

## ORIGINAL RESEARCH

# Analysis of Real-World Dosing Patterns for the 3 FDA-Approved Medications in the Treatment of Fibromyalgia

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**BACKGROUND:** Fibromyalgia is a chronic condition characterized by widespread pain, fatigue, and sleep disturbances that affects approximately 2% to 4% of the adult population in the United States, with minimal real-world data related to the use of medications and associated dosages for this condition.

**OBJECTIVE:** To analyze the real-world dosing patterns of the 3 medications approved by the US Food and Drug Administration for fibromyalgia—pregabalin, duloxetine, and milnacipran.

**METHODS:** Using QuintilesIMS' (now IQVIA) electronic medical record data linked to administrative claims, we identified adults with fibromyalgia who were newly prescribed pregabalin, duloxetine, or milnacipran between January 1, 2006, and December 31, 2014. We summarized and compared the starting and maximum doses with United States prescribing information (USPI) dosing recommendations.

**RESULTS:** In all, 1043 patients who were receiving pregabalin, 1281 receiving duloxetine, and 326 patients receiving milnacipran with similar age and comorbidity profiles were included in the study. The mean starting dose was 176 mg daily, 56 mg daily, and 95 mg daily for pregabalin, duloxetine, and milnacipran, respectively. More patients receiving pregabalin (35%) had a starting dose lower than recommended compared with patients receiving duloxetine (7%) or milnacipran (17%;  $P < .0001$ ). Of the patients who received pregabalin, 27% had USPI-recommended maintenance dosing versus 91% of patients who received duloxetine and 80% who received milnacipran ( $P < .0001$ ). The mean duration of treatment was longer for duloxetine (205 days;  $P < .0001$ ) than for pregabalin (167 days) and milnacipran (167 days). The duration of using the maximum dose of each medication as a percentage of the total time of medication use was 77% for pregabalin, 84% for duloxetine, and 90% for milnacipran ( $P < .0001$ ).

**CONCLUSIONS:** Patients using pregabalin were the most likely of the 3 cohorts to receive lower than label-recommended starting doses and the least likely to receive the recommended maintenance doses during follow-up compared with those receiving duloxetine or milnacipran. Real-world prescribing patterns indicate that factors other than label recommendations may be influencing prescribed dosing.

**KEY WORDS:** dosing patterns, duloxetine, fibromyalgia, milnacipran, pregabalin, recommended dose, treatment duration

Fibromyalgia, a chronic disease that results from neurobiologic abnormalities, affects approximately 2% to 4% of the US adult population.<sup>1,2</sup> It is characterized by widespread physiologic pain, a heightened and painful response to physical pressure, fatigue, cognitive

impairment, and sleep disturbances.<sup>1,2</sup> Women are twice more likely than men to be diagnosed with fibromyalgia.<sup>1,2</sup> Other known risk factors for fibromyalgia include age, comorbid lupus or rheumatoid arthritis, stressful or traumatic life events, repetitive injuries, illnesses (such as viral infections), family history of fibromyalgia, and obesity.<sup>3</sup>

Common comorbidities for patients with fibromyalgia include chronic joint pain or degenerative arthritis, hyperlipidemia, migraines or chronic headaches, obesity, and hypertension.<sup>3</sup> These comorbidities require treatment in addition to the treatment the patient is receiving for fibromyalgia and resulting in higher rates of depression.<sup>3</sup>

Currently, 3 medications are approved by the US Food and Drug Administration (FDA) for the treatment of fibromyalgia, including pregabalin (Lyrica, approved

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## KEY POINTS

- Fibromyalgia affects millions of people in the United States, but there are limited real-world data on its treatment.
- This retrospective cohort study assessed real-world dosing patterns of pregabalin, duloxetine, and milnacipran for the treatment of fibromyalgia.
- The duration of treatment was longer for patients receiving duloxetine (205 days) than for pregabalin or milnacipran (167 days each).
- Only approximately 34% of patients with fibromyalgia were prescribed FDA-approved drugs at the recommended starting dose.
- Compared with duloxetine or milnacipran users, patients using pregabalin were more likely to receive a lower than label-recommended starting dose and to receive the recommended maintenance doses.
- More studies are needed to analyze medication efficacy and tolerability among patients with fibromyalgia.

in 2007),<sup>4</sup> duloxetine (Cymbalta, approved in 2008),<sup>5</sup> and milnacipran (Savella, approved in 2009).<sup>6-8</sup> In addition to medications, other treatments for fibromyalgia include educational approaches, cognitive behavioral therapy, relaxation techniques, biofeedback, and other physical therapies.<sup>9</sup>

Data on the dosing patterns of these 3 medications in real-world practice are limited. It is important to assess how dosing patterns align with FDA-approved dosing instructions to understand how well these medications are meeting patients' needs, and whether the current dosing recommendations are being followed in real-world practice. The objective of this study was to examine the real-world dosing patterns of the 3 FDA-approved medications in patients with fibromyalgia who use these medications.

## Methods

This retrospective cohort study used QuintilesIMS' (now IQVIA) electronic medical record (EMR) data linked to administrative claims from the Truven Health MarketScan Commercial database between January 1, 2005, and December 31, 2015. This EMR is compliant with the Health Insurance Portability and Accountability Act of 1996 and includes deidentified patient data from ambulatory care records obtained from a national network of primary care practices.

The clinical data include activity from more than 38

million patients from 49 states. The EMR database includes patients with commercial insurance and Medicare and provides a longitudinal medical record for each patient containing diagnoses, prescribed medications, and laboratory test results from reporting physicians. Employers and health insurance companies contribute to the MarketScan claims data, which contain service-level detail regarding inpatient and outpatient medical services and outpatient prescription drugs.

The linked EMR-claims data source provides information from EMRs and medical claims records on the key variables of demographics, clinical characteristics, *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*-based medical diagnoses, insurance information, and prescription details.

Eligible patients had a new prescription for  $\geq 1$  of the 3 FDA-approved medications between January 1, 2006, and December 31, 2014 (the date of first prescription was used as the index date), without evidence of that medication during the preceding 12 months (ie, the baseline period). In addition, patients had to be aged  $\geq 18$  years, have a diagnosis of fibromyalgia (ICD-9-CM code 729.1) in claims or the EMR data within 30 days before the index date or any time after the index date, and be continuously enrolled in the health plan during the 12-month baseline and 12-month postindex periods (Figure 1).

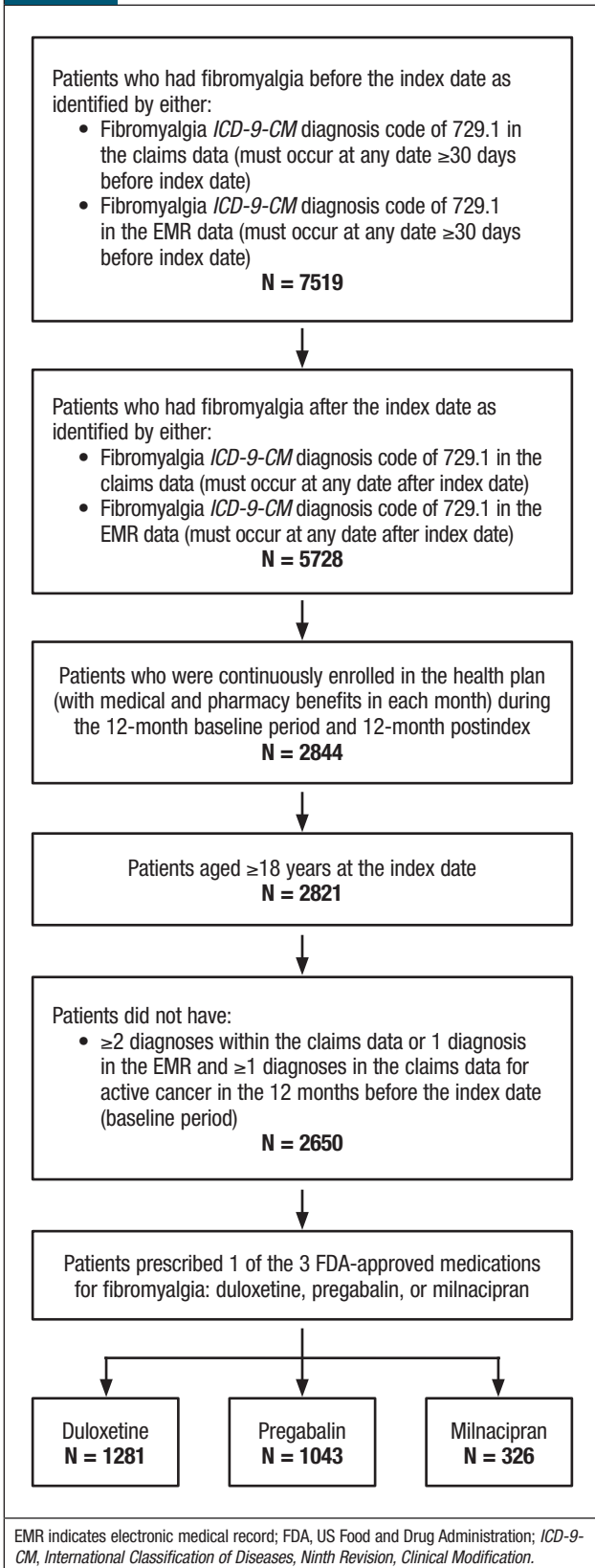
The patients were classified into 3 cohorts based on their index fibromyalgia medication of pregabalin, duloxetine, or milnacipran. Patients who had cancer during the baseline period or those who received  $\geq 2$  FDA-approved medications for fibromyalgia at index were excluded. However, patients were allowed to receive an additional FDA-approved medication or to switch to an alternative medication during follow-up. During the baseline period, the patients were allowed to be prescribed 1 of the FDA-approved medications for fibromyalgia, as long as they did not have a corresponding diagnosis of fibromyalgia within 30 days.

## Study Measures

The patients' demographic characteristics (ie, age, sex, race/ethnicity, US census-based geographic region, and insurance type), fibromyalgia-related comorbidities, and use of common fibromyalgia medications were assessed. The Charlson Comorbidity Index score was calculated based on the diagnoses associated with medical claims incurred in the 12-month preindex period to give an overall view of the patient's health status at the time of prescription of the index fibromyalgia medication.<sup>10</sup>

The treatment duration of the index drug was calculated as the number of days from the index date up to and including the last day of supply for the last prescription dispensed. Dosing information was gathered from pre-

**Figure 1** Study Cohort Selection



**Table 1** Dosing Categorization Used in the Analysis

Dosing	Pregabalin, mg/d	Duloxetine, mg/d	Milnacipran, mg/d
Label-recommended starting dose	150	30	12.5
Label-recommended maintenance dose	300-450	30-60	100-200
Label-recommended maximum dose	450	60	200
Starting dose			
Lower than PI	<150	<30	<12.5
Within PI range	150-300	30	12.5-50
Higher than PI	>300	>30	>50
Maximum dose			
Lower than PI	<300	<30	<100
Within PI range	300-450	30-60	100-200
Higher than PI	>450	>60	>200

PI indicates prescribing information.

scription claims data, which was calculated as dose strength multiplied by quantity dispensed divided by the days of supply.

The starting dose and maximum dose received during study follow-up were summarized and compared with US prescribing information (USPI) dosing recommendations (Table 1).

The maintenance dose was measured based on the dosing information for all prescription claims except the first prescription during follow-up. It is recommended to do a 1-day titration with milnacipran,<sup>6</sup> which is often combined with the initial prescription for milnacipran; therefore, the exact starting dose may be underestimated for milnacipran. Patients prescribed the titration pack for milnacipran (NDC 0456-1500-55) were assumed to receive the USPI-recommended starting dose.

The doses were categorized as lower than, within, or higher than the USPI recommendations for each of the 3 index medications (Table 1). Dosing was defined as unknown if the number of days for the prescription was unknown, the daily dose exceeded 10 times the label-recommended maximum, the dose was less than 10% of the label-recommended minimum dose, or the dose strength was unknown.

**Statistical Analysis**

Statistical analyses were performed using SAS version 9.4 maintenance release 3 and SAS/STAT version 14.1 (SAS Institute, Inc; Cary, NC). Descriptive analyses of all the study measures were performed across the medication cohorts. The patients' demographics and other clinical characteristics, as well as their treatment patterns (ie, dosing and duration), were described as counts and percentages for categorical variables and mean ± standard deviation (SD) for continuous variables.

**Table 2** Baseline Characteristics of Patients with Fibromyalgia Initiating FDA-Approved Medications, 2006-2014

Characteristics	Pregabalin (N = 1043)	Duloxetine (N = 1281)	Milnacipran (N = 326)	P value	Characteristics	Pregabalin (N = 1043)	Duloxetine (N = 1281)	Milnacipran (N = 326)	P value
<b>Age, yrs</b>				.31	<b>Charlson comorbidities, N (%)</b>				
Mean ± SD	50.0 ± 11.6	49.6 ± 11.4	49.0 ± 11.1		Diabetes with chronic complications	145 (13.9)	154 (12.0)	33 (10.1)	.16
<b>Age category, yrs, N (%)</b>				.71	Hemiplegia or paraplegia	2 (0.2)	10 (0.8)	1 (0.3)	.13
18-34	98 (9.4)	136 (10.6)	31 (9.5)		Metastatic solid tumor	0 (0.0)	0 (0.0)	0 (0.0)	N/A
35-44	206 (19.8)	264 (20.6)	74 (22.7)		Mild liver disease	47 (4.5)	69 (5.4)	22 (6.8)	.25
45-54	381 (36.5)	428 (33.4)	113 (34.7)		Moderate or severe liver disease	1 (0.1)	1 (0.1)	0 (0.0)	1.00
55-64	278 (26.7)	366 (28.6)	88 (27.0)		Myocardial infarction	4 (0.4)	4 (0.3)	2 (0.6)	.61
65+	80 (7.7)	87 (6.8)	20 (6.1)		Peptic ulcer disease	12 (1.2)	16 (1.3)	3 (0.9)	.93
<b>Sex, N (%)</b>				<.05 <sup>a</sup>	<b>Other comorbidities, N (%)</b>				
Male	132 (12.7)	143 (11.2)	17 (5.2)		Fatigue	345 (33.1)	530 (41.4)	145 (44.5)	<.0001 <sup>a</sup>
Female	911 (87.3)	1138 (88.8)	309 (94.8)		Hypertension	347 (33.3)	449 (35.1)	112 (34.4)	.67
<b>Insurance type, N (%)</b>				.51	Generalized anxiety disorder	44 (4.2)	83 (6.5)	17 (5.2)	.05
Commercial	956 (91.7)	1185 (92.5)	305 (93.6)		Migraine/headache	301 (28.9)	391 (30.5)	95 (29.1)	.67
Medicare	87 (8.3)	96 (7.5)	21 (6.4)		Musculoskeletal pain disorders	430 (41.2)	523 (40.8)	140 (42.9)	.78
<b>Race, N (%)</b>				.82	Neuropathic pain disorders	47 (4.5)	52 (4.1)	12 (3.7)	.80
Native American	2 (0.2)	5 (0.4)	1 (0.3)		Gastrointestinal disorders	251 (24.1)	312 (24.4)	79 (24.2)	.99
Asian	7 (0.7)	12 (0.9)	4 (1.2)		Obesity	90 (8.6)	160 (12.5)	38 (11.7)	<.05 <sup>a</sup>
Black	58 (5.6)	61 (4.8)	17 (5.2)		Epilepsy	16 (1.5)	14 (1.1)	2 (0.6)	.43
Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)		Sleep disorder	183 (17.6)	271 (21.2)	70 (21.5)	.06
White	778 (74.6)	948 (74.0)	238 (73.0)		<b>Medication use, N (%)</b>				
Unknown	177 (17.0)	226 (17.6)	53 (16.3)		Fibromyalgia medications				
<b>Ethnicity, N (%)</b>				.88	Pregabalin	N/A (N/A)	29 (2.3)	2 (0.6)	N/A
Hispanic	49 (4.7)	58 (4.5)	13 (4.0)		Duloxetine	54 (5.2)	N/A (N/A)	9 (2.8)	N/A
Not Hispanic	817 (78.3)	997 (77.8)	260 (79.8)		Milnacipran	6 (0.6)	7 (0.6)	N/A (N/A)	N/A
Unknown	177 (17.0)	226 (17.6)	53 (16.3)		Antidepressants	639 (61.3)	785 (61.3)	200 (61.4)	1.0000
<b>Region, N (%)</b>				.16	Tetracyclic antidepressants	130 (12.5)	150 (11.7)	31 (9.5)	.36
Northeast	147 (14.1)	235 (18.4)	59 (18.1)		Tricyclic antidepressants	160 (15.3)	218 (17.0)	63 (19.3)	.21
North Central	206 (19.8)	242 (18.9)	69 (21.2)		SSRIs	380 (36.4)	499 (39.0)	108 (33.1)	.11
South	551 (52.8)	638 (49.8)	158 (48.5)		SNRIs	167 (16.0)	124 (9.7)	45 (13.8)	<.05 <sup>a</sup>
West	139 (13.3)	166 (13.0)	40 (12.3)		Antimigraine (triptans)	122 (11.7)	133 (10.4)	34 (10.4)	.58
Charlson Comorbidity score, mean ± SD	0.65 ± 1.02	0.66 ± 1.01	0.55 ± 0.80	.20	Benzodiazepines	431 (41.3)	527 (41.1)	141 (43.3)	.78
<b>Charlson comorbidities, N (%)</b>					Gabapentin	249 (23.9)	283 (22.1)	60 (18.4)	.11
AIDS/HIV	0 (0.0)	0 (0.0)	0 (0.0)	N/A	NSAIDs, nonselective <sup>b</sup>	417 (40.0)	512 (40.0)	131 (40.2)	.99
Any malignancy <sup>b</sup>	11 (1.1)	23 (1.8)	0 (0.0)	<.05 <sup>a</sup>	Skeletal muscle relaxants	520 (49.9)	577 (45.0)	155 (47.6)	.07
Cerebrovascular disease	41 (3.9)	72 (5.6)	9 (2.8)	<.05 <sup>a</sup>	Sedative/hypnotics	242 (23.2)	271 (21.2)	68 (20.9)	.44
Chronic pulmonary disease	153 (14.7)	203 (15.9)	52 (16.0)	.71	Oral corticosteroids	510 (48.9)	585 (45.7)	147 (45.1)	.24
Congestive heart failure	29 (2.8)	30 (2.3)	4 (1.2)	.28	Topical corticosteroids	181 (17.4)	206 (16.1)	44 (13.5)	.25
Dementia	1 (0.1)	0 (0.0)	0 (0.0)	.52	Opioids, long acting	99 (9.5)	102 (8.0)	37 (11.4)	.12
Depression	266 (25.5)	418 (32.6)	72 (22.1)	<.0001 <sup>a</sup>	Opioids, short acting	795 (76.2)	887 (69.2)	232 (71.2)	<.05 <sup>a</sup>
Diabetes without chronic complications	37 (3.6)	25 (2.0)	6 (1.8)	<.05 <sup>a</sup>	Topical analgesics	69 (6.6)	87 (6.8)	22 (6.8)	.98

NOTES: Results are reported as number and percentage, unless otherwise specified. Regions were defined using US Census regions as Northeast: ME, NH, VT, MA, CT, RI, NY, PA, NJ; North Central: ND, MN, WI, MI, SD, NE, KS, IA, MO, IL, IN, OH; South: TX, OK, AR, LA, MS, TN, KY, AL, GA, SC, NC, FL, VA, WV, DC, MD, DE; and West: WA, OR, ID, MT, WY, UT, CO, AZ, NM, NV, CA.

<sup>a</sup>Significant at P < .05.

<sup>b</sup>Including lymphoma and leukemia, except for malignant neoplasm of skin.

FDA indicates US Food and Drug Administration; N/A, not available; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

The differences between the 3 cohorts were examined using Monte Carlo approximation or Fisher's exact test and analysis of variance for continuous variables. All statistical tests were performed assuming 2-sided alpha of 0.05. **Appendix 1** (available at [www.AHDBonline.com](http://www.AHDBonline.com)) lists the diagnosis codes used to determine the comorbidities and **Appendix 2** (available at [www.AHDBonline.com](http://www.AHDBonline.com)) lists the medications in each drug class category.

**Results**

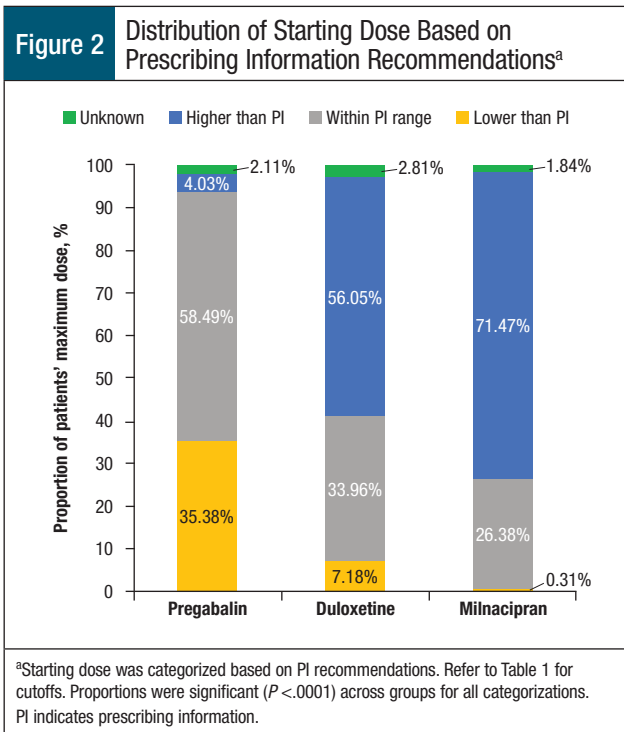
We identified 7519 patients with a diagnosis of fibromyalgia and a new prescription for 1 of the 3 FDA-approved medications (ie, pregabalin, duloxetine, or milnacipran) between January 1, 2006, and December 31, 2014, who did not have evidence of that medication during the 12-month baseline period. Of the 7519 patients, 2650 met all the study inclusion criteria. These patients were further stratified into 3 cohorts, including pregabalin (N = 1043), duloxetine (N = 1281), and milnacipran (N = 326), for analysis (Figure 1).

The demographic characteristics of the study cohorts are shown in **Table 2**. Across cohorts, the mean age was 50 years (SD, 12 years), with a plurality of 45 to 54 years. More than 90% of each cohort had commercial insurance, and the majority of the patients were white and from the South region. The demographic characteristics were similar across the 3 fibromyalgia medication cohorts, except for a higher proportion of female patients in the milnacipran cohort (95%) than in the pregabalin and duloxetine cohorts (87% and 89%, respectively;  $P < .05$ ).

The Charlson Comorbidity score was similar across the 3 fibromyalgia medication cohorts (Table 2), with a mean score of 0.65 (SD ± 1.02) for pregabalin, 0.66 (SD ± 1.01) for duloxetine, and 0.55 (SD ± 0.80) for milnacipran. The most frequently observed comorbidities during the baseline period were depression, other musculoskeletal pain disorders, sleep disorders, fatigue, hypertension, migraine or headache, and gastrointestinal disorders.

The use of antidepressants, benzodiazepines, nonselective nonsteroidal anti-inflammatory drugs, musculoskeletal relaxants, oral corticosteroids, and short-acting opioids in the 12 months before the index fibromyalgia medication was common (Table 2). During the baseline period, a significantly higher percentage of patients in the pregabalin cohort received short-acting opioids (76.2%) compared with duloxetine (69.2%) and milnacipran (71.2%;  $P < .05$ ). Between 18% and 24% of patients had received gabapentin in the 12 months before the index fibromyalgia medication date. The use of a fibromyalgia medication other than the index drug during baseline was low.

The starting, maintenance, and maximum doses for



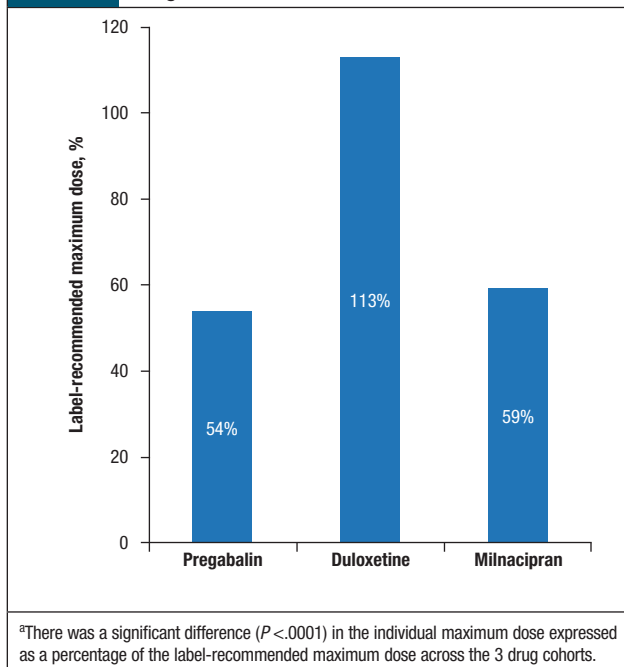
the 3 index drugs were available for almost the entire patient sample (96% overall).

The mean treatment duration was significantly longer for duloxetine (205 days; SD, 146 days) than for pregabalin (167 days; SD, 141 days) and milnacipran (167 days; SD, 143 days;  $P < .0001$ ). The mean starting doses were 176 mg daily (SD, 220 mg/d) for pregabalin, 56 mg daily (SD, 64 mg/d) for duloxetine, and 95 mg daily (SD, 97 mg/d) for milnacipran. A significantly higher proportion of patients receiving pregabalin (35%) were prescribed a starting dose lower than is recommended by the USPI compared with milnacipran (0.31%) and duloxetine (7%; **Figure 2**).

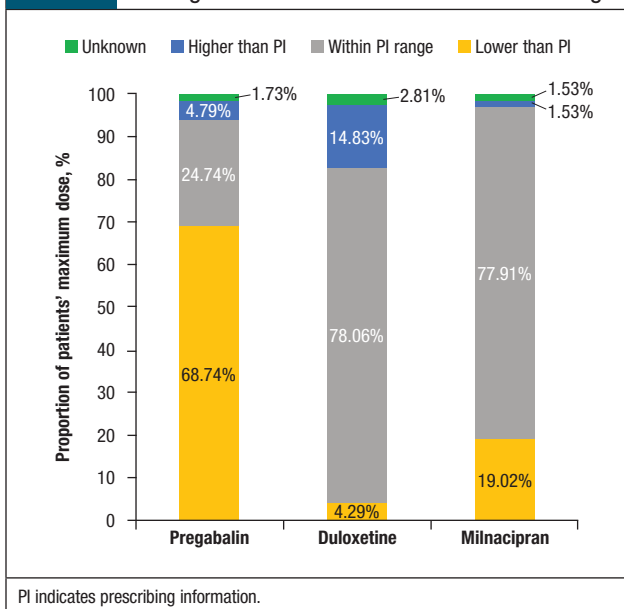
Only 27% of the patients who received pregabalin were prescribed a maintenance dose within the USPI-recommended maintenance range at any point during follow-up compared with 91% of the patients who received duloxetine and 80% of the patients who received milnacipran ( $P < .0001$ ). In addition, patients who used pregabalin received a dose that was consistent with the USPI maintenance dose recommendations for a significantly lower percentage of the time they used pregabalin (69% of days; SD, 30%) compared with duloxetine (92% of days; SD, 20%) and milnacipran (94% of days; SD, 16%;  $P < .0001$ ).

The mean maximum dose prescribed to patients as a percentage of the USPI maximum recommended dose was 54% for pregabalin (242 mg/d ± 310 mg/d), 113%

**Figure 3** Mean Maximum Dose as a Percentage of the Drug Label Recommendations<sup>a</sup>



**Figure 4** Distribution of Maximum Dose as a Percentage of Drug Label Recommendations for the 3 Drugs



(68 mg/d  $\pm$  73 mg/d) for duloxetine, and 59% (119 mg/d  $\pm$  135 mg/d) for milnacipran ( $P < .0001$ ; **Figure 3**). Among the 3 drugs, duloxetine had a significantly higher volume of patients being prescribed above 100% of the label-recommended maximum dose, with approximately 15% of patients receiving doses of  $\geq 100\%$ , and nearly

10% of patients receiving doses between 175% and 200% of the label-recommended doses between 175% and 200% of the label-recommended maximum dose (**Figure 4**).

A greater proportion of patients who used duloxetine (15%) received doses above the USPI-recommended maximum dose than those who received pregabalin (5%) or milnacipran (2%;  $P < .0001$ ). Similar to the maintenance dose, patients who used pregabalin received a maximum dose for a lower proportion of the time ( $77\% \pm 31\%$ ) compared with patients who used duloxetine ( $84\% \pm 26\%$ ) or milnacipran ( $90\% \pm 22\%$ ;  $P < .0001$ ).

### Discussion

Our findings showed that patients frequently receive FDA-approved fibromyalgia treatments at doses that are not concordant with the drug label recommendations. Only approximately 34% of patients were prescribed FDA-approved drugs for fibromyalgia at the recommended starting dose. The initial underdosing was more common among patients who were prescribed pregabalin than in those who were prescribed duloxetine or milnacipran, despite similar baseline demographics and comorbid conditions.

Patients who received pregabalin were also the least likely among the 3 cohorts to be prescribed the USPI-recommended maintenance dose at any point during follow-up compared with patients who received duloxetine or milnacipran, and they also had shorter treatment durations of the maximum dose.

The discrepancy in maintenance dosing between the 3 medications may be related to the effectiveness of pregabalin at a lower dose. In a previous meta-analysis, the use of pregabalin at doses of 300 mg daily, 450 mg daily, and 600 mg daily, but not 150 mg daily, was found to improve subjective pain assessment in patients with fibromyalgia.<sup>11</sup> In our study, 89% of the cohort receiving pregabalin were prescribed a dose that was lower than the recommended maintenance range ( $<300$  mg/d), and 35% were initially prescribed a dose that was  $<150$  mg daily. Our findings on pregabalin underdosing were consistent with those reported by Liu and colleagues, who found that 77% of patients received  $<300$  mg daily of pregabalin.<sup>12</sup>

Although these findings may suggest that many patients who received pregabalin were underdosed according to the label recommendations, the appropriate dose of fibromyalgia medications can be individualized to optimize the benefits and reduce side effects. Even when patients who received pregabalin were prescribed doses in the recommended maintenance range, we found that the duration of time spent at that recommended maintenance dose was significantly shorter compared with patients who were prescribed duloxetine or milnacipran. It is possible that patients' tolerability of pregabalin may have prevented staying at the recommended maintenance

nance dose for an extended period of time, but we could not confirm this in the absence of additional clinical information in the database. Further research is warranted to examine this topic and expand on the differences in the use of maintenance dosing between pregabalin, duloxetine, and milnacipran.

Because many patients with fibromyalgia are receiving multiple medications to manage their disease, medication duration and adherence may be affected by complicated polypharmacy regimens.<sup>13,14</sup> Consistent with findings from other studies,<sup>15-18</sup> opioid utilization was high in our study sample, and patients who received pregabalin had the highest frequency of short-acting opioids use. Opioids are not recommended by the American College of Rheumatology for the treatment of fibromyalgia.<sup>19</sup> The impact of opioid use on dosing, duration, and adherence for fibromyalgia medications warrants further investigation.

Patients with fibromyalgia have considerable comorbidities and medication burden.<sup>16,18,20</sup> The presence of comorbid conditions may complicate the management of patients with fibromyalgia. The FDA-approved fibromyalgia medications also have multiple indications, with different dosing recommendations. These 2 factors have made assessing the appropriateness of fibromyalgia medication dosing a challenging task.

For example, the maximum recommended dose for duloxetine for depression is 120 mg daily (double that of the recommended maximum dose for fibromyalgia).<sup>5</sup> In our study, the mean individual maximum dose for patients receiving duloxetine was 113% of the label-recommended maximum dose for fibromyalgia, and duloxetine doses as high as 200% of the recommended dose for fibromyalgia were prescribed for some patients. Approximately 33% of the patients with fibromyalgia who were prescribed duloxetine had comorbid depression, and 7% had generalized anxiety. It is possible that higher doses of duloxetine were used for the treatment of depression in these patients with fibromyalgia.

## Limitations

This study is subject to limitations that are common to retrospective analyses of secondary data, including possible missing data, coding errors, and the fact that the data were not collected for research purposes.

In addition, because the EMR system includes ambulatory practice data only, we are unable to analyze data from patients in the inpatient setting or in other facilities, such as long-term care or other settings where patients with fibromyalgia may seek treatment.

Although we identified differences in the prescribing patterns based on these data, we lack the ability to ascertain the reasons behind the differences in the pre-

scribing patterns; future studies would be needed to examine the reasoning.

We identified patients who were newly initiating fibromyalgia medications via prescription claims records, and we excluded patients who had evidence of the use of index fibromyalgia medications in the previous 12-month period. It is possible that patients might have used their index medication before the 12-month baseline or have received a sample of the medication that was not recorded in our data set. The previous use of index medication may bias the starting dose observed in our analysis.

In addition, although our inclusion criteria preclude patients' use of 2 or more FDA-approved medications at index, patients were permitted to initiate other fibromyalgia medications during the study period.

Furthermore, the use of nonpharmacologic treatment is common in patients with fibromyalgia.<sup>21,22</sup> Any changes in nonpharmacologic treatment during the study period might also have affected the effectiveness of fibromyalgia medications and the dosing patterns.

In addition, the use of prescribed medications that were paid in cash (eg, generics) would not appear in the claims data, and may therefore be underreported. Future studies considering these potential confounders are warranted to confirm our study findings.

## Conclusion

This study explored real-world dosing patterns of the 3 FDA-approved medications for fibromyalgia in comparison with the recommended dosing instructions. Many patients with fibromyalgia did not receive the recommended dosage of fibromyalgia medications, which was most pronounced among patients receiving pregabalin. Information regarding the real-world dosing of fibromyalgia medications is critical to understanding the effectiveness and use patterns of those medications. These data indicate that real-world prescribing patterns may be driven by factors other than recommended dosing. The reasons for this discordance should be elucidated in future investigations. ■

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### Author Disclosure Statement

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## STAKEHOLDER PERSPECTIVE



### Real-World Drug Prescribing and Utilization Studies Can Inform Optimized Patient Care and Insurance Coverage

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Key findings from real-world data are likely to continue to provide evidence that can drive improvements toward optimizing care delivery along with benefit designs that influence the healthcare domains of cost, quality, and access. The study by White and colleagues in this issue of the journal regarding real-world dosing patterns for the treatment of patients with fibromyalgia is an example of how multiple stakeholders may benefit from insights derived from such data.<sup>1</sup>

**PROVIDERS:** In many chronic conditions with comorbidities, such as fibromyalgia, providers must balance their decision-making and ultimately focus on patient care outcomes. Data-derived insights that illustrate the concerns about drug use fundamentals, such as dosing, should be a wake-up call when making prescribing decisions. Inefficient and ineffective dosing is an issue that

can be addressed by all care providers, including physicians and pharmacists.

The implications of such measures include improved and measurable clinical outcomes, which can engage patients positively to maintain adherence to appropriately prescribed medications. However, often the healthcare insurance coverage conundrums may negatively affect the balanced practice of provider prescribing. Patients' out-of-pocket costs, step therapy, or preferred drug requirements could be areas of future study to optimize prescribing decision-making and positively guide proper dosing.

**PATIENTS:** Chronic conditions include multiple symptoms with comorbidities that need to be effectively managed by providers using a personalized treatment strategy that is in sync with the individual patient.



STAKEHOLDER PERSPECTIVE *Continued*

Without achieving effective drug dosing to ameliorate symptoms or stop disease progression, patients can be less likely to adhere to their medication therapies. Such patient nonadherence could result from a perceived lack of medication effectiveness or lack of improvement in their clinical condition, as well as from unreported side effects at higher doses. Nonadherence may also result from out-of-pocket costs at a higher dose or greater frequency, which causes patients to limit medication use at proper dosing. From the start of treatment, proper medication dosing is critical to achieving effective patient outcomes, as demonstrated in phase 1, 2, and 3 clinical trials conducted with drugs to obtain US Food and Drug Administration approval.

Insurance coverage considerations of a drug should include any potential impact of the drug cost, including but not limited to out-of-pocket cost, on patient medication use patterns. Real-world studies of prescribing patterns and real-world utilization data can inform improved actions that support optimal patient care incentives or disincentives.

**PURCHASERS/PAYERS:** The need to avoid inappropriate medication prescribing includes a wide spectrum of issues—with fibromyalgia, that includes the use of opioids, which are not a recommended treatment option for this chronic disease. Purchasers can be more aligned with patients by seeking optimal outcomes from drug therapies over the long-term versus having a single fiscal year mentality. Resulting in part from third-party payers who are incentivized to manage economics con-

siderations primarily, purchasers who are seeking long-term benefits from their investments in medication use could do a better job of allowing for the optimization of drug therapies at the provider–patient interface. Designating more effective metrics that are meaningful and actionable could lead to desired real-world prescribing patterns thanks to improved execution of benefit design throughout the healthcare system.

**More studies that will elucidate real-world data on chronic condition treatments can go a long way to help providers, patients, and payers to improve healthcare system efficiencies.**

More studies that will elucidate real-world data on chronic condition treatments can go a long way to help providers, patients, and payers to improve healthcare system efficiencies. In addition, such studies could inform benefit structure or design considerations that support optimal health plan performance that is driven by purchasers. Furthermore, such efforts can begin to address more effectively drug use fundamentals, such as dosing, that are associated with gaps that need to be resolved. ■

1. White C, Kwong WJ, Armstrong H, et al. Analysis of real-world dosing patterns for the 3 FDA-approved medications in the treatment of fibromyalgia. *Am Health Drug Benefits*. 2018;11(6):292-301.