

# Impact of potential pregabalin or duloxetine drug–drug interactions on health care costs and utilization among Medicare members with fibromyalgia

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**Purpose:** To examine the impact of newly initiated pregabalin or duloxetine treatment on fibromyalgia (FM) patients' encounters with potential drug–drug interactions (DDIs), the health care cost and utilization consequences of those interactions, and the impact of treatment on opioid utilization.

**Patients and methods:** Subjects included those with an FM diagnosis, a pregabalin or duloxetine prescription claim (index event),  $\geq 1$  inpatient or  $\geq 2$  outpatient medical claims, and  $\geq 12$  months preindex and  $\geq 6$  postindex enrollment. Propensity score matching was used to help balance the pregabalin and duloxetine cohorts on baseline demographics and comorbidities. Potential DDIs were defined based on Micromedex 2.0 software and were identified by prescription claims.

**Results:** No significant differences in baseline characteristics were found between matched pregabalin ( $n=794$ ) and duloxetine cohorts ( $n=794$ ). Potential DDI prevalence was significantly greater ( $P<0.0001$ ) among duloxetine subjects (71.9%) than among pregabalin subjects (4.0%). There were no significant differences in all-cause health care utilization or costs between pregabalin subjects with and without a potential DDI. By contrast, duloxetine subjects with a potential DDI had higher mean all-cause costs (\$9,373 versus \$7,228;  $P<0.0001$ ) and higher mean number of outpatient visits/member (16.0 versus 13.0;  $P=0.0009$ ) in comparison to duloxetine subjects without a potential DDI. There was a trend toward a statistically significant difference between pregabalin and duloxetine subjects in their respective pre- versus post-differences in use of  $\geq 1$  long-acting opioids (1.6% and 3.4%, respectively;  $P=0.077$ ).

**Conclusion:** The significantly higher prevalence of potential DDIs and potential cost impact found in FM duloxetine subjects, relative to pregabalin subjects, underscore the importance of considering DDIs when selecting a treatment.

**Keywords:** Cymbalta, morphine equivalents, Lyrica

## Introduction

Difficult to diagnose and a painful experience for patients, fibromyalgia (FM) is a musculoskeletal disease with a large number of symptoms and a record of only partial treatment success.<sup>1,2</sup> Recent studies have estimated the prevalence of FM in the United States to range from an age- and sex-adjusted prevalence of 6.4%<sup>3</sup> to an age-, sex-, and race-adjusted prevalence of 9.5%.<sup>4</sup> FM presents more often in women than men (9:1);<sup>5</sup> however, the difference is linked to the decreased number of tender points found in men, and the prevalence ratio decreases to 3:1 if the definition is broadened to “chronic widespread pain syndrome”.<sup>6</sup> The most common symptom of this disease is described by

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patients as a penetrating burning ache located at various areas in the body.<sup>7,8</sup> In addition to the pervasive pain often reported by patients, other concomitant symptoms often include cognitive defects, sleep disturbance, fatigue, and soreness of joints, muscles, and tendons.<sup>9,10</sup> The American College of Rheumatology has recently updated its clinical case definition of FM based on the widespread pain index (WPI) and a symptom severity (SS) scale, with a FM diagnosis defined as either 1) a WPI  $\geq 7$  and SS  $\geq 5$ ; or 2) a WPI 3–6 and SS  $\geq 9$ .<sup>11</sup>

Treatment considerations for patients with FM are complex due to the concomitant disease states often experienced by these patients. For example, there is a two- to sevenfold increase in the possibility patients with FM will present with chronic fatigue syndrome, irritable bowel syndrome, rheumatic conditions, anxiety, and depression.<sup>11,12</sup> These conditions, along with possible impaired cognition and decision making, impose a major burden of illness on FM patients. Although nonpharmacologic therapies have been shown to significantly improve FM symptoms, they are less preferred by patients than drug alternatives.<sup>13,14</sup> Several guidelines have been published to guide pharmacological treatment of FM.<sup>15–19</sup> Additionally, while opioid use for FM-associated pain control is seen in clinical practice, the use of chronic opioid therapy is not recommended due to the clinical and societal consequences,<sup>20</sup> with the most recent guidelines discouraging use of strong opioids.<sup>17–19</sup>

Only three drugs have been approved by the Food and Drug Administration (FDA) for treatment of FM: pregabalin (2007), duloxetine (2008), and milnacipran (2009). All three agents have received a strong recommendation for use in FM from the more recent pharmacological treatment guidelines<sup>16–19</sup> and a modest evidence for efficacy rating from the older American Pain Society 2005 guideline.<sup>15</sup> No head-to-head comparative trials of the three FDA-approved FM treatments have been conducted. A recent meta-analysis of eleven randomized-controlled trials indirectly compared the benefits, harms, and adverse event-related study withdrawal of pregabalin, duloxetine, and milnacipran.<sup>21</sup> Adjusted indirect comparisons revealed no significant differences between the three drugs for achieving 30% pain relief and study withdrawal due to adverse events.<sup>21</sup> Significant differences were found across the three drugs at the symptom level and side effect level. For example, duloxetine was superior to milnacipran and pregabalin in improving depressed mood, whereas milnacipran and pregabalin were superior to duloxetine in alleviating fatigue.<sup>21</sup> Duloxetine had a higher risk of headache, nausea, and diarrhea compared to pregabalin.<sup>21</sup> The authors of this meta-analysis conclude, similarly to the aforementioned

pharmacological guidelines, that drug therapy selection should be based on symptomology, concomitant comorbidities, drug adverse effect profiles, and patient preference.<sup>21</sup> Furthermore, drug–drug interactions (DDIs) due to the number of possible comorbid conditions also being treated pose a significant challenge to providers with regard to choosing the most appropriate FM medication for their patients.

Within a population of patients taking pregabalin or duloxetine, there is a paucity of data regarding the real-world prevalence of potential DDIs, the economic and clinical impact of those interactions, and the potential opioid-sparing effect from taking pregabalin or duloxetine instead of opioid agents. To address this gap in knowledge, this study examines the impact of newly initiated pregabalin or duloxetine treatment on FM patients' encounters with potential DDIs, the health care cost and utilization consequences of those interactions, and on opioid utilization.

## Methods

### Study design and subject selection

The research protocol was reviewed and approved prior to study initiation by an independent Institutional Review Board and was granted a waiver of informed consent and a waiver of authorization to use protected health information.

This study is a retrospective, matched cohort study using medical and pharmacy claims collected from a large Medicare Advantage Prescription Drug (MAPD) health plan. Medical and pharmacy claims data collected between January 1, 2007 and December 31, 2012 were utilized. The index date was defined as the date of the first prescription fill for pregabalin or duloxetine with no use in the prior 12 months (to classify subjects as new initiators). Index prescriptions were identified between January 1, 2008 and June 30, 2012. Milnacipran was not included as a comparator, as the study period did not allow for sufficient sample size to analyze those patients.

Study subjects were MAPD members who were diagnosed with FM identified by *International Classification of Disease*, 9th revision, Clinical Modification (ICD-9-CM) codes. To be included in the study, subjects were required to meet all of the following criteria: at least one prescription claim for pregabalin or duloxetine between January 1, 2008 and June 30, 2012, and diagnosis for FM (729.1) in any position on one or more inpatient medical claims or two or more outpatient medical claims observed during the observation period (January 1, 2007 to December 31, 2012) with at least one claim within 90 days of the index date. Subjects with any of the following were excluded from the analysis: age < 18

or >89 years; continuous enrollment <12 months preindex or <6 months postindex; diagnosis of diabetic peripheral neuropathy at any time after the index date; diagnosis and/or procedure indicative of pregnancy, cancer, or transplant surgery during study period; residence in a long-term care facility  $\geq 90$  days during the study period; or one or more prescription claims for the nonindex comparator drug (eg, if index drug is duloxetine, then nonindex comparator drug is pregabalin) 12 months prior to or on the index date.

## Baseline measures

The medication filled on a subject's index date determined the subject's assignment to either the pregabalin cohort or the duloxetine cohort. Age was calculated as of the index date. Sex and race/ethnicity were obtained from enrollment data. Geographic region was based on the subject's state of residence on the index date. Low-income subsidy status, defined as Medicare beneficiaries with income below 150% of poverty level, and Medicare dual eligibility status were obtained from enrollment data and based on status on the index date. Comorbidity burden was measured by the Deyo–Charlson Comorbidity Index (DCCI). The DCCI uses 17 categories of comorbidity to calculate a score that reflects cumulative increased likelihood of 1-year mortality.<sup>22,23</sup> It is based on ICD-9 diagnoses and procedure codes and their associated weights. The DCCI score can range from 0 to 33, with higher scores indicating increased disease burden and an increased likelihood of 1-year mortality. Several pain-related comorbid medical conditions were identified by the presence of at least one medical claim with an ICD-9-CM diagnosis code for the comorbidity in any diagnosis code position.

Preindex and postindex opioid utilization (any claims, one claim, and two or more claims) was defined as one or more prescription fills during the respective observation period. Opioids were categorized as long-acting, short-acting less potent, and short-acting more potent.<sup>24</sup> Further, all oral and transdermal opioids were converted to morphine equivalents (MEq) based on conversion factors.<sup>24</sup> The opioid dose strength and quantity of fill for each adjudicated (ie, insurer payment determined) opioid prescription claim was converted to MEq and summed for the respective observation period. Morphine equivalents for each member were then normalized to an average MEq per 30 days.

## Study outcomes

### Drug–drug interaction status

Medications with high potential for DDI with duloxetine or pregabalin (Table 1) were identified based on a

drug interaction report generated from Micromedex 2.0 (Truven Health Analytics Inc., Greenwood Village, CO, USA). Interactions classified as contraindicated, major, or moderate were included, whereas minor or unknown interactions were not included. Prescription claims records were used to identify subjects using medication(s) that potentially interact with the index medication. Subjects were flagged as having a potential DDI if they had one or more of the following: A prescription claim observed for the interaction medication during the preindex period and a corresponding days' supply indicative of coverage that overlapped the index date; or an adjudicated prescription claim for an interacting medication filled within 30 days after the index date.

### Health care resource utilization and costs

All-cause medical service utilization and costs were identified using medical claims. Place of service was used to distinguish inpatient, emergency room, physical therapy (PT), or non-PT outpatient utilization and costs. Total pharmacy costs were defined as the sum of costs associated with all adjudicated pharmacy claims. Total all-cause health care costs were defined as the sum of the respective total medical cost and total pharmacy cost components. All cost calculations included both member and plan paid components. Postindex opioid utilization was determined both categorically and as MEq per 30 days as previously described for the preindex period.

### Analysis

Propensity score (PS) matching was utilized to reduce selection bias in this nonrandomized, observational study.<sup>25,26</sup> All baseline demographic characteristics and comorbidities present were included in the PS matching process. The PS matching process, matching a duloxetine member to a pregabalin member, was based on the nearest neighbor approach, without replacement, and utilized a caliper width of 0.005. Diagnostic evaluations to examine balance in preindex covariates (from the PS model) between matched treatment groups were considered. Means, standard deviations, medians, and interquartile ranges were calculated for continuous measures. Comparisons for preindex continuous measures were performed using Wilcoxon rank-sum tests. Counts and percentages were calculated for categorical data. Preindex categorical comparisons were evaluated using chi-square tests. Wilcoxon rank-sum test and chi-square tests were also performed for postindex outcomes.<sup>27</sup>

**Table 1** Pregabalin and duloxetine drug–drug interactions

Severity	Brief description of potential harm due to DDI	Interacting drug
Pregabalin		
Major	Reduced pregabalin effectiveness	naproxen, ketorolac
Duloxetine		
Contraindicated	CNS toxicity or serotonin syndrome	isocarboxazid, linezolid, procarbazine, rasagiline, selegiline, tranylcypromine
	Increased serum concentrations of interacting drug and risk of cardiac arrhythmia	thioridazine
	Increased risk of extrapyramidal reactions or neuroleptic malignant syndrome	metoclopramide
	Increased risk of serotonin syndrome or neuroleptic malignant syndrome-like reactions	methylene blue
Major	Increased interacting drug plasma level and increased risk of QT prolongation	clozapine
	Increased risk of bleeding	antiplatelet agents, escitalopram
	Increased risk of serotonin syndrome	almotriptan, citalopram, cyclobenzaprine, desvenlafaxine, dextromethorphan, eletriptan, fluoxetine, fluvoxamine, frovatriptan, hydroxytryptophan, lithium, lorcaserin, methadone, milnacipran, naratriptan, paroxetine, rizatriptan, sertraline, sumatriptan, tapentadol, tramadol, trazodone, tryptophan, venlafaxine, zolmitriptan vilazodone
	Increased risk of serotonin syndrome or neuroleptic malignant syndrome-like reactions	Class IC antiarrhythmic agents
Moderate	Increased serum concentrations of interacting drugs and an increased risk of cardiotoxicity	tamoxifen
	Decreased plasma concentrations of the active metabolites of interacting drug	ciprofloxacin, clobazam, enoxacin, mirabegron, quinidine
	Increased duloxetine serum concentrations and risk of adverse effects	phenothiazines, tamsulosin, tricyclic antidepressants
	Increased exposure to interacting drug and potential toxicity	acenocoumarol, dabigatran, dalteparin, danaparoid, desirudin, enoxaparin, fondaparinux, nonsteroidal anti-inflammatory agents, phenindione, phenprocoumon, tinzaparin, warfarin
	Increased risk of bleeding	

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The relationship between the presence of a potential DDI and health care costs was examined in more detail via fitting of a multivariable statistical model.<sup>28</sup> A generalized linear mixed model (GLMM) with a gamma distribution and log link was fitted to model all-cause total health care costs. The GLMM was adjusted for the presence of a potential DDI, index drug used (“Drug”), DDI\*drug interaction term, baseline demographic characteristics, baseline comorbidities present, and preindex medication utilization. Model-based means and confidence intervals were derived from the models and retransformed into dollar values through exponentiation of the least square (LS) means estimates. All comparisons of total all-cause health care costs between and within cohorts were assessed using Wald chi-square tests.

Differences in all-cause total health care costs were compared between the cohorts (ie, by pregabalin/duloxetine and DDI status) via difference-in-differences (DID)

analyses, utilizing the model-based LS means estimates and corresponding standard errors, as follows:

$$\text{DID} = (\text{DDI present} - \text{DDI absent in the pregabalin cohort}) - (\text{DDI present} - \text{DDI absent in the duloxetine cohort}).$$

Two-sample *t*-tests were performed to formally test the DID values for statistical significance.

Differences in preindex and postindex opioid utilization and MEq were compared between pregabalin and duloxetine cohorts via DID analysis. The *t*-statistic for the opioid utilization DID analysis was derived from a GLMM with a logit link and binary distribution adjusting for baseline demographics, DCCI, and pre- and postindex nonopioid pain medication utilization. The *t*-statistic for the MEq DID analysis was derived from a GLMM with an identity link and a Gaussian distribution adjusting for baseline demographics, DCCI, and pre- and postindex nonopioid

pain medication utilization. The MEQ DID analysis spanned opioid prescription claims from 6 months preindex and 6 months postindex.

All data analyses were conducted using SAS version 9.3/SAS Enterprise Guide 5.1 (SAS Institute, Inc., Cary, NC, USA). The a priori alpha level for all inferential analyses was set at 0.05, and all statistical tests were two-tailed.

## Results

### Patient characteristics

A total of 2,965 subjects met the study inclusion and exclusion criteria (pregabalin  $n=839$ , duloxetine  $n=2,126$ ). The PS matching process resulted in 794 matched pairs (1,588 total study subjects). The lack of statistically significant differences between the two matched cohorts in the distributions of baseline demographics (Table 2) or preindex comorbidity measures (Table 3) provides evidence to support that the matching was successful.

### Potential DDIs

Thirty-two subjects (4.0%) in the pregabalin cohort were identified as having one or more potential DDIs present during the 6-month postindex period. In contrast, a significantly greater prevalence was found in the duloxetine cohort, wherein 571 subjects (71.9%) had one or more potential DDIs ( $P<0.0001$  for comparison to

**Table 2** Patient Characteristics

	Pregabalin N=794		Duloxetine N=794		P value*
	n	%	n	%	
Sex					0.8577
Male	180	22.7	183	23.0	
Female	614	77.3	611	77.0	
Race/Ethnicity					0.6976
White	692	87.2	704	88.7	
Black	76	9.6	67	8.4	
Hispanic	13	1.6	14	1.8	
Other	13	1.6	9	1.1	
Geographic Region					0.9929
Northeast	12	1.5	13	1.6	
Midwest	187	23.6	185	23.3	
South	531	66.9	534	67.3	
West	64	8.1	62	7.8	
Low Income Status	150	18.9	142	17.9	0.6043
Dual Eligibility Status	93	11.7	97	12.2	0.7571
	<b>Mean</b>	<b>SD</b>	<b>Mean</b>	<b>SD</b>	
Age, years	62.9	12.6	62.4	12.0	0.3415
Propensity Score	0.32	0.12	0.32	0.12	0.9582

**Notes:** \*All *P* values for categorical variables calculated using chi-square tests. All *P* values for continuous variables calculated using Wilcoxon rank-sum tests.  
**Abbreviation:** SD, Standard Deviation.

**Table 3** Preindex comorbid conditions

	Pregabalin N=794		Duloxetine N=794		P value*
	n	%	n	%	
Abdominal pain/cramping	228	28.7	223	28.1	0.7808
Anxiety disorder	184	23.2	196	24.7	0.4803
Arthritis	368	46.3	377	47.5	0.6509
Back pain with neuropathic involvement	315	39.7	323	40.7	0.6822
Causalgia and other painful neuropathies	211	26.6	210	26.4	0.9547
Depression	247	31.1	243	30.6	0.828
Diabetes	150	18.9	143	18.0	0.6507
Epilepsy	20	2.5	23	2.9	0.6428
Fatigue	278	35.0	277	34.9	0.958
Irritable bowel syndrome	26	3.3	29	3.7	0.6806
Migraine headache	59	7.4	58	7.3	0.9235
Muscle weakness	62	7.8	54	6.8	0.4404
Neck pain with neuropathic involvement	129	16.2	131	16.5	0.8921
Other back pain	461	58.1	468	58.9	0.7215
Other mental disorders	5	0.6	6	0.8	0.7622
Other musculoskeletal pain	693	87.3	690	86.9	0.8224
Other neck pain (spinal)	216	27.2	223	28.1	0.6945
Sleep disorders	169	21.3	180	22.7	0.505
Substance abuse or dependence	142	17.9	146	18.4	0.7945
Tension headache	7	0.9	8	1.0	0.7953
Thinking/memory loss	23	2.9	20	2.5	0.6428
Trigeminal nerve disorders	7	0.9	14	1.8	0.1241
	<b>Mean</b>	<b>SD</b>	<b>Mean</b>	<b>SD</b>	
Deyo–Charlson Comorbidity Index score	0.9	1.2	0.9	1.2	0.9188

**Notes:** \*All *P* values for categorical variables calculated using chi-square tests. All *P* values for continuous variables calculated using Wilcoxon rank-sum tests.

**Abbreviation:** SD, standard deviation.

pregabalin cohort). There were 41 potential DDIs involving pregabalin, all of which were of “major” severity. There were 1,377 potential DDIs involving duloxetine, including 23 “contraindicated” interactions and 1,083 “major” interactions (Table 4).

### Health care resource utilization

The 6-month postindex all-cause health care utilization of the matched cohorts, segmented by the presence or absence of a potential DDI, is described in Table 5. There were no significant differences in any form of health care utilization between pregabalin subjects with and without a potential DDI. The same can be said for duloxetine, except that the mean number of visits per member for all-cause nonphysical therapy outpatient visits was significantly greater in duloxetine subjects with a potential DDI than those without a potential DDI (16.0 versus [vs] 13.0;  $P=0.0009$ ).

**Table 4** Observed pregabalin and duloxetine drug–drug interactions by severity and interacting drug

Severity*	Interacting drug	Number of interactions
Pregabalin		
Major	ketorolac	4
Major	naproxen	37
Total major for pregabalin		41
Grand total for pregabalin		41
Duloxetine		
Contraindicated	metoclopramide	22
Contraindicated	rasagiline	1
Total contraindicated for duloxetine		23
Major	tramadol	132
Major	trazodone	118
Major	cyclobenzaprine	88
Major	meloxicam	86
Major	citalopram	71
Major	clopidogrel	62
Major	methadone	60
Major	fluoxetine	51
Major	ibuprofen	46
Major	escitalopram	45
Major	sertraline	44
Major	diclofenac	40
Major	sumatriptan	34
Major	paroxetine	29
Major	celecoxib	24
Major	naproxen	23
Major	venlafaxine	22
Major	nabumetone	20
Major	etodolac	15
Major	aspirin	15
Major	piroxicam	9
Major	lithium	8
Major	indomethacin	6
Major	cilostazol	6
Major	milnacipran	5
Major	flecainide	4
Major	salsalate	4
Major	oxaprozin	3
Major	dipyridamole	3
Major	ketorolac	2
Major	zolmitriptan	2
Major	sulindac	2
Major	rizatriptan	2
Major	ticlopidine	1
Major	eletriptan	1
Total major for duloxetine		1,083
Moderate	amitriptyline	81
Moderate	warfarin	42
Moderate	promethazine	38
Moderate	ciprofloxacin	36
Moderate	tamsulosin	21
Moderate	doxepin	17
Moderate	nortriptyline	11
Moderate	prochlorperazine	6
Moderate	enoxaparin	6
Moderate	imipramine	5

(Continued)

**Table 4** (Continued)

Severity*	Interacting drug	Number of interactions
Moderate	chlorpromazine	3
Moderate	perphenazine	3
Moderate	fluphenazine	2
Total moderate for duloxetine		271
Grand total for duloxetine		1,377

**Notes:** \*Severity category according to Micromedex 2.0 (Truven Health Analytics Inc.), as of May 31, 2013.

## Health care costs

The 6-month postindex all-cause health care costs and component costs of the matched cohorts, segmented by the presence or absence of a potential DDI, are described in Table 6. There were no significant differences in all-cause health care costs, or component costs (eg, pharmacy), between pregabalin subjects with and without a potential DDI. Conversely, duloxetine subjects with a potential DDI exhibited significantly greater costs in comparison to duloxetine members without a potential DDI. Among duloxetine subjects, all-cause total health care costs were significantly higher for those with a potential DDI than those without (\$9,373 vs \$7,228;  $P < 0.0001$ ). The component health care costs of total medical, outpatient-related, and total pharmacy costs were also significantly higher in duloxetine members with a potential DDI compared to those without a potential DDI.

## Model-adjusted health care costs

A DID analysis was conducted to study the associations of index medication and mean all-cause health care costs (Table 7). No significant differences were found in model-adjusted mean all-cause health care costs for subjects with a potential DDI versus those members without a potential DDI in either the pregabalin cohort (\$18,382 vs \$17,337, respectively;  $P = 0.727$ ) or the duloxetine cohort (\$15,678 vs \$14,541, respectively;  $P = 0.3124$ ). In accordance with those findings, the DID analysis found no significant difference in all-cause health care costs associated with the presence of a potential DDI attributable to the index medication ( $P = 0.8500$ ).

## Opioid utilization and MEq

The DID analyses for the associations of index medication with opioid utilization and MEq utilization are described in Tables 8 and 9, respectively. There was a trend toward a difference between pregabalin and duloxetine members in their respective pre- versus post-differences in presence of  $\geq 1$  pharmacy claims for long-acting opioids (1.6% and 3.4%,

**Table 5** Six-month postindex all-cause health care utilization stratified by drug–drug interaction status

	Pregabalin			Duloxetine		
	No DDI present n=762	DDI present n=32	P value*	No DDI present n=223	DDI present n=571	P value*
All-cause inpatient visits						
Members with hospitalization, n (%)	160 (21.0)	7 (21.9)	0.905	41 (18.4)	118 (20.7)	0.4706
Hospitalizations per member, mean (SD)	0.4 (1.7)	0.4 (0.9)	0.8637	0.4 (1.4)	0.5 (1.8)	0.4578
All-cause emergency room visits						
Members with visit, n (%)	200 (26.2)	10 (31.3)	0.5296	54 (24.2)	164 (28.7)	0.2010
Visits per member, mean (SD)	0.5 (1.3)	0.5 (0.8)	0.6506	0.5 (1.2)	0.6 (1.4)	0.1886
All-cause outpatient visits (nonphysical therapy)						
Members with visit, n (%)	752 (98.7)	32 (100.0)	0.5143	220 (98.7)	566 (99.1)	1.0
Visits per member, mean (SD)	15.5 (10.2)	19.2 (12.7)	0.0943	13.0 (8.5)	16.0 (10.8)	0.0009
All-cause physical therapy visits						
Members with visit, n (%)	123 (16.1)	7 (21.9)	0.3905	37 (16.6)	85 (14.9)	0.5492
Visits per member, mean (SD)	0.9 (3.3)	1.5 (4.0)	0.3359	0.9 (3.5)	0.6 (2.5)	0.4887

**Notes:** \*All P values for categorical variables calculated using chi-square tests. All P values for continuous variables calculated using Wilcoxon rank-sum tests.

**Abbreviations:** DDI, potential drug–drug interaction; SD, standard deviation.

respectively;  $P=0.077$ ). The DID analysis of preindex and postindex MEq revealed no significant difference associated with the index medication.

## Discussion

The current study adds to the limited knowledge regarding the real-world impact of newly initiated pregabalin or duloxetine treatment on FM patients' encounters with potential DDIs, the health care cost and utilization consequences of those interactions, and on opioid utilization.

The results show that the prevalence of potential pregabalin DDIs was markedly lower than that of potential duloxetine DDIs. This finding is not surprising given the respective metabolic pathways that these two drugs follow and the comorbidity burden and polypharmacy risk common to FM. While pregabalin has minimal pharmacokinetic or pharmacodynamic interactions with other medications, duloxetine's hepatic metabolism by and inhibition of cytochrome P-450 (CYP450) isoenzymes

2D6 and 1A2 and its high level of plasma protein binding result in many potential DDIs with other medications.<sup>29,30</sup>

The substantial burden of comorbid conditions found in the matched pregabalin and duloxetine cohorts, and the medications used for treatment of those conditions, align with previous studies of FM patients<sup>31–33</sup> and play a major role in the observed potential DDI prevalence. Studies of other chronic pain conditions have found that patients receiving treatment for pain are at increased risk for exposure to potential DDIs compared to those patients not being treated for those conditions.<sup>34,35</sup> A recent study, while in a predominantly commercially insured diabetic peripheral neuropathy (DPN) population, substantiates the findings of the present study. Specifically, Johnston et al<sup>36</sup> found the frequency of potential contraindicated, major, and moderate DDIs in DPN patients newly initiated on duloxetine to be 3.9%, 36.9%, and 33.8%, respectively. Conversely, no DPN patients newly initiated on pregabalin encountered a potential DDI of any severity.

**Table 6** Six-month postindex all-cause health care costs and component costs stratified by drug–drug interaction status

	Pregabalin			Duloxetine		
	No DDI present n=762	DDI present n=32	P value*	No DDI present n=223	DDI present n=571	P value*
All-cause total health care costs, mean (SD)	9,089 (12,064)	11,896 (14,781)	0.3974	7,228 (11,389)	9,373 (13,022)	<0.0001
All-cause total medical costs, mean (SD)	6,559 (11,539)	9,304 (14,391)	0.427	5,480 (11,231)	6,532 (11,488)	0.0082
Outpatient-related (nonphysical therapy), mean (SD)	2,651 (3,950)	2,929 (2,618)	0.2273	1,946 (2,408)	2,476 (3,552)	0.002
Physical therapy-related, mean (SD)	112 (442)	144 (342)	0.339	98 (405)	79 (318)	0.7411
Inpatient-related, mean (SD)	2,876 (9,269)	5,078 (11,656)	0.6729	2,656 (9,541)	2,985 (9,460)	0.5224
ER-related, mean (SD)	304 (9,001)	205 (390)	0.6413	239 (612)	351 (991)	0.1900
All-cause total pharmacy costs, mean (SD)	2,529 (3,041)	2,591 (2,872)	0.7218	1,748 (1,603)	2,841 (5,476)	<0.0001

**Notes:** All costs are in US dollars. \*All P values for categorical variables calculated using chi-square. All P values for continuous variables calculated using Wilcoxon rank-sum tests.

**Abbreviations:** DDI, potential drug–drug interaction; SD, standard deviation.

**Table 7** Model-based\* 6-month postindex all-cause total health care costs by index medication and DDI status and difference-in-difference comparison between pregabalin and duloxetine

	All-cause health care costs	
	Mean	95% confidence interval
<b>Pregabalin</b>		
No DDI present	\$17,337	\$10,322–\$29,118
DDI present	\$18,382	\$9,959–\$33,930
Difference**	\$1,045	–
P value	0.727	–
<b>Duloxetine</b>		
No DDI present	\$14,541	\$8,499–\$24,878
DDI present	\$15,678	\$9,368–\$26,239
Difference**	\$1,137	–
P value	0.3124	–
Difference-in-difference comparison	\$1,045 versus \$1,137 P=0.8500	

**Notes:** \*GLMM model with gamma distribution and log link. Model-based means, standard errors, and confidence intervals were derived from model and transformed into dollar values through exponentiation. All P values are calculated using Wald chi square tests through LSMEANS option. Presence of potential DDI, drug used (duloxetine versus pregabalin), DDI\*Drug interaction term, baseline demographic characteristics, baseline comorbidities present, and preindex medication utilization controlled for in GLMM model; \*\*represents the additional health care costs associated with the presence of a potential DDI.

**Abbreviations:** DDI, potential drug–drug interaction; GLMM, generalized linear mixed model; LSMEANS, least square means.

Previous research reported no statistically significant differences in postinitiation costs for FM patients newly initiated on pregabalin or duloxetine.<sup>31,33</sup> While not an objective of this study, newly initiated pregabalin subjects were found to have higher absolute pre- and postindex all-cause health care costs

**Table 8** Opioid utilization\* in 6-month pre- and postindex periods and difference-in-difference comparison between pregabalin and duloxetine

	Long-acting opioids	Short-acting less potent opioids	Short-acting more potent opioids
	%	%	%
<b>Pregabalin</b>			
Preindex	15.4	60.8	22.7
Postindex	17.0	62.2	25.1
Difference	+1.6	+1.4	+2.4
<b>Duloxetine</b>			
Preindex	14.5	60.2	23.4
Postindex	17.9	59.4	25.6
Difference	+3.4	–0.8	+2.1
Difference-in-difference comparison**	1.6 vs 3.4      1.4 vs –0.8      2.4 vs 2.1		
Statistical difference**	t=–1.77, P=0.077	t=0.80, P=0.424	t=0.04, P=0.970

**Notes:** \*Defined as one or more opioid prescription fills during period; \*\*difference-in-difference t-statistic derived from a generalized linear mixed model with a logit link and binary distribution, adjusting for baseline demographics, Deyo–Charlson Comorbidity Index, and pre- and postindex nonopioid pain medication utilization. **Abbreviations:** vs, versus.

**Table 9** Morphine equivalents utilization in pre- and postindex 6-month periods and difference-in-difference comparison between pregabalin and duloxetine

	Morphine equivalents milligrams/30 days	
	Mean	Standard deviation
<b>Pregabalin</b>		
Preindex	930.6	2,300.9
Postindex	1,070.2	2,609.7
Difference	139.6	1,245.3
<b>Duloxetine</b>		
Preindex	968.0	2,294.2
Postindex	1,149.4	2,549.6
Difference	181.3	1,384.4
Difference-in-difference comparison*	139.6 versus 181.3 t=–0.63, P=0.528	

**Notes:** \*Difference-in-difference t-statistic derived from a generalized linear mixed model with an identity link and a Gaussian distribution, adjusting for baseline demographics, Deyo–Charlson Comorbidity Index, and pre- and postindex nonopioid pain medication utilization.

than newly initiated duloxetine subjects. The present study endeavored to determine the impact of potential pregabalin and duloxetine DDIs on 6-month postinitiation costs. Among duloxetine subjects, mean all-cause total health care costs, total medical, outpatient-related, and total pharmacy costs were significantly higher for those with a potential DDI than those without a potential DDI. Nonstatistically significant cost increases were found between the pregabalin members with and without a potential DDI. Furthermore, the model-based analysis found no significant difference between the all-cause health care costs increases observed in both the pregabalin DDI group (vs pregabalin with no DDI) and the duloxetine DDI group (vs duloxetine with no DDI).

The nonsignificant findings for within-pregabalin cohort comparisons and the DID analysis must be tempered by the small number of pregabalin subjects with a potential DDI (n=32). However, the statistically significant increase in costs associated with potential DDIs within the duloxetine cohort cannot be overlooked. While causality cannot be assigned to the presence of DDIs alone within the duloxetine cohort in the present study, other studies of chronic pain conditions have found that CYP450 interactions between specific opioids (codeine, fentanyl, hydrocodone, methadone, oxycodone, and tramadol) and concomitant medications that serve as substrates or inhibitors of CYP450 isoenzymes 3A4 and 2D6, the latter of which includes duloxetine, result in higher costs and greater health care utilization.<sup>37–39</sup>

One such study, a retrospective analysis of 170,086 patients using claims data from 2004 to 2008, found



significantly higher mean total 6-month costs in noncancer, chronic pain subjects with an exposure to a potential DDI compared to matched subjects without an exposure (\$8,165 vs \$7,498, respectively;  $P < 0.01$ ).<sup>37</sup> This same study found that potential DDI exposed patients versus nonexposed patients experienced significantly more office visits (19.10 vs 18.29;  $P < 0.01$ ), outpatient visits (6.71 vs 6.39;  $P < 0.01$ ), emergency department visits (0.46 vs 0.43;  $P < 0.01$ ), and inpatient hospitalizations (0.13 vs 0.12;  $P < 0.01$ ).<sup>36</sup> While these overpowered statistically significant differences may be difficult to interpret in terms of absolute clinical relevance, the increase in health care utilization in the presence of potential DDI exposure is directionally consistent. The only significant, albeit directionally consistent, finding in the present study regarding health care utilization was an increase in all-cause, nonphysical therapy outpatient visits for duloxetine members exposed to a potential DDI.

Changes in opioid utilization after initiation of pregabalin or duloxetine were also assessed in the present study. Previous retrospective studies across various patient populations and utilizing disparate definitions of opioid utilization have incongruent findings regarding the opioid-sparing effect of pregabalin<sup>31,40,41</sup> and duloxetine.<sup>31,42</sup> In the lone head-to-head retrospective analysis of these drugs in a FM population, no changes in pre- to postinitiation of long-acting, short-acting, strong opioid, weak opioid, or any opioid use were found for pregabalin.<sup>31</sup> These findings held for duloxetine with the exception of a decrease in weak opioid use from pre- to postinitiation periods (55.1% vs 49.3%, respectively;  $P = 0.0027$ ), as defined by the percentage of patients with one or more pharmacy claims for those categories of opioids. The present study found no difference between pregabalin and duloxetine members in their respective pre- versus post- differences in the percentage of members with  $\geq 1$  pharmacy claims for long-acting opioids, short-acting more potent, or short-acting less potent. A robust DID analysis of preindex and postindex MEq used also revealed no significant difference between pregabalin and duloxetine.

As with all studies involving administrative claims data, several limitations must be noted. The use of secondary data is limited by the threat of validity posed by missing, incomplete, or inaccurate data within health care information technology systems as well as by provider, region, or site-specific coding and documentation practices. The use of paid pharmacy claims as a proxy for actual medication consumption cannot assess the true medication-taking behavior of patients nor capture the use of over-the-counter medications or remedies impactful to the disease state in

question. It is possible that patients may have discontinued a preindex interacting agent even though the days' supply of the interacting agent overlapped the index date. Patient medication behavior after initiation of index drug and switching or discontinuation of the index drug after the index prescription fill was not assessed. Indirect costs were not considered as part of this study. The observational nature of this study cannot assign a causal effect. Although PS matching and multivariate modeling attempted to control for potential confounding, these approaches can only reduce bias resulting from only covariates included in the statistical models. Even so, residual confounding from those covariates can still occur. More serious, full-fledged confounding from unknown or unmeasured covariates (eg, severity of FM) remains a possibility. Lastly, actual clinical harm due to the presence of a potential DDI was not assessed.

## Conclusion

The results of this retrospective analysis suggest that the real-world prevalence of potential duloxetine DDIs in a MAPD population is substantially greater than that of potential pregabalin DDIs. While the low prevalence of potential pregabalin DDIs is desirable, it places limits on the ability or sensitivity to assess the impact of those DDIs on health care utilization and costs within-cohort or across comparator drugs. The significantly higher prevalence of DDIs and potential cost impact found in FM duloxetine users, relative to pregabalin users, underscore the importance of considering DDIs when selecting a treatment.

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JJE and BTS are employees of Competitive Health Analytics Inc., a wholly owned subsidiary of Humana Inc. CRB is an employee of Humana Inc. BTS is a stockholder of Humana Inc. Competitive Health Analytics Inc. received funding support from Pfizer Inc. in connection with conducting this study and for the development of this article. ABS, JCC, and

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