Treatment Patterns Associated with ACR-Recommended Medications in the Management of Fibromyalgia in the United States

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ABSTRACT

BACKGROUND: Fibromyalgia (FM) affects up to 6% of U.S. adults, resulting in a significant burden on the health care system and poor quality of life for patients. Duloxetine, pregabalin, and milnacipran are approved for management of FM; however, consensus is lacking regarding optimal therapy. Patients with FM taking approved medications often do not experience meaningful symptom relief, and many experience intolerable adverse events.

OBJECTIVE: To assess treatment patterns associated with available and commonly used medications for the management of FM using U.S. health insurance claims.

METHODS: This retrospective analysis used the MarketScan claims database to identify adults with a first diagnosis of FM (ICD-9-CM code 729.1) between 2009 and 2011 with continuous health plan enrollment for 12 months pre- and post-index. Medications of interest were pregabalin, gabapentin, duloxetine, milnacipran, cyclobenzaprine, and tramadol. These are 6 of the 8 medications recommended by the American College of Rheumatology (ACR) for treating FM; the other 2 (amitriptyline and venlafaxine) were only included in some initial assessments. The Charlson Comorbidity Index (CCI) was used to assess overall comorbidity burden. Endpoints included proportion of patients treated within 1 year after first diagnosis; initial treatment pattern; adherence over the first-year follow-up period for the medications of interest; and discontinuation, switching, and combination therapy patterns among pain medications of interest at different time points. Proportion of days covered (PDC; defined as number of days in the period when the patient had drug supply divided by the number of days in the period) was used to define adherence, which was categorized as low (PDC < 50%), medium (PDC 50% to < 80%), or high (PDC ≥ 80%). The time to discontinuation (defined as the first drug supply gap ≥ 90 days) was estimated using Kaplan-Meier analysis.

RESULTS: Overall, 240,144 patients met the inclusion criteria. Patients were predominantly women (68%), had preferred provider organization insurance coverage (68%), and had a CCI score < 1 at baseline (69%). Only 31% (n = 74,738) initiated a treatment with a prescription medication listed in the ACR guidelines, and many patients received less than the recommended dose. Most (n = 70,919) patients initially received monotherapy with one of the 8 prescription medications. Of those who started with ≥ 2 medications (n=3,819), cyclobenzaprine plus tramadol was the most frequent combination. Adherence was suboptimal for all 6 medications of interest. Duloxetine had the highest mean PDC (59%); for all other agents, mean PDC was < 50%. With the exception of duloxetine, discontinuation rates at 6 months were > 50% for all agents. Alterations in therapy were common. Among patients who discontinued their initial treatment of duloxetine, pregabalin, or milnacipran, approximately one-third had switched treatments within 90 days after their first prescription. For those who maintained their initial treatment agent, approximately 50% of patients added a second pain medication within 1 year of treatment initiation.

CONCLUSIONS: The evidence suggests that patients with FM often do not receive 1 of the prescription medications recommended by ACR guidelines, and those who do are commonly prescribed lower-than-recommended doses, potentially resulting in poor effectiveness and tolerability. Discontinuation, switching, and addition of new pain medications are common, which may indicate low levels of satisfaction with initial treatment. New therapies with improved effectiveness and better tolerability are urgently needed for patients with FM.

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What is already known about this subject

- Of those pain therapies approved to manage fibromyalgia (FM), none appear to combine the effectiveness necessary to control symptoms and tolerability needed for long-term use.
- Many patients with FM use polypharmacy (including a variety of off-label prescriptions, over-the-counter medications, and non-drug treatments, possibly to address different symptoms.
- Treatment discontinuation is prevalent among patients with FM, and common reasons for stopping treatment include the occurrence of adverse events (in up to 40% of patients with FM) and lack of effectiveness (in up to 23% of patients with FM).

What this study adds

- We found that more than two thirds of patients diagnosed with FM were not treated with an American College of Rheumatology-recommended prescription medication for a year after diagnosis.
- Of those patients who received treatment, approximately 26% were prescribed FDA-approved therapies, and even fewer received the approved dose. Adherence was suboptimal for all treatments, and discontinuation rates were high.
- The results of this analysis show that discontinuation, switching, and addition of new pain medications are common, which may indicate low levels of satisfaction with initial treatment.

Pain is a common symptom reported by patients in primary care and accounts for 40% to 60% of outpatient visits.[1] Fibromyalgia (FM), a disorder characterized by widespread chronic musculoskeletal pain, is estimated to affect up to 6% of the adult population in the United States and 3% of adults worldwide.[2-5] Women are diagnosed with FM at a rate 3- to 6-fold higher than men[6]; however, recent research suggests that there are no sex differences in the overall clinical picture of FM (e.g., patient age, time since diagnosis, number of pain sites, and somatic and depressive symptoms).[7] The

precise cause and pathophysiology of FM is unclear, although it seems to involve disordered afferent processing and might be triggered or exacerbated by biological stressors such as physical trauma, infection, and some forms of psychological stress.[8]

Establishing an accurate diagnosis of FM is essential to successful disease management. Measures for the classification of FM were first published by the American College of Rheumatology (ACR) in 1990, with an update in 2010, which made the diagnostic criteria easier to use by primary care physicians.[5,9,10] A patient is diagnosed with FM if he or she has a widespread pain index (WPI) score ≥ 7 and symptom severity (SS) scale score ≥ 5 or WPI score 3 to 6 and SS scale score ≥ 9, symptoms have been present for at least 3 months, and there is no other disorder present that would explain the pain.[9] In addition to pain, patients might also report sleep disturbance and fatigue, as well as mood disturbances, stiffness, and cognitive difficulties.[2,3] However, many physicians do not use ACR criteria to diagnose FM.[8] The mean time taken to diagnose FM is 5 years, and many people with the condition remain undiagnosed, which might result in suboptimal medical care and potentially incur additional health care costs.[2]

An estimated 200,000 U.S. hospitalizations annually are associated with FM. Patients commonly have comorbidities (such as cardiac disorders, psychiatric disorders, hypertension, diabetes, and disorders of lipid metabolism) that necessitate additional medical treatment.[11] Approximately half of patients diagnosed with FM report some disruption of employment, missing an average of 2 workdays per month because of symptoms.[12] Medical costs, drug costs, and indirect costs (e.g., lost productivity at work) associated with FM are estimated to be > $10,000 per patient per year and are nearly twice those of people without FM.[13] Patients with FM, compared with other chronic diseases such as rheumatoid arthritis or osteoarthritis, commonly score lower on quality of life measurements and are more likely to have depression and other affective disorders than people without FM.[3,14,15]

Because the pathogenesis of FM is not fully understood, FM treatments focus on symptom management.[16] Of those pain therapies approved to treat FM, none appears to combine the effectiveness necessary to control symptoms with the tolerability needed for long-term use.[17,18] Currently, pregabalin (Lyrica, Pfizer, 2007),[19] duloxetine (Cymbalta, Eli Lilly, 2008),[20] and milnacipran (Savella, Forest Laboratories, 2009)[21] have been approved for management of FM.[8,22] However, debate continues over the best choice of treatment for FM,[23] and there seems to be no consistency in prescribing patterns among physicians.[24] Although some patients with FM experience symptom relief with some medications, often the benefits do not outweigh the side effects, and many patients find the adverse events (AEs) intolerable.[1,17] Many patients with FM use polypharmacy, possibly to address different symptoms.[13,25-27] The most commonly used therapeutic classes are narcotic analgesics, skeletal muscle relaxants, selective serotonin reuptake inhibitors (SSRIs), benzodiazepines, non-benzodiazepine sleep aids, serotonin norepinephrine reuptake inhibitors (SNRIs), and tramadol.[13] The use of opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) to manage FM persists, despite the lack of evidence supporting their analgesic effect in FM.[8] Treatment discontinuation is prevalent among patients with FM. Clinical trial data from duloxetine FM studies suggest that the 2 most common reasons for stopping treatment were the occurrence of AEs (in up to 40% of patients) and lack of effectiveness (in up to 23% of patients).[28]

To improve treatment for patients with FM, analyses of real-world evidence are needed to understand current treatment patterns and to examine gaps in achieving treatment goals. We used a health insurance claims database to assess the treatment patterns associated with available and commonly used medications for the management of FM.

Methods

Patients

This retrospective analysis used the MarketScan claims database to identify patients who had a first FM diagnosis code (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 729.1) in 2009-2011 with a repeat diagnosis (to confirm FM and reduce the possibility of misdiagnosis and exclude rule-out visits) within a year. The 2009-2011 period was selected to provide the most recent data and to include milnacipran, which was approved in January 2009.

Inclusion criteria included the following: patients ≥18 years old selected from the MarketScan claims database and patients ≥ 65 years of age identified from the Medicare supplemental database; patients with a first FM diagnosis (ICD-9-CM code 729.1) between April 1, 2009, and December 31, 2011, (primary or secondary diagnosis) with a repeat diagnosis within a year; and continuous enrollment in a health plan during the 12 months preceding the index date (baseline period) and the 12 months after the index date (follow-up period). The first diagnosis date was defined as the index date. Because this analysis focused on patients newly diagnosed with FM, patients with a prior diagnosis of FM were excluded.

Assessments and Endpoints

Eight treatments were assessed, in 4 therapeutic classes, using all National Drug Code numbers associated with the generic names: anticonvulsants (pregabalin and gabapentin [Gralise, Horizant, Neurontin]); antidepressants (duloxetine, milnacipran, amitriptyline [Elavil], and venlafaxine [Effexor]; a muscle relaxant (cyclobenzaprine [Flexeril]); and an opioid analogue (tramadol [Ultram]). ACR treatment recommendations were considered when identifying these prescription medications[29]; however, only duloxetine, milnacipran, and pregabalin are U.S. Food and Drug Administration (FDA)-

FIGURE 1 Patient Selection Flowchart

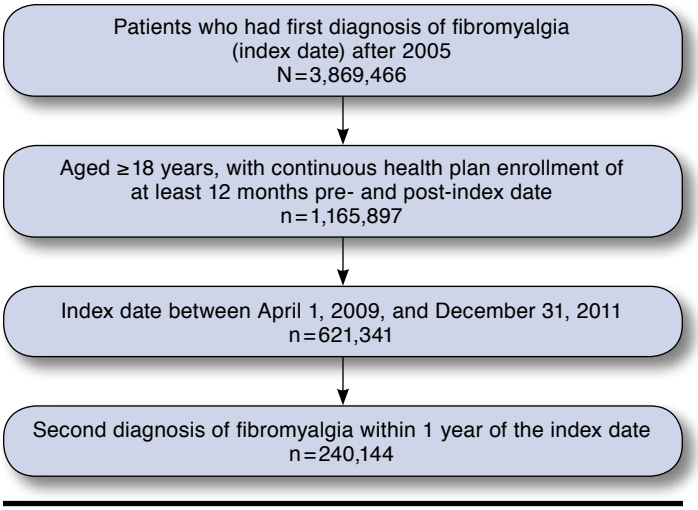
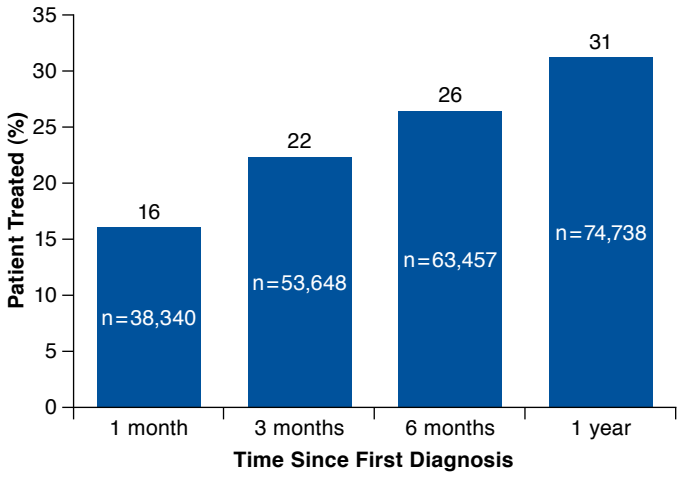


FIGURE 2 Percentage of Patients Receiving 1 of the 8 Medications of Interest at Each Time Point Since First Diagnosis of Fibromyalgia (N=240,144)



approved for the management of FM. These 3 approved medications and 3 other treatments most frequently used (milnacipran, cyclobenzaprine, and tramadol) were considered the medications of interest for all evaluations.

Patient baseline characteristics (age, sex, type of claim, comorbidity status) were recorded. To assess patient overall comorbidity burden, the Charlson Comorbidity Index (CCI) was calculated using the algorithm developed by Quan et al. (2011).[30] Endpoints included the proportion of patients treated within 1 year after first diagnosis; the initial treatment pattern (including first medication, initial daily dose and frequency, maintenance dose over 1 year, and use of combination therapy); adherence over the first-year follow-up period for the medications of interest; and discontinuation, switching, and combination therapy patterns among pain medications of interest at different time points.

Statistical Analysis

Baseline characteristics were recorded using descriptive statistics. Proportion of days covered (PDC; defined as number of days in the period when the patient had drug supply divided by the number of days in the period) was used to define adherence; this ratio can be multiplied by 100 to yield a percentage.[31] Adherence was categorized as low (PDC < 50%), medium (PDC 50% to < 80%), or high (PDC ≥ 80%), as described in previous publications.[32-34] The time to discontinuation (defined as the first drug supply gap ≥ 90 days) was estimated using Kaplan-Meier analysis. At any given time, if a patient had discontinued the initial medication and a new medication was filled between the final fill date of the initial medication and 90 days after the discontinuation date, switching of medication was considered to have occurred. Add-on treatment was defined as use of another pain medication in addition to the initial treatment before discontinuation. Only the first switch or first add-on therapy was considered in this analysis.

Results

Patients

A total of 240,144 patients met the inclusion criteria (Figure 1). As expected, the population was composed of more women (68%) than men (32%), and mean (standard deviation [SD]) age was 48 (13.8) years. Overall, 68% of patients had preferred provider organization insurance coverage; 9.6% had a health maintenance organization plan; 6.9% had a point of service (POS) plan; 6.3% had a comprehensive plan; 3.5% had a consumer-driven health plan; and 5.7% had high-deductible health plans, exclusive provider organizations, or POS with capitation.

Most patients included in the analysis (69%) had CCI scores < 1; 25% had CCI scores of 1-2; and 6% had CCI scores ≥ 3. The most common comorbidities at baseline were back pain (37%), abdominal pain (17%), chest pain (15%), and headache/migraine (14%). Almost one quarter of patients (23%) were taking prescription NSAIDs at baseline.

Treatment

Only 31% (n = 74,738) of patients initiated a prescription medication of interest, per ACR guidelines (pregabalin, gabapentin, duloxetine, milnacipran, cyclobenzaprine, tramadol, amitriptyline, or venlafaxine) within a year after the index date (Figure 2).[29] The 3 most frequently dispensed medications were cyclobenzaprine (27%), tramadol (18%), and gabapentin (16%;

TABLE 1 Frequency of Medication Initiation (First Prescription; N = 70,919)

Medication	Frequency, n (%)	
Cyclobenzaprine	19,420	(27)
Tramadol	12,681	(18)
Gabapentin	11,552	(16)
Duloxetine	9,648	(14)
Pregabalin	6,297	(9)
Amitriptyline	4,978	(7)
Venlafaxine	3,677	(5)
Milnacipran	2,666	(4)

Table 1). The FDA-approved medications duloxetine, pregabalin, and milnacipran accounted for 14%, 9%, and 4% of treated patients, respectively. Approved medications and/or the treatments most frequently used were considered the medications of interest for the remainder of the evaluation.

Recommended dosages for approved treatments are 60 mg per day for duloxetine,[20] 300 mg per day for pregabalin (up to 450 mg per day),[19] and 100 mg per day for milnacipran (up to 200 mg per day).[21] Although most patients used milnacipran at 100 mg per day, 34% of patients used <60 mg per day of duloxetine, and 77% used <300 mg per day of pregabalin. Cyclobenzaprine, tramadol, and gabapentin are not approved for the management of FM, but the usual dosages for other conditions are 15 to 30 mg per day,[35] 200 to 400 mg per day,[36] and 900 to 1,800 mg per day,[37] respectively. Most patients in this analysis were receiving lower dosages of these agents; in particular, gabapentin dosing was below 900 mg per day for 53% of patients.

Because the prescribing information recommends that pregabalin dosing begin at 150 mg per day with titration up to 300 mg per day,[19] we also evaluated dosing changes for patients starting at 150 mg per day. Among patients with at least 3 prescription fills, when the first dosage was 150 mg per day (n = 1,215), the last dose remained at or below 150 mg per day for 56% (n = 678) of patients. Only 36% (n = 441) of patients followed the recommendation and titrated up to 300 mg per day. The other patients (8%; n = 96) were titrated to >300 mg per day.

Among 74,738 patients treated with 1 of the 8 prescription medications of interest after diagnosis of FM, 95% (n = 70,919) initially received monotherapy. Of those patients who started with ≥2 of such medications (n = 3,819), cyclobenzaprine plus tramadol was the most frequent combination (n = 895; 23%). One quarter of patients (n = 59,133 [25%]) used prescription NSAIDs and 3.0% used celecoxib (n = 7,107) within 1 year after the first diagnosis of FM.

TABLE 2 Adherence to Treatment During First Year of Therapy Based on Proportion of Days Covered

Treatment	Number	Mean PDC[a]	High Adherence %[b]	Medium Adherence %[c]	Low Adherence %[d]
Cyclobenzaprine	15,388	0.20	5	7	88
Gabapentin	9,605	0.44	22	20	58
Tramadol	9,043	0.27	9	12	79
Duloxetine	8,607	0.59	38	22	40
Pregabalin	5,637	0.47	24	21	55
Milnacipran	2,370	0.43	20	18	62

[a]PDC calculated as number of days in the period when the patient had drug supply (i.e., "covered" by medication)/number of days in the period.
[b]High adherence, PDC ≥ 0.8.
[c]Medium adherence, PDC 0.5 to <0.8.
[d]Low adherence, PDC < 0.5.
PDC = proportion of days covered.

Adherence and Discontinuation

Adherence was suboptimal for all treatments (Table 2). Most patients had low adherence during the first year of treatment for all therapies evaluated. Duloxetine had the highest mean PDC (59%); for all other agents, mean PDC was <50%. Adherence to duloxetine was generally better than adherence to the other FDA-approved agents and better than adherence to the non-approved agents. Adherence to non-approved medications was extremely low.

Rates of discontinuation were high for most agents (Figure 3A). With the exception of duloxetine, discontinuation rates at 6 months were >50% for all agents. Because cyclobenzaprine is not recommended for long-term use, it is unsurprising that 63% of patients discontinued treatment (5% switched and 58% discontinued without switching) within 30 days after initiation. Many patients who initiated treatment with tramadol also discontinued within a short period.

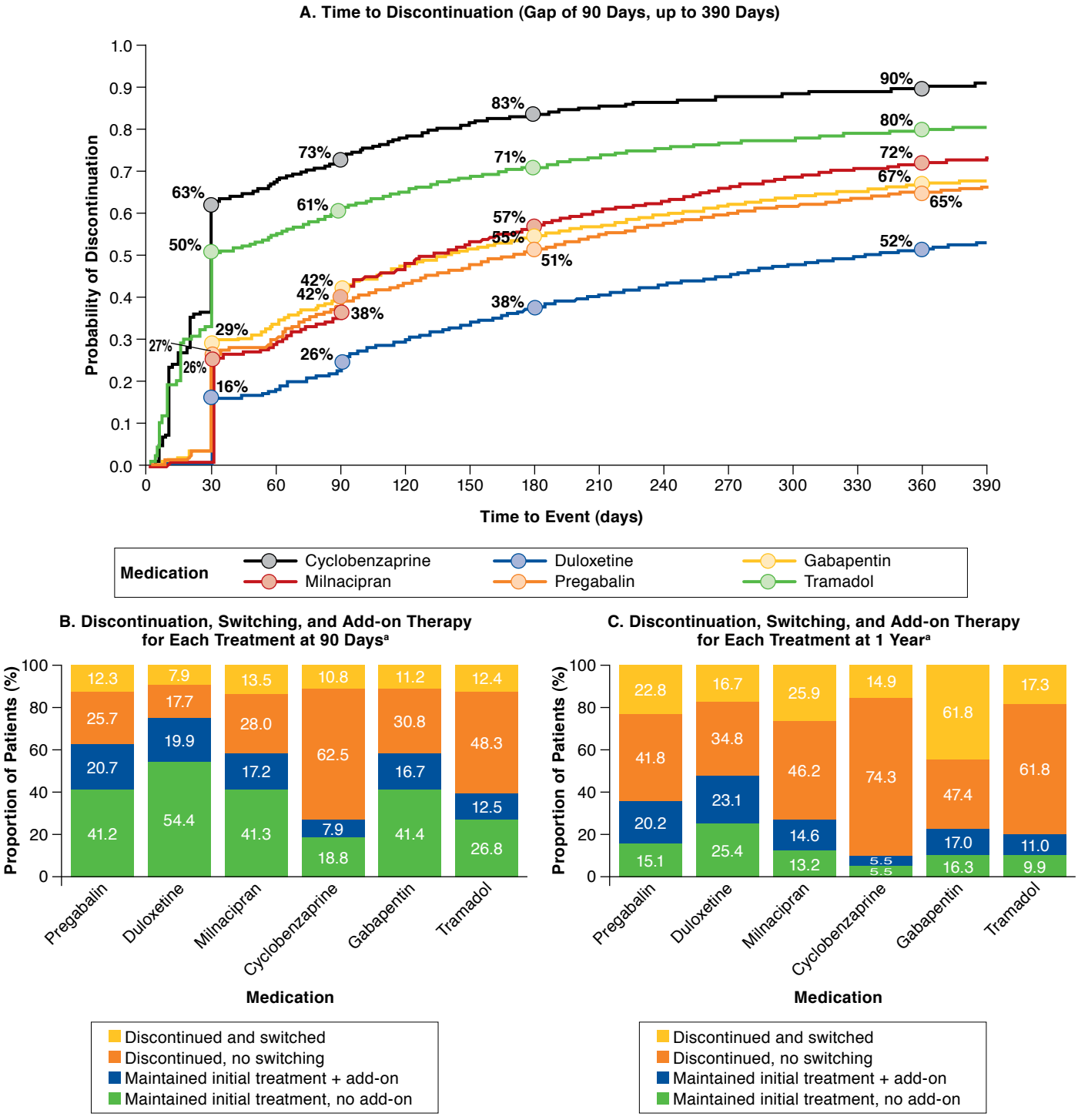
Treatment Alterations

Rates of treatment alterations were high for some agents. Among patients who discontinued initial treatment with duloxetine, pregabalin, or milnacipran, approximately one third had already switched to other ACR-recommended prescription medications of interest within 90 days after their first prescription (Figure 3B). Many patients who discontinued cyclobenzaprine did not switch to another medication. For patients who continued with the initial treatment agent, approximately 50% added a second medication of interest within 1 year of treatment initiation (Figure 3C).

Discussion

Our analysis describes real-world treatment patterns associated with 8 medications of interest for FM using a health

FIGURE 3 Alterations in Use of the Medications of Interest over the First Year of Therapy



[a]*Switches and add-on therapies were tracked within the 6 medications of interest only.*

insurance claims database. We found that more than two thirds of patients diagnosed with FM were not treated with a prescription medication of interest for a year after diagnosis. Of those who did receive treatment with a medication of interest, 27% were prescribed FDA-approved therapies, and even fewer received the approved dose. Adherence was suboptimal for all treatments of interest, and discontinuation rates were high.

To date, only 3 agents are approved by the FDA for management of FM.[8,22] In clinical studies, pregabalin, a nonselective ligand for α2δ subunits of voltage-gated calcium channels, provided significant improvement in FM pain and sleep symptoms compared with placebo.[38-40] Typical AEs reported by patients with FM treated with pregabalin include somnolence, dizziness, peripheral edema, and weight gain.[41] The SNRI duloxetine has also been shown to improve pain scores, mood, and daily functioning in patients with FM.[42-44] The most common AEs with duloxetine were nausea, headache, dry mouth, insomnia, fatigue, constipation, diarrhea, and dizziness.[45] The most recently approved treatment for FM, the SNRI milnacipran, has also been shown to be superior to placebo in reducing FM pain and fatigue and in improving mental and physical functioning.[46-49] The most frequently reported AEs with milnacipran were nausea, headache, constipation, hot flashes, and dizziness.[50] Comparative studies of the 3 treatments indicated that there were no differences in pain relief; however, there were key differences in specific symptom reduction (e.g., sleep disturbances, depressed mood, and fatigue) and drug-specific AEs (e.g., headache, nausea, and diarrhea).[18,51]

In addition to FDA-approved treatments, various other pain medications are used to treat patients with FM.[51-53] In a retrospective analysis of 2,613 patients, the most commonly prescribed medications before and after diagnosis of FM were short-acting opioids (42%-48%) followed by NSAIDs (34%-41%).[22] In a survey of >2,500 people with FM, more than two thirds of respondents indicated that opioids such as hydrocodone and oxycodone were helpful in alleviating symptoms; however, by far most people with FM used over-the-counter (OTC) treatments.[54] The exact reasons driving prescription medication use are unknown, and they may include lower costs and ease of obtaining OTC medications, lack of awareness about FM and the available prescription medications, and treatment satisfaction/dissatisfaction.

In this analysis, less than one third of patients (31%) diagnosed with FM were treated with 1 of 8 prescription medications recommended by ACR guidelines within a year of diagnosis. For those who did receive such treatment, the most commonly used agent was cyclobenzaprine. Furthermore, many patients did not receive the treatment dose recommended by the prescribing information. A significant number of patients using pregabalin were using much lower doses than recommended, possibly because of physician concerns about AEs,[55] despite evidence that these doses may not be effective in reducing pain severity.[43] Although the pregabalin prescribing information recommends initiating treatment at 150 mg per day with uptitration to 300 mg per day,[19] our data show that only about 36% of patients received this regimen.

Because FM is a chronic condition, medication should be administered regularly rather than as needed. Adherence and persistence were poor for most of the 6 medications we describe, possibly because of suboptimal dosing patterns. Adherence levels for all medications included in this analysis, with the exception of duloxetine, were <50%. This might be a result of the medications being prescribed on an as needed basis by physicians; being used as needed by patients, possibly because of affordability issues; or a desire to avoid AEs associated with taking medication. Persistence levels were also low, with patients discontinuing treatment as soon as 4 weeks after initiation. These results are in line with those from previous evaluations of pregabalin and duloxetine, which have reported mean medication possession ratios of 0.7 (duloxetine) and 0.5 (pregabalin).[33,56] Similar real-world evaluations of milnacipran are not yet available.

We cannot determine the reason patients discontinued or changed treatments, although poor effectiveness and AEs have been reported previously. Results of long-term safety studies of FDA-approved treatments report discontinuation rates with approved doses of pregabalin of 12% because of AEs and 9% because of other reasons, including lack of effectiveness.[57] In placebo-controlled trials of patients with FM, up to one quarter of patients discontinued approved therapies because of AEs (pregabalin, 19%[19]; duloxetine, 18%-20%[20,45]; milnacipran, 23%-26%[21,58]). Similarly, in a real-world, 12-month, observational study of 1,700 patients with FM in the United States and Puerto Rico, 47.7% of pregabalin-treated, 42.4% of duloxetine-treated, and 35.1% of milnacipran-treated patients discontinued their medications at 12 months, with intolerable AEs given as the most common reason in all cohorts (63.4%), followed by lack of effectiveness (30.3%).[59] For pregabalin, discontinuation because of an AE is dose-dependent, meaning that patients who require higher doses to control their symptoms might not be able to tolerate the AEs that occur as the dose increases.[19] For duloxetine, the discontinuation rates in clinical studies were 8%-17% owing to AEs and 8%-10% owing to lack of effectiveness.[42,60] In 1 milnacipran study, discontinuations because of AEs were 20% for 100 mg per day and 27% for 200 mg per day, although discontinuations because of treatment failure remained constant at 11%-12%.[47] In our analysis, many patients discontinued treatment early (within 30 days), which might indicate poor tolerability because many AEs occur soon after treatment initiation.

Many patients initiated treatment with cyclobenzaprine, which should not be used for long-term therapy, and subsequently discontinued within a short period without switching to 1 of the 8 medications of interest. Therefore, results from

this study suggest that many people with FM are suboptimally treated and likely experience poor pain management. Rates of add-on therapy were also high in the present analysis, suggesting that pain reduction with the initial medication was suboptimal.

Overall, these results indicate that new, more effective, and better-tolerated treatments are necessary for management of FM. A search of the ClinicalTrials.gov database (www.clinicaltrials.gov) shows that multiple drugs are being evaluated for management of FM, including antidepressants, cannabinoids, dopamine agonists, hormones, hypnotics, and neurotropines. It remains to be seen which, if any, of these agents might prove safe and effective.[61,62] However, each drug must be evaluated individually because it is clear that even drugs within the same class (pregabalin/gabapentin, duloxetine/milnacipran) can exert differing effects and produce different outcomes.

Limitations

Our analysis has several limitations common to retrospective health insurance claims databases. Only patients with FM with insurance were included in the analysis, and only those with 12-month continuous enrollment before and after the index date were selected. In addition, this analysis focused only on pain medications recommended by the ACR, which are all available by prescription only, and that could be evaluated using a medical claims database. However, it is clear from other studies that many patients with FM use OTC and nonpharmacologic treatments,[54] which cannot be evaluated by claims data analysis. Therefore, the effect of adding OTC therapies to prescription medication cannot be assessed. Furthermore, PDC is a proxy measure of adherence to medication regimens, which is based on reimbursed prescriptions, and could be less accurate than measures based on the observed number of pills taken by patients each day. PDC thresholds were based on previously published literature[32-34] and equally applied to all medications, regardless of potential instructions to use on an as-needed basis. In the future, a patient and physician surveys might provide insight into use of OTC and nonpharmacologic therapy, the rationale for physician prescribing behavior, and the reasons for patient nonadherence and nonpersistence.

Conclusions

Most patients newly diagnosed with FM are not treated with an FDA-approved medication for a year after diagnosis. Lack of diagnosis and effective pain management might be burdens to the health care system. Patients who are treated with approved therapies might receive a lower-than-recommended dose, potentially resulting in poor effectiveness. Conversely, use of higher doses might be prohibited by poor tolerability. Discontinuation, switching, and use of additional pain medications are common, indicating low levels of satisfaction with initial treatment. The reasons for the high rates of discontinuation and lack of adherence to prescribed medications merit further investigation. Based on this analysis, new therapies with improved effectiveness and better tolerability are urgently needed for FM.

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DISCLOSURES

No outside funding supported this research. Yang was an employee of Daiichi Sankyo while this study was conducted. Qian is an employee of Daiichi Sankyo. Liu has nothing to disclose.

Yang, Qian, and Liu interpreted the data and critically reviewed and edited the paper. Qian provided the analyses. All authors had access to the data. Qian is the guarantor for this work and, as such, takes responsibility for the integrity of the data and the accuracy of the data analysis.

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