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Clinical and economic burden of prescribing tramadol and other opioids for patients with osteoarthritis in a commercially insured population in the United States

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Abstract

In 2019, the American College of Rheumatology conditionally recommended tramadol and conditionally recommended against nontramadol opioids for patients with hip and knee osteoarthritis. Although tramadol is known to be less prone to opioid use disorders, little is known about the differing magnitude of negative clinical outcomes, health care resource utilization, and costs of tramadol relative to nontramadol opioids. Administrative claims records for commercially insured patients with osteoarthritis who were prescribed opioids were used to compare clinical and cost outcomes during a 3-year follow-up period by conducting a pre–post analysis and a matched case–cohort analysis. Data for 14,491 patients were analyzed: 4048 (28%) were initiated on tramadol, and 10,443 (72%) were initiated on nontramadol opioids. After matching, 4048 patients per cohort were analyzed. In each empirical analysis, tramadol patients did develop opioid use disorders; however, opioid use disorder rates were 3.5-fold higher in the nontramadol cohort (1.2% vs 4.2%). In addition, rates of other opioid-related clinical outcomes (falls, fractures, nausea, fatigue, and constipation) were also directionally lower among the tramadol cohort, although quantitatively similar (<5% difference) to the nontramadol cohort. Finally, in both analyses, the nontramadol cohort incurred higher levels of inpatient and emergency department visits and all-cause costs during the 3-year follow-up period. However, tramadol patients incur a higher incremental change (+$24,013) in costs relative to their pretreatment baseline compared with nontramadol (+$18,191). These real-world findings demonstrated lower risks with tramadol relative to other opioids, albeit risks and increased health care costs were present with tramadol, highlighting the need for further strategies to improve outcomes.

Keywords: Tramadol, Opioids, Osteoarthritis, Negative outcomes, Economic burden

1. Introduction

The Institute of Medicine has estimated that over 100 million US adults suffer from chronic pain stemming from conditions including osteoarthritis (OA), the most common form of arthritis, as well as back pain, fibromyalgia, and others.[5,8] Many of these conditions affect physical functioning and restrict the ability to perform daily routines.[19] Opioids are among one of the most effective medications for managing chronic pain. Although there is a consensus on their utility as a treatment for chronic cancer pain, their long-term use for chronic nonmalignant pain remains controversial. This, in part, is due to the significant abuse and misuse potential associated with opioids, together with other negative outcomes such as constipation, fatigue, falls, fractures, and nausea, all of which impose significant economic burden.[11,16]

In recent years, tramadol, an opioid medication that is a partial agonist of mu receptors,[20] has been increasingly prescribed in place of (or before) other prescription opioids because of its classification as having a lower abuse profile by the US Drug Enforcement Agency and frequent recommendations in certain pain management guidelines.[2,21] For example, in 2019, the American College of Rheumatology conditionally recommended tramadol for patients with hip and/or knee OA; however, nontramadol opioids were conditionally recommended against.[9]

Although tramadol is known to be less prone to opioid use disorders (OUD), less is understood about the degree to which the magnitude of OUD or other opioid-related outcomes differ among those receiving tramadol.[7] This is especially the case given that patients can and do segue from tramadol to nontramadol opioids throughout the course of their treatment. In these cases, the potentially lowered abuse profile associated with tramadol is mitigated only during the duration of their tramadol-specific treatment regimen.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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2. Methods

2.1. Overview

This study had 2 objectives. The primary objective was to evaluate the clinical burden associated with the use of opioids among patients with OA of the hip and/or knee by determining the prevalence of negative clinical outcomes associated with opioid use—namely OUD, medications commonly used to treat opioid addictions, constipation, fatigue, falls, fractures, and nausea—in patients diagnosed with OA of the hip and/or knee among those initiated on treatment with tramadol relative to nontramadol opioids. The secondary objective was to examine differences in all-cause health care resource use and costs among these cohorts, particularly given that the economic burden of OA is already significant.[4]

To do so, this study used administrative claims records from a database for commercially insured populations in the United States. We used 2 methods to compare differences in clinical and health care resource utilization (HRU) among patients with OA of the hip and/or knee who were prescribed opioids: (1) a pre–post analysis and (2) a matched case–cohort analysis. Under the pre–post treatment study design, we observe within-patient outcomes after tramadol/nontramadol opioid treatment relative to preinitiation levels. In this analysis, each patient serves as their own control, and therefore, confounders such as disease severity and comorbidities are accounted for when evaluating the clinical and economic burden of being prescribed opioids among patients with OA. A matched case–cohort study design was used to compare outcomes across patients with OA who initiated on tramadol ("tramadol cohort") to patients not initiated on tramadol but rather a nontramadol opioid ("nontramadol cohort"). Patients with OA who received a prescription for tramadol were matched to patients who received a prescription for a nontramadol opioid to adjust for the underlying differences between the 2 cohorts (such as age, sex, rates of comorbidities, and previous health care resource use), and this allows for a more direct comparison focusing on tramadol relative to nontramadol opioids.

2.2. Data source

This study used data from OptumHealth Care Solutions, Inc (Optum), a database containing health care utilization records for approximately 19 million privately insured lives (including employees, spouses, dependents, and retirees) from more than 84 large, self-insured, US-based companies. The Optum database contains information regarding patient demographics (age, sex, and enrollment history), medical diagnoses, procedures performed, dates and place of service, and payment amounts for the time period spanning January 1, 2012, to March 31, 2017 (study period). Prescription drug claims (including fill dates, national drug codes, and payment amounts) are available for all beneficiaries.

2.3. Sample selection

Patients with at least 2 diagnoses of OA of the hip and/or knee (according to the *International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification* [*ICD-9-CM* and *ICD-10-CM*]) and who received at least 1 prescription for an opioid (according to generic product identifier codes) during the study period were identified. The list of *ICD-9-CM*, *ICD-10-CM*, and generic product identifier codes used are available upon request. The index date was defined as the date of the earliest opioid prescription occurring after each patient's first OA diagnosis. Patients were required to be at least 18 year old on the index date and be continuously enrolled during the 6 months before (baseline period) and 36 months after (follow-up period) the index date to ensure that all relevant drug and medical claims were captured. The index date was included in the 36-month follow-up period. In addition, consistent with previous research on "chronic opioid use" and to help ensure that the prescription opioid(s) were prescribed for OA (as opposed to short-term, acute pain), patients were required to have at least 90 days of cumulative supply of opioids during the follow-up period.[12,15] Finally, patients were divided into 2 mutually exclusive cohorts based on the index drug: Patients initiated on tramadol or a nontramadol opioid.

2.4. Study measures

The following characteristics were described during baseline: age (on index), sex, geographic region (census division), Charlson Comorbidity Index (CCI; a composite measure of the patient's underlying chronic conditions predictive of high costs and health care resource use),[13] type(s) of OA diagnosis (hip, knee, hip and knee, other OA), and all-cause HRU and all-cause costs. Resource utilization and costs were categorized by place of service to identify sources of differential utilization. Place of service categories included the following: inpatient, outpatient/physician office, emergency department (ED), and other (eg, skilled nursing facilities and home health). All costs were adjusted to calendar year 2017 (the last year of the data) using the medical component of the Consumer Price Index.

Selected opioid-related negative clinical outcomes that were present during the follow-up period were summarized and compared. Opioid-related negative clinical outcomes included those diagnosed with an OUD; use of certain medication-assisted treatment (MAT) therapies (ie, methadone and buprenorphine) that are associated with opioid misuse (even if undiagnosed); and other opioid-related outcomes (ie, constipation, fatigue and nausea, falls, and fractures). These outcomes were based on *ICD-9-CM* and *ICD-10-CM* codes (available upon request).

2.5. Pre–post analysis

For the pre–post analysis, we compared selected patient-level clinical, HRU, and cost of outcomes over time for each cohort. For prevalence and incidence of clinical outcomes, we compared the changes in the underlying prevalence between baseline and follow-up periods. Continuous measures (eg, costs and number of inpatient visits) were normalized by extrapolating by a factor of 6 to account for the fact that the follow-up period was 6 times longer than the baseline period.

2.6. Propensity score matching

In addition to the pre–post analysis tracking changes in clinical characteristics and costs over time for a given patient, we used a propensity score–matching model to compare outcomes across cohorts. Given the retrospective nature of the study (patients were not randomly assigned into treatment cohorts), to account for the underlying differences between cohorts, each patient in the tramadol cohort was propensity score ($\pm$1/8 SD) matched 1:1 to a patient in the nontramadol cohort using a "greedy" matching methodology.[3] This approach, which is commonly used in matched health care utilization studies,[10,14,17,18,22] selects a patient among the eligible controls for each subsequent tramadol patient based on the nearest propensity score. Propensity scores

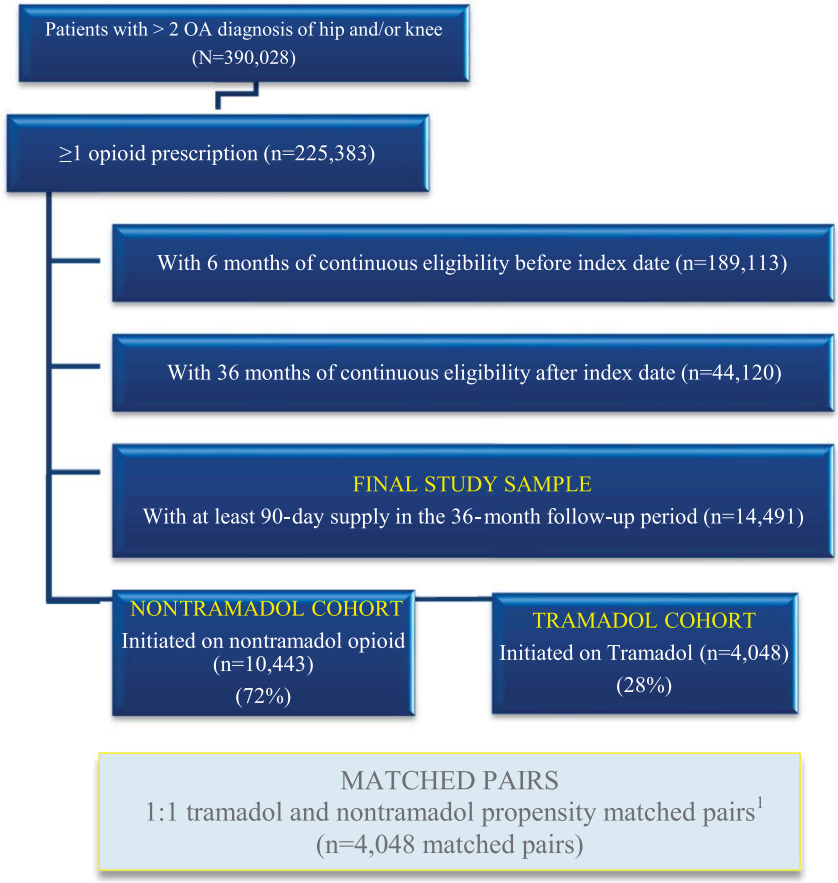

Figure 1. Sample selection for patients with OA. OA, osteoarthritis. [1]Patients in the tramadol cohort were matched 1:1 to patients in the nontramadol cohort using a propensity score, accounting for baseline characteristics (demographics, underlying comorbid conditions, health care resource utilization, and direct medical costs).

were calculated for patients using a multivariate logistic regression with the following covariates measured at baseline: age, sex, region, CCI, presence of selected comorbidities (anxiety, depression, and alcohol dependence), number of medical visits (ED, inpatient, outpatient, or other), medical costs (ED, inpatient, outpatient, or other), and prescription drug costs.

2.7. Statistical comparisons

Standardized differences were used for comparing HRU, costs, and outcomes between the baseline and follow-up period to assess whether there were any enduring differences. Statistical significance was assessed between the unmatched samples using the χ^2 test for categorical variables and the Wilcoxon rank-sum test for continuous variables and was assessed between the matched samples using the McNemar test for categorical variables and the Wilcoxon signed-rank test for continuous variables. All analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, NC).

3. Results

3.1. Sample selection

Between January 1, 2012, and March 31, 2017, a total of 390,028 patients had at least 2 diagnoses of OA of the hip and/or knee, of those, 225,383 patients received at least 1 opioid prescription. After applying the sample selection criteria, the final analytic sample consisted of 14,491 total individuals: 4048 (28%) in the tramadol cohort and 10,443 (72%) in the nontramadol cohort (**Fig. 1**).

3.2. Baseline characteristics

In the full sample, tramadol patients were substantially different from nontramadol opioids patients on age, sex, anxiety, depression, and most all-cause HRU characteristics during baseline period (**Table 1**). Between the 2 cohorts, patients had a similar mean CCI (0.6 vs 0.6) and quantitatively similar profile of OA diagnoses during the baseline period in terms of number and type of joints affected (hip only: 15.4% vs 16.3%, $P = 0.20$; knee only: 53.5% vs 55.5%, $P = 0.04$). Patients who received a prescription for tramadol were older (65.2 vs 62.3 years, $P < 0.01$), more likely to be female (67% vs 61%, $P < 0.01$), and had lower rates of baseline HRU, such as at least 1 inpatient visit (12.3% vs 22.7%, $P < 0.01$) and ED visit (15.8% vs 21.3% $P < 0.01$), respectively. These differences resulted in baseline all-cause health care costs among tramadol patients that were 38% lower than nontramadol patients ($5018 vs $8,096, $P < 0.01$), respectively. However, the tramadol cohort had higher prescription costs ($635 vs $557, $P < 0.01$).

After propensity score matching, final cohort count was 4048 in each cohort with no statistically significant differences between cohorts in terms of demographics or comorbidities (**Table 1**). The matched tramadol and nontramadol patients also had similar HRU during the baseline period, specifically patients with ≥1

Table 1

Baseline characteristics.

Baseline characteristics (6 mo)	Unmatched		P*	Matched		P
	Tramadol cohort (n = 4048)	Nontramadol cohort (n = 10,443)		Tramadol cohort (n = 4048)	Nontramadol cohort (n = 4048)	
Demographic characteristics						
Age, mean ± SD [median]	65.2 ± 12.1 [63]	62.3 ± 11.7 [61]	<0.01	65.2 ± 12.1 [63]	65.0 ± 12.2 [63]	0.39
≥ 65	46.7%	36.8%	<0.01	46.7%	45.2%	0.12
Sex, female	67%	61%	<0.01	67.1%	66.3%	0.41
Region						
East North Central	30.9%	30.9%	0.97	30.9%	31.1%	0.83
East South Central	2.9%	3.8%	<0.01	2.9%	2.7%	0.58
Middle Atlantic	22.3%	21.3%	0.21	22.3%	22.2%	0.92
Mountain	3.2%	4.3%	<0.01	3.2%	3.3%	0.70
New England	2.1%	2.3%	0.42	2.1%	2.0%	0.75
West South Central	8.4%	7.1%	<0.01	8.4%	8.5%	0.90
Pacific	2.5%	3.9%	<0.01	2.5%	2.1%	0.22
South Atlantic	11.8%	10.1%	<0.01	11.8%	11.9%	0.86
West North Central	7.2%	7.5%	0.52	7.2%	7.6%	0.42
Unknown	9%	9%	0.99	8.7%	8.8%	0.69
Clinical characteristics						
Charlson Comorbidity Index, mean ± SD [median]	0.6 ± 1.0 [0]	0.6 ± 1.1 [0]	0.06	0.6 ± 1.0 [0]	0.6 ± 1.0 [0]	0.97
Anxiety	4.0%	5.9%	<0.01	4.0%	3.7%	0.49
Depression	7.3%	11.0%	<0.01	7.3%	6.9%	0.56
Alcohol dependence	0.3%	0.5%	0.19	0.3%	0.3%	0.83
OA diagnosis						
Hip only	15.4%	16.3%	0.20	15.4%	15.2%	0.81
Knee only	53.5%	55.5%	0.04	53.5%	54.3%	0.46
Knee and others	15.4%	14.9%	0.46	15.4%	15.7%	0.71
Hip and others	4.4%	4.6%	0.59	4.4%	4.3%	0.79
Only hip and knee	3.1%	2.6%	0.10	3.1%	3.3%	0.66
Hip, knee, and other	1.0%	0.9%	0.70	1.0%	0.9%	0.73
All-cause health care resource utilization						
Medical						
Inpatient						
Patients with ≥ 1 visit	12.3%	22.7%	<0.01	12.3%	11.8%	0.40
Visits per patient, mean ± SD [median]	0.2 ± 0.9 [0]	0.4 ± 1.2 [0]	<0.01	0.2 ± 0.9 [0]	0.2 ± 0.7 [0]	0.13
Days per visit, mean ± SD [median]	1.0 ± 5.2 [0]	1.5 ± 5.5 [0]	<0.01	1.0 ± 5.2 [0]	0.8 ± 3.9 [0]	0.15
Outpatient						
Patients with ≥ 1 visit	98.8%	99.0%	0.27	98.8%	98.9%	0.75
Visits per patient, mean ± SD [median]	9.9 ± 7.2 [8]	10.7 ± 7.5 [9]	<0.01	9.9 ± 7.2 [8]	10.2 ± 7.3 [9]	0.04
Emergency department						
Patients with ≥ 1 visit	15.8%	21.3%	<0.01	15.8%	15.0%	0.31
Visits per patient, mean ± SD [median]	0.2 ± 0.7 [0]	0.3 ± 0.9 [0]	<0.01	0.2 ± 0.7 [0]	0.2 ± 0.7 [0]	0.74
Other visits						
Patients with ≥ 1 visit	29.8%	32.2%	<0.01	29.8%	29.2%	0.53
Visits per patient, mean ± SD [median]	1.2 ± 3.2 [0]	1.3 ± 3.2 [0]	<0.01	1.2 ± 3.2 [0]	1.2 ± 3.1 [0]	0.90
All-cause health care cost, ($) mean ± SD [median]						
Total cost	5018 ± 12,784 [1786]	8096 ± 19,272 [2495]	<0.01	5018 ± 12,784 [1786]	4878 ± 10,542 [1839]	0.39
Medical cost	4383 ± 12,598 [1197]	7540 ± 19,180 [1952]	<0.01	4383 ± 12,598 [1197]	4262 ± 10,338 [1305]	0.12
Inpatient	1512 ± 9356 [0]	3717 ± 16,112 [0]	<0.01	1512 ± 9356 [0]	1391 ± 7132 [0]	0.81
Outpatient	2306 ± 4758 [887]	3103 ± 6534 [1275]	<0.01	2306 ± 4758 [887]	2311 ± 4410 [970]	0.08
Emergency department	207 ± 1153 [0]	327 ± 1509 [0]	<0.01	207 ± 1153 [0]	194 ± 1162 [0]	0.59
Other	359 ± 2336 [0]	393 ± 2252 [0]	<0.01	359 ± 2336 [0]	366 ± 2539 [0]	0.92
Prescription cost	635 ± 1653 [70]	557 ± 1720 [40]	<0.01	635 ± 1653 [70]	616 ± 1868 [51]	0.04

* Statistical significance was assessed between the unmatched samples using the chi-squared test for categorical variables and the Wilcoxon rank-sum test for continuous variables (mean values) and was assessed between the matched samples using the McNemar test for categorical variables and the Wilcoxon signed-rank test for continuous variables (mean values).

Table 2

Clinical outcomes.

Preselected negative outcomes	Nontramadol cohort (n = 10,443)			Tramadol cohort (n = 4048)			Matched patients (n = 4048)		
	Baseline period	Follow-up period	*P*	Baseline period	Follow-up period	*P*	Tramadol cohort	Nontramadol cohort	*P*
Any identified select negative clinical outcome	20.2%	60.9%	<0.01	17.4%	54.6%	<0.01	54.6%	61.2%	<0.01
Opioid abuse/dependence/misuse	1.1%	5.0%	<0.01	0.2%	1.2%	<0.01	1.2%	4.2%	<0.01
Abuse	0.1%	0.5%	<0.01	0.1%	0.1%	1.00	0.1%	0.3%	<0.01
Dependence	0.9%	4.1%	<0.01	0.1%	1.0%	<0.01	1.0%	3.4%	<0.01
Poisoning/overdose	0.1%	0.4%	<0.01	0.0%	0.1%	1.00	0.1%	0.4%	0.03
At least 1 MAT prescription									
Methadone	0.0%	2.0%	1.00	0.0%	0.5%	1.00	0.5%	1.9%	<0.01
Buprenorphine	0.0%	3.5%	1.00	0.0%	1.4%	1.00	1.4%	3.2%	<0.01
Other opioid-related outcomes									
Constipation	2.6%	14.1%	<0.01	2.8%	12.9%	<0.01	12.9%	15.0%	<0.01
Fatigue	10.1%	36.6%	<0.01	9.9%	33.5%	<0.01	33.5%	37.1%	<0.01
Nausea	4.4%	20.4%	<0.01	3.0%	17.4%	<0.01	17.4%	20.0%	<0.01
Falls	1.7%	8.5%	<0.01	1.4%	7.9%	<0.01	7.9%	9.2%	0.03
Fractures	5.1%	18.7%	<0.01	15.6%	15.6%	<0.01	15.6%	17.9%	<0.01

MAT, medication-assisted treatment.

inpatient visits (12.3% vs 11.8%, $P = 0.40$) and ED visits (15.8% vs 15.0%, $P = 0.31$), and baseline total health care costs ($5018 vs $4,878, $P = 0.39$). After matching, the average number of outpatient visits per patient (9.9 vs 10.2, $P = 0.04$) and average prescription costs ($635 vs $616, $P = 0.04$) were numerically closer but remained statistically different.

3.3. Opioid use disorders and other opioid-related outcomes

3.3.1. Pre–post analysis

The prevalence of clinical outcomes in the baseline and follow-up periods is reported in **Table 2** for the tramadol cohort. The prevalence of OUD increased by 500% from the baseline period to the follow-up period (0.2%-1.2%, $P < 0.01$). There was also reported use of buprenorphine (0.0%-1.4%, $P < 0.01$) and methadone (0.0%-0.5%, $P < 0.01$) in the follow-up period, while in the baseline period, there was no reported use. Analysis of other selected opioid-related outcomes found a higher prevalence of negative clinical outcomes in the follow-up period relative to the baseline period. Specifically, there was a 361% increase in constipation (2.8%-12.9%, $P < 0.01$), a 238% increase in fatigue (9.9%-33.5%, $P < 0.01$), a 480% increase in nausea (3.0%-17.4%, $P < 0.01$), a 464% increase in falls (1.4%-7.9%, $P < 0.01$), and a 359% increase in fractures (3.4%-15.6%, $P < 0.01$).

Table 2 also reports the outcomes for the nontramadol cohort. The prevalence of OUD in the nontramadol cohort increased 355% from the baseline period to the follow-up period (1.1%-5.0%, $P < 0.01$). Consistent with these higher OUD rates relative to the tramadol cohort, the nontramadol cohort also had higher reported use of buprenorphine (0.0%-3.5%, $P < 0.01$) and methadone (0.0%-2.0%, $P < 0.01$) in the follow-up period. In addition, consistent with the tramadol cohort, analysis of other negative opioid-related clinical outcomes found higher prevalence rates from baseline period to the follow-up period including a 442% increase in constipation (2.6%-14.1%, $P < 0.01$), a 262% increase in fatigue (10.1%-36.6%, $P < 0.01$), a 261% increase in nausea (4.4%-20.4%, $P < 0.01$), a 400% increase in falls (1.7%-8.5%, $P < 0.01$), and a 267% increase in fractures (5.1%-18.7%, $P < 0.01$).

3.3.2. Matched cohort

Consistent with the pre–post analysis above, the prevalence of OUD during the follow-up period was lower in the matched tramadol cohort relative to the nontramadol cohort (1.2% vs 4.2%, $P < 0.01$) (**Table 2**), and a smaller proportion of the tramadol cohort received at least 1 prescription for buprenorphine (1.4% vs 3.2%, $P < 0.01$) or methadone (0.5% vs 1.9%, $P < 0.01$). In addition, a statistically significantly lower proportion of tramadol patients experienced negative clinical outcomes compared with the nontramadol cohort, although quantitatively similar in magnitude. Specifically, rates of constipation (12.9% vs 15.0%, $P < 0.01$), fatigue (33.5% vs 37.1%, $P < 0.01$), nausea (17.4% vs 20.0%, $P < 0.01$), falls (7.9% vs 9.2%, $P < 0.03$), and fractures (15.6% vs 17.9%, $P < 0.01$).

3.4. Direct health care resource use and costs

3.4.1. Pre–post analysis

Table 3 reports all-cause HRU and costs during the baseline and follow-up period for the unmatched tramadol cohort. All-cause inpatient admissions increased 431% (12.3% to 65.3% of patients with at least 1 visit) and ED visits increased 254% (15.8% to 56.0% of patients with at least 1 visit). Over this same timeframe, all-cause total health care costs increased by 80%, with prescription costs increasing by 233% ($635 [$3809 normalized] to $12,694) and outpatient costs increasing by 25% ($2306 [$13,833 normalized] to $17,255).

Table 3 also reports all-cause HRU and costs during the baseline and follow-up period for the unmatched nontramadol cohort. From the baseline period to follow-up period, all-cause inpatient admissions increased 202% (22.7%-68.6% of patients with at least 1 visit, $P < 0.01$) and ED visits increased 190% (21.3%-61.7% of patients with at least 1 visit, $P < 0.01$). Over this same timeframe, all-cause mean total health care costs increased by 37%, with prescription costs increasing by 364% ($557 [$3339 normalized] to $15,504, $P < 0.01$) and outpatient costs increasing by 15% ($3103 [$18,616 normalized] to $21,473, $P < 0.01$.

Table 3

Resource utilization and costs: pre–post analysis.

	Nontramadol cohort (n = 10,443)				Tramadol cohort (n = 4048)			
	Baseline period	Follow-up period	*P*	Relative difference	Baseline period	Follow-up period	*P*	Relative difference
All-cause HRU								
Inpatient								
Patients with ≥ 1 visit	22.7%	68.6%	<0.01	202%	12.3%	65.3%	<0.01	431%
Visits per patient, mean ± SD [median]	0.4 ± 1.2 [0]	2.3 ± 5.2 [1]	<0.01	6%	0.2 ± 0.9 [0]	2.0 ± 4.5 [1]	<0.01	57%
Days per visit, mean ± SD [median]	1.5 ± 5.5 [0]	9.4 ± 20.2 [4]	<0.01	2%	1.0 ± 5.2 [0]	8.2 ± 18.7 [4]	<0.01	37%
Outpatient								
Patients with ≥ 1 visit	99.0%	99.9%	<0.01	1%	98.8%	100.0%	1.00	1%
Visits per patient, mean ± SD [median]	10.7 ± 7.5 [9]	65.8 ± 36.3 [60]	<0.01	2%	9.9 ± 7.2 [8]	61.7 ± 35.9 [55]	<0.01	4%
Emergency department								
Patients with ≥ 1 visit	21.3%	61.7%	<0.01	190%	15.8%	56.0%	<0.01	254%
Visits per patient, mean ± SD [median]	0.3 ± 0.9 [0]	1.9 ± 3.7 [1]	<0.01	0%	0.2 ± 0.7 [0]	1.6 ± 3.2 [1]	<0.01	16%
Other visits								
Patients with ≥ 1 visit	32.2%	75.6%	<0.01	135%	29.8%	72.1%	<0.01	142%
Visits per patient, mean ± SD [median]	1.3 ± 3.2 [0]	10.3 ± 17.6 [4]	<0.01	36%	1.2 ± 3.2 [0]	9.3 ± 16.6 [4]	<0.01	31%
All-cause health care cost, ($) mean ± SD [median]								
Total cost	8096 ± 19,272 [2495]	66,770 ± 84,245 [40,962]	<0.01	37%	5018 ± 12,784 [1786]	54,122 ± 79,382 [32,338]	<0.01	80%
Medical cost	7540 ± 19,180 [1952]	51,267 ± 76,457 [27,245]	<0.01	13%	4383 ± 12,598 [1197]	41,428 ± 72,799 [20,388]	<0.01	58%
Inpatient	3717 ± 16,112 [0]	24,417 ± 51,361 [3848]	<0.01	9%	1512 ± 9356 [0]	19,915 ± 50,226 [2279]	<0.01	120%
Outpatient	3103 ± 6534 [1275]	21,473 ± 34,864 [12,011]	<0.01	15%	2306 ± 4758 [887]	17,255 ± 32,594 [8832]	<0.01	25%
Emergency department	327 ± 1509 [0]	2237 ± 7298 [253]	<0.01	14%	207 ± 1153 [0]	1502 ± 4471 [60]	<0.01	21%
Other	393 ± 2252 [0]	3139 ± 10,489 [325]	<0.01	33%	359 ± 2336 [0]	2755 ± 9617 [184]	<0.01	28%
Prescription cost	557 ± 1720 [40]	15,504 ± 27,328 [7296]	<0.01	364%	635 ± 1653 [70]	12,694 ± 23,405 [5930]	<0.01	233%

HRU, health care resource utilization.

3.4.2. Matched cohort

Table 4 reports all-cause HRU and costs. A lower percentage of tramadol patients had an inpatient visit during the 36-month follow-up period compared with nontramadol patients (65.3% vs 67.9%, $P = 0.01$). During the follow-up period, tramadol patients also had lower average inpatient visits per patient (2.0 vs 2.2, $P < 0.01$) and shorter average days per visit (8.2 vs 9.3, $P < 0.01$). Similarly, tramadol patients were less likely to visit the ED than patients who received a nontramadol opioid prescription (56.0% vs 61.5%, $P < 0.01$). With respect to health care costs, tramadol patients had lower all-cause total health care costs ($54,122 vs $60,303, $P < 0.01$) during the follow-up period. Total medical costs were $41,428 in the tramadol cohort relative to $45,215 in the nontramadol cohort ($P < 0.01$), and pharmacy costs were $12,694 in the tramadol cohort relative to $15,088 in the nontramadol cohort ($P < 0.01$).

4. Discussion

To the authors' knowledge, this study was the first of its kind to use a large, real-world, database with national coverage to compare the long-term clinical and economic outcomes between patients with OA initiated with tramadol with those using nontramadol opioids. The analysis used 2 empirical study designs: a pre–post design to assess within patient changes before and after tramadol/nontramadol initiation and a matching method to compare outcomes across pairs of patients in each cohort. Specifically, using data for 14,491 patients with OA of the hip and/or knee, consistent with literature in other settings,[1,6] this study demonstrably showed that in each empirical analysis, tramadol patients had an elevated risk of abuse; however, risk of abuse was almost 3-fold higher in the nontramadol cohort. Consistent with those findings, in both analyses, rates of methadone and buprenorphine were also elevated in the nontramadol cohort relative to the tramadol cohort. Finally, rates of other opioid-related clinical outcomes (falls, fractures, nausea, fatigue, and constipation) were also lower among the tramadol cohort, although quantitatively similar to the nontramadol cohort.

In terms of costs, the analyses also showed a consistent story, although one that sheds additional light on cost trends. In both analyses, the nontramadol opioid cohort incurred higher levels of all-cause costs during the 3-year follow-up period. However, as the pre–post analysis shows, tramadol patients incur a higher incremental change relative to their pretreatment baseline.

Table 4

Resource utilization and costs: matched analysis.

Health care resource utilization	Matched patients (n = 4048)			
	Tramadol cohort	Nontramadol cohort	*P*	Relative difference
All-cause HRU				
Inpatient				
Patients with ≥ 1 visit	65.3%	67.9%	0.01	−4%
Visits per patient, mean ± SD [median]	2.0 ± 4.5 [1]	2.2 ± 4.3 [1]	<0.01	−7%
Days per visit, mean ± SD [median]	8.2 ± 18.7 [4]	9.3 ± 18.4 [4]	<0.01	−12%
Outpatient				
Patients with ≥ 1 visit	100.0%	99.9%	1.00	0%
Visits per patient, mean ± SD [median]	61.7 ± 35.9 [55]	63.7 ± 35.0 [58]	<0.01	−3%
Emergency department				
Patients with ≥ 1 visit	56.0%	61.5%	<0.01	−9%
Visits per patient, mean ± SD [median]	1.6 ± 3.2 [1]	1.8 ± 3.9 [1]	<0.01	−13%
Other visits				
Patients with ≥ 1 visit	72.1%	73.7%	0.11	−2%
Visits per patient, mean ± SD [median]	9.3 ± 16.6 [4]	10.3 ± 17.9 [4]	0.03	−10%
All-cause health care cost, ($) mean ± SD [median]				
Total cost	54,122 ± 79,382 [32,338]	60,303 ± 76,933 [36,713]	<0.01	−10%
Medical cost	41,428 ± 72,799 [20,388]	45,215 ± 69,340 [23,254]	<0.01	−8%
Inpatient	19,915 ± 50,226 [2279]	21,793 ± 48,443 [3094]	0.02	−9%
Outpatient	17,255 ± 32,594 [8832]	18,289 ± 28,723 [10,342]	<0.01	−6%
Emergency department	1502 ± 4471 [60]	1838 ± 7439 [196]	<0.01	−18%
Other	2755 ± 9617 [184]	3295 ± 11,104 [247]	<0.01	−16%
Prescription cost	12,694 ± 23,405 [5930]	15,088 ± 26,828 [7153]	<0.01	−16%

HRU, health care resource utilization.

These findings suggest several takeaways and potential areas for future scientific inquiry. First, these findings show that although treatment initiation with tramadol is associated with lower rates of OUD and lower costs, diagnosed OUD nonetheless did occur among the tramadol cohort. Furthermore, certain other negative and clinically relevant outcomes (eg, falls and fractures) remain prevalent among tramadol patients and at similar levels relative to nontramadol opioid patients. As a result, the general reduction in negative outcomes and costs in patients receiving tramadol relative to other opioids is consistent with the American College of Rheumatology recommendations and highlights the need for clinicians and researchers to differentiate tramadol from nontramadol opioids; however, it also highlights that negative outcomes do nonetheless occur in this cohort. Second, these findings suggest that future inquiry into treatment patterns among tramadol initiators would be important. Namely, it is likely that some tramadol patients switched to nontramadol treatment and may have incurred their abuse-related outcomes after that switch. Assessing the magnitude of these outcomes could shed meaningful light on treatment guidelines and clinical practice and answer questions such as those of whether tramadol itself is associated with abuse outcomes or if it is merely delaying an inevitable switch with no ultimate changes to abuse-related outcomes.

This study had certain limitations, primarily inherent to claims-based analysis. First, in terms of cost outcomes, the study was not able to completely rule out that the increased costs were attributable to opioid treatment vs other factors (eg, OA disease progression). Although we expect that the matched analysis accounts for this to a large degree, no retrospective analysis is able to rule out these external factors completely. Relatedly, tramadol is a centrally acting mu opioid that also acts upon serotonin nonrepinephrine, and some of the outcomes observed in the tramadol cohort may be driven by these nonopioid effects. Second, we cannot ensure that patients are using the treatments solely for pain due to OA, although the study design strengthens the linkage by including patients diagnosed with OA and using opioids long-term. Relatedly, some patients may be using opioids for other painful conditions (such as low back pain) before their OA diagnosis or during the follow-up period. Although the dual pre–post and matching approaches control for numerous baseline confounding factors, the degree to which certain baseline variables, such as previous opioid use, interact with risk of certain clinical consequences or HRU remains a subject for future research. Third, claims analysis relies on the accuracy of diagnosis codes to identify patients and to evaluate their comorbidity profiles at baseline and outcomes, resource use, and cost information in the follow-up period. As a result, the analyses are unable to assess outcomes such as pain levels or function change. Furthermore, any miscoding along these lines would affect our results, and specifically, we anticipate that (as previous research has found) rates of abuse and other outcomes (eg, nausea, fatigue, and falls) are likely undiagnosed and therefore underreported. Fourth, costs and HRU figures in the pre–post analyses were scaled by a factor of 6 to account for differential period lengths; however, it is possible that this adjustment may be inaccurate for some patients. Finally, the underlying data reflect a commercially insured patient population with data through early 2017, and therefore may not be representative of other populations (such as Medicare or Medicaid), or more recent periods where prescribing trends may have changed with updated guidelines and evolving controversies over the use of opioids.[9]

Despite these limitations, this study is the first to use rigorous methodologies to estimate incremental clinical and economic burden associated with tramadol and nontramadol treatments

using a large national database and multiple empirical study designs. As a result, the findings of this study may help health plans and health care providers quantify the substantial incremental costs associated with the various treatment approaches. The findings are supportive of evaluating other new treatments for such patients with OA, specifically treatments that may have a more favorable negative outcome profile.

Conflict of interest statement

S. Silverman is a paid consultant to Pfizer and Eli Lilly and Company in connection with this study. J. B. Rice, A. G. White, and C. Fernan are employees of the Analysis Group, who were paid consultants to Pfizer and Eli Lilly and Company for this study and development of this article. R. L. Robinson is an employee and minor stockholder of Eli Lilly and Company. P. Schepman and Crag Beck are employees of Pfizer with stock and/or stock options.

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