrictions. There may be additional unmeasured confounding variables that differ between this cohort and the other three that influence treatment selection and use of other health care resources.

Caregivers, often family members, experience considerable burden. In this study, patients were cared for by an unpaid caregiver or relative on average for more than 30 days in a 12-month period. Further, during the study, patients stayed in bed for most of the day on an average of approximately 40 days and reported that they cut down on daily activities on approximately 86 days, presumably leaving family members to take care of household chores and care for the family.

Results need to take into account the following limitations. First, the study was not designed to assess comparative effectiveness of specific medications. Patients were not randomized to medication cohorts; thus selection bias remains an issue. While regression and propensity adjustment methods can account for a substantial bias due to measured confounders, one cannot account for potential bias due to unmeasured confounders (a standard assumption for all observational research). Second, small sample sizes, especially for the milnacipran and TCA groups (both of these groups had fewer than 200 subjects), limits the statistical power for cohort comparisons. Third, while the repeated-measure methodology can address missing data that is missing at random, if patients dropped out of the study due to any factors not included in the model, the overall results can be biased. Lastly, medication cohorts were based on the newly initiated medication, yet the majority of patients were treated with multiple medications, and many switched or stopped the medications during the trial, making conclusions regarding specific effects of individual medications challenging. The study was also conducted at a time when duloxetine and milnacipran were newly approved for use in FM.

In conclusion, this study illustrates the health and economic outcomes of patients with FM and describes the use of medications in this population over time. The strength of the study is that it was conducted in patients in actual clinical practice with results assessed outside of the medical office via structured CATI. This study substantiates the complexity of FM treatment that is suggested by retrospective claims studies in “real-world” patients in clinical practice and expands the information gained from clinical trials, from which patients with medical comorbidities or concomitant medication use are excluded. Of note is that the study documented slight improvements in symptoms and satisfaction with treatment in these reportedly difficult-to-treat patients. The study documented that most patients took combinations of prescription medications for their FM. Most patients entered the study on two or more medications, and many patients continued use of opioids or NSAIDs throughout the study. Future studies might focus on whether patients with FM receive an adequate course of therapy with appropriate dosing and duration of monotherapy medication before advancing to new and more complex regimens. A recent review by Mease et al. [52] highlights the importance of future research to examine the efficacy and safety of combination therapies for FM and to learn more about the pathogenesis of the various symptoms associated with FM so that therapies can be developed that adequately target these pathogenetic pathways and symptomatic domains. Despite the complexity of treatment and the modest improvements seen in symptoms, patients with FM in this study reported satisfaction with the overall care they received and with the medications prescribed for them by their health care providers.

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