

Economic Outcomes Related to Persistence and Dosing of Celecoxib in Patients with Osteoarthritis (OA) Using a Retrospective Claims Database Analysis

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Objective: This study describes treatment patterns, healthcare resource utilization (HCRU), and costs associated with persistence, switching, and dosing of branded celecoxib in osteoarthritis (OA) patients.

Methods: This retrospective claims database analysis used MarketScan[®] Commercial Claims and Encounters (MarketScan) data from 2009 to 2013. Included patients were adult (≥ 18 years), incident celecoxib users with ≥ 1 OA claim. The treatment switch analysis analyzed outcomes in patients persistent on celecoxib versus switched to a generic nonsteroidal anti-inflammatory drug (NSAID). The dosing analysis stratified patients as under-dose (<200 mg per day) and standard dose (≥ 200 mg per day). HCRU, costs, and treatment duration were compared in persistent versus switched and standard dose versus under-dose patients using descriptive, multivariate logistic regression, and Kaplan–Meier analysis.

Results: A total of 65,530 patients met the inclusion criteria. During follow-up, 83% discontinued celecoxib without switching, 10% were persistent, and 5% switched to a generic NSAID. Ninety percent received a standard dose of celecoxib. Switched (versus persistent) patients had significantly higher all-cause hospital admissions, length of stay, emergency room (ER) visits, and office visits per person year (PPY), all $P < 0.001$; and under-dosed (versus standard dose) patients had significantly higher hospital admissions ($P < 0.001$), length of stay ($P < 0.001$), and ER visits ($P = 0.021$) PPY. Persistent versus switched patients had lower mean total all-cause costs PPY (\$20,378 vs \$23,949, $P < 0.001$). Standard dose versus under-dose patients had lower mean total all-cause costs (\$23,680 vs \$26,955 PPY, $P < 0.001$), and not statistically significant higher mean total OA-related costs (\$5698 vs \$5524 PPY, $P = 0.441$).

Conclusion: Patients that switched from branded celecoxib to a generic NSAID or received an under-dose of branded celecoxib had higher average overall HCRU and costs. OA-related inpatient and outpatient cost savings may offset the higher drug cost of celecoxib for persistent patients.

Keywords: generic, healthcare resource use, Celebrex, NSAIDS, switching, discontinuation

Introduction

Pharmacological treatment for osteoarthritis (OA) is dependent on location and severity of disease, patient comorbidities, and concomitant medication use among other factors. In patients with knee or hip OA that have not received adequate pain relief from acetaminophen, the usually prescribed first-line therapy, guidelines suggest providers prescribe a low dose nonsteroidal anti-inflammatory drug

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(NSAID) such as a cyclooxygenase-2 (COX-2) selective inhibitor or nonselective NSAID for second-line therapy, dependent on patient comorbidities and risk factors.¹⁻⁴ Because of the possibility for treatment emergent cardiovascular (CV), renal, and/or gastrointestinal (GI) adverse events (AEs), guidelines suggests the NSAID treatments be used for the shortest period of time at the lowest possible dose.²⁻⁴

Celecoxib (Celebrex[®], Pfizer) is a NSAID that selectively inhibits COX-2, an enzyme responsible for inflammation and pain.⁵ As a COX-2 selective NSAID, celecoxib has demonstrated a reduced risk of gastrointestinal harm compared to traditional NSAIDs that inhibit both isoforms of the cyclooxygenase enzyme.⁶⁻⁸ Celecoxib has also recently demonstrated a similar cardiovascular safety profile to the non-selective NSAIDs naproxen and ibuprofen in the PRECISION trial of >20,000 patients with risk factors for cardiovascular disease or established cardiovascular disease.⁹ Similarly, secondary analysis of the PRECISION trial has demonstrated some further benefit with regard to reduced GI, and renal adverse events.¹⁰ Celecoxib is approved by the Food and Drug Administration (FDA) and is indicated for OA and other musculoskeletal conditions, and the lowest approved dose for OA is 200 mg per day.¹¹⁻¹³ There is little data on real-world celecoxib dosing patterns, with results from literature suggesting most OA patients persist on treatment for around 2-4 months after start of therapy.¹⁴⁻¹⁶

To our knowledge, no study has assessed the treatment patterns and economic outcomes of patients that switch from branded celecoxib to a generic NSAID or receive a standard dose or greater (≥ 200 mg) versus under-dose (< 200 mg) of celecoxib. Therefore, the objectives of this novel study were to describe treatment patterns, dosing, and persistence to branded celecoxib, and compare health-care resource utilization (HCRU) and direct costs for patients persistent on branded celecoxib (versus switched to a generic NSAID) and patients that received a standard dose of celecoxib (versus under-dose).

Methods

Data Source

A retrospective claims database analysis was conducted using data from the 2009 to 2013 MarketScan[®] Commercial Claims and Encounters database (MarketScan). The MarketScan database contains patient-level inpatient, outpatient, procedure, prescription, and payment information for more than

30 million people in the US with private or public health insurance; and the longitudinal nature of the database allows multiple health care encounters to be tracked over a long follow-up period.¹⁷ Because the analyses in this study utilized de-identified secondary data, institutional review board approval was not required.

Study Population

Patients included in the study were adult (≥ 18 years or older), incident (new) celecoxib users with at least one primary or non-primary OA claim (International Classification of Diseases 9th Edition Clinical Modifications [ICD-9-CM] claim of 715.XX) prior to or within 30 days of first celecoxib prescription (index date), at least two celecoxib claims within the data cut period, and 12 months of continuous enrollment before and after index date. Patients meeting the inclusion criteria were defined as the incident celecoxib cohort (Figure 1), from which a treatment switch and dosing analysis were conducted. Patients were followed from index date to end of continuous enrollment or December 31, 2013 (whichever came first).

The treatment switch analysis stratified patients from the incident celecoxib cohort into four groups; patients that were persistent on celecoxib (reference group), switched from celecoxib to a generic NSAID (cohort of interest), switched from celecoxib to a branded NSAID, or discontinued celecoxib (without switching) (Figure 2). Generic and branded treatment switch were defined as having a claim for a generic or branded NSAID within ≤ 30 day of estimated end of celecoxib prescription coverage.

The dosing analysis defined under-dose and standard dose (reference group) based on average daily dose of celecoxib, calculated as total celecoxib dose received during the follow-up period divided by total number days of supply of celecoxib. Because 200 mg per day is the celecoxib dose indicated for OA treatment,^{12,18} the standard dose group were patients prescribed an average daily dose of 200 mg of celecoxib, and under-dose group were patients prescribed an average daily dose of less than 200 mg of celecoxib during the follow-up period. Although the standard dose is 200 mg, there was a small percent of patients ($<0.5\%$) whose calculated fill rate was greater than 200 mg per day of celecoxib. Given that this is claims data and not actual patient usage data, and medication possession is calculated from fill dates and patients may have filled their celecoxib prescription early, we assumed patients with a celecoxib dose of > 200 mg were likely just using the 200 mg/day labelled

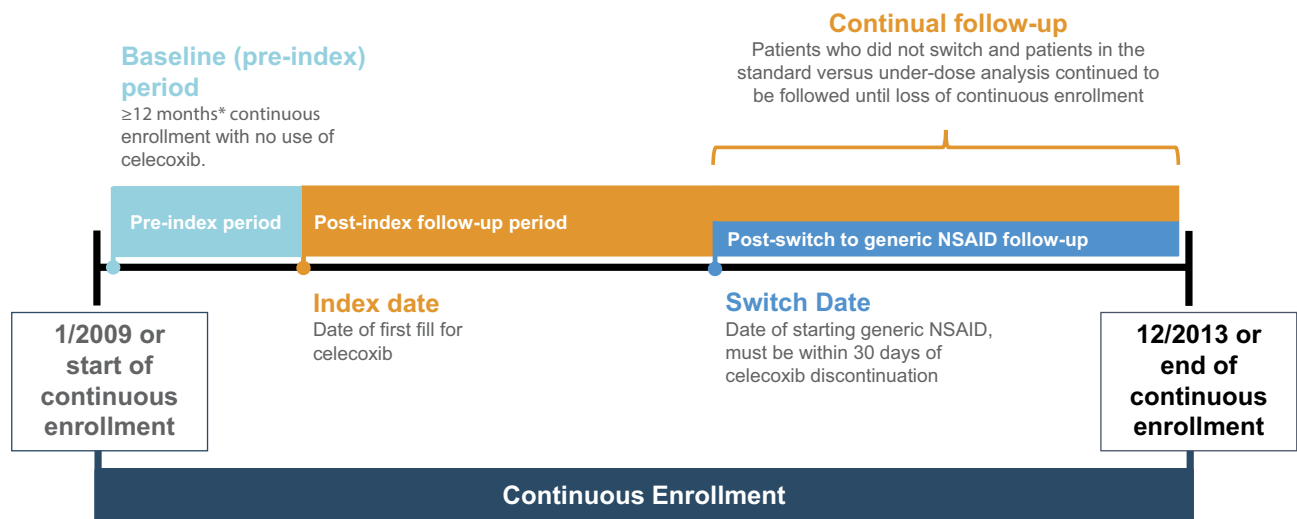


Figure 1 Study design.

dose. These patients were therefore included in the standard dose group.

Medication Exposure

National Drug Codes (NDC) were used to identify celecoxib (only branded celecoxib was available at time of research) and generic NSAIDs (diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, sulindac, and tolmetin).¹⁹ Pre-index gastroprotective agents (proton pump inhibitors [PPIs], H2 blockers, cytoprotective, and prostaglandins), and non-NSAID pain medications (narcotic analgesics, non-narcotic analgesics and salicylates) were also identified.

Outcomes

The primary outcomes of this study were celecoxib persistence, HCRU, and costs during the follow-up period. Persistence was defined as continuous treatment with celecoxib without a prescription refill gap of >30 days during the follow-up period and no prescription refill for generic NSAIDs in ± 30 days following the end of celecoxib supply. Secondary outcomes included celecoxib adherence and patient characteristics associated with treatment switch or dosing.

Celecoxib adherence was measured using medication possession ratio (MPR), calculated as the summation of day's supply of celecoxib (measured from index celecoxib prescription to date of last celecoxib fill) divided by celecoxib refill interval (number of days from index

celecoxib prescription to last date of celecoxib fill). A MPR > 0.8 was considered fully adherent. Additionally, patient characteristics associated with switching to a generic NSAID versus remaining persistent on celecoxib, and characteristics associated with receiving under-dose versus standard dose of celecoxib were analyzed.

All-cause HCRU was calculated per patient year (PPY) of follow-up and included hospital admissions, length of stay, emergency room (ER) visits, and outpatient visits. Outpatient visits included office, independent clinic, and rural health clinic visits. All-cause and OA-related costs were calculated per patient year of follow-up (inflated to 2014 US Dollars, reflecting our data cut and the year generic celecoxib became available) and included inpatient, outpatient, ER, and drug costs. HCRU and costs (not including drugs) were considered OA-related if they had an associated primary or secondary OA ICD-9-CM code (715.XX). OA-related drug costs included celecoxib, NSAIDs (inclusive of non-selective NSAIDs and co-formulated NSAIDs), non-NSAIDs (narcotic and non-narcotic analgesics), and gastroprotective agents (PPI, H2 blocker, cytoprotective agent). HCRU and costs were compared among patients persistent on celecoxib versus those who switched to a generic NSAID, and between standard versus under-dose celecoxib patients.

Statistical Analyses

Continuous covariates were compared using Student's t-tests, and categorical covariates were compared using chi-square tests. Multivariable logistic regression was used to find patients characteristics associated with treatment and dosing patterns. Pre-determined variables in the

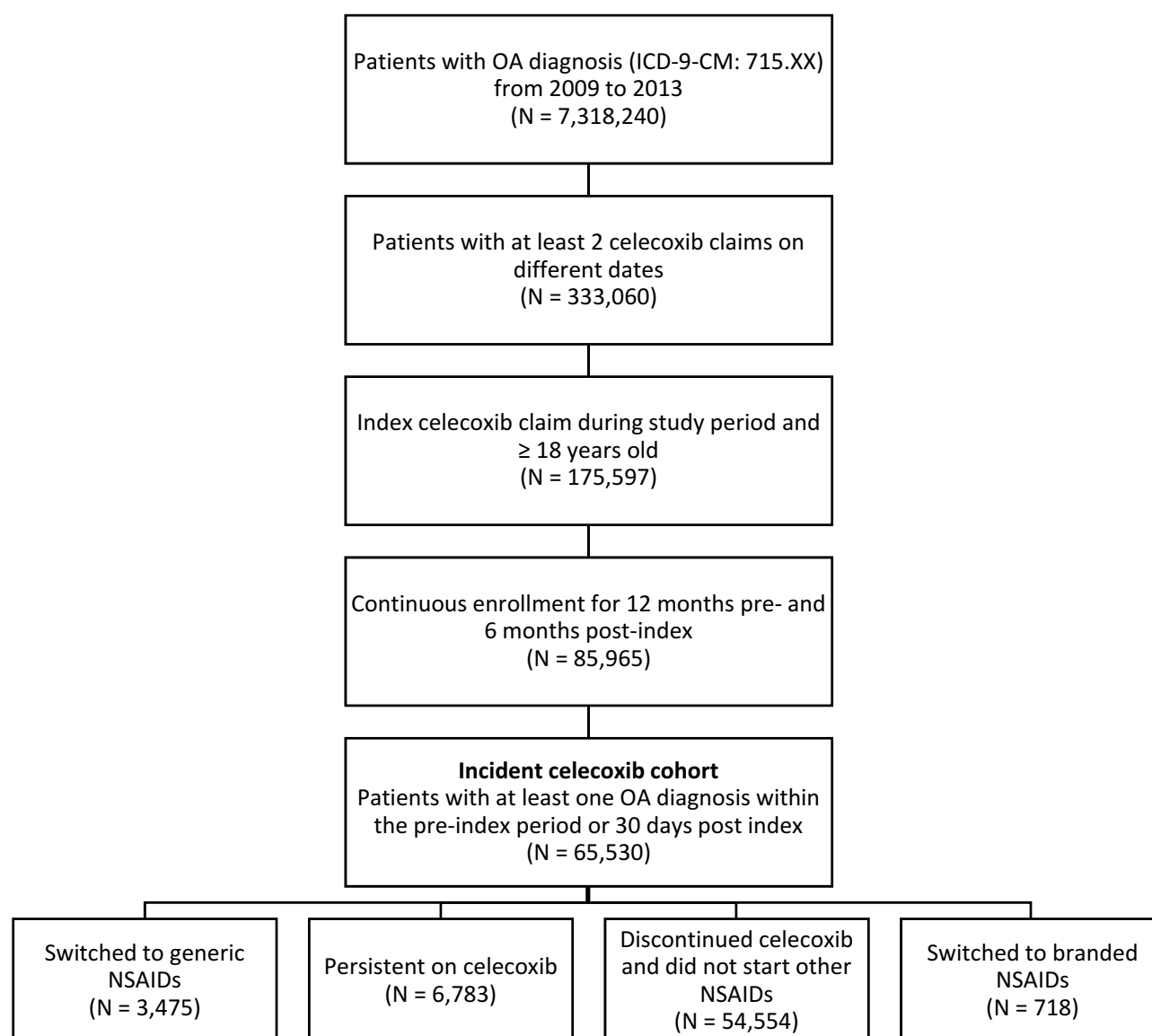


Figure 2 Celecoxib persistence flow chart.

Notes: NSAIDs included: diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, sulindac, and tolmetin.

Abbreviations: OA, osteoarthritis; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; NSAID, nonsteroidal anti-inflammatory drug.

logistic model included age, sex, payer, region, Charlson-Deyo comorbidity index (CCI), celecoxib MPR, pre-index OA-related costs (inpatient, outpatient, drug), and clinical events (GI, CV, renal, musculoskeletal) prior to switch or discontinuation. Kaplan–Meier methods were used to estimate time to celecoxib discontinuation, and patients not experiencing the event of interest were censored at the end of follow-up.²⁰

Propensity scores were used to control for potential differences and confounding between patients who switched from celecoxib to generic NSAIDs as compared with those persistent on celecoxib, and patients who

received an under-dose relative to standard dose of celecoxib. Patients were matched on baseline characteristics including age, sex, payer, region, CCI, celecoxib MPR, pre-index OA-related costs (inpatient, outpatient, drug), and clinical events (GI, CV, renal, musculoskeletal) prior to switch or discontinuation. Patients were matched with a 1:1 ratio and a caliper of 0.15, which was equal to 0.15 of the standard deviation of the logit of the propensity score, and were sampled without replacement.^{21–23} Two matched cohorts were created: patients persistent on celecoxib versus switched to generic NSAID, and patients receiving an under-dose versus standard dose of celecoxib.

Results

Patient Characteristics

A total of 65,530 patients met the inclusion criteria, and were stratified by celecoxib persistence (Figure 2) and dose received. Ten percent of the patients were persistent on celecoxib and 5% switched from celecoxib to a generic NSAIDs. Most patients (90%) received a standard dose of celecoxib (200 mg/day). The mean (and median) celecoxib dose was 126 mg (100 mg) in the under-dose group, and 201 mg (200 mg) in the standard dose group. OA patients newly receiving celecoxib were a mean age of 61 years old (SD 12), and majority were female (63%) (Table 1). Less than half of patients had any comorbidities in pre-index

period (41%), with diabetes (18%) and chronic obstructive pulmonary disease (COPD) (15%) being the most frequent.

Pre-index gastroprotective agents were used by 32% of patients, most receiving PPIs (30%) and pre-index non-NSAID pain medications were used by 64% of patients, most receiving a narcotic analgesic (Table 2). Gastroprotective agent use was slightly higher in the under-dose group compared with patients who were treated with a standard dose of celecoxib (35% vs 32%, $P < 0.001$), and in persistent versus switchers to generic NSAIDs (36% vs 32%, $P < 0.001$). More switchers to generic NSAIDs used pre-index non-NSAID pain medications relative to persistent patients (71% vs 63%,

Table 1 Patient Demographic and Clinical Characteristics by Treatment or Dosing Pattern

Variable Description	All	Persistence/Switch Analysis		Average Daily Dose Analysis	
	Incident Celecoxib Cohort (N= 65,530)	Switched to Generic NSAID (N= 3475)	Persistent on Celecoxib (N= 6783)	Standard Dose (N= 59,095)	Under-Dose (N= 6435)
Age, mean (SD)	61 (11.9)	60 (11.3)	62 (11.6)	60.9 (11.7)	64.9 (13.7)
Male, N (%)	24,574 (37.5)	1305 (37.6)	2573 (37.9)	22,523 (38.1)	2051 (31.9)
Region, N (%)					
North Central	17,964 (27.4)	980 (28.2)	1988 (29.3)	16,203 (27.4)	1761 (27.4)
Northeast	9186 (14)	409 (11.8)	884 (13)	8011 (13.6)	1175 (18.3)
South	26,797 (40.9)	1552 (44.7)	2665 (39.3)	24,595 (41.6)	2202 (34.2)
West	10,671 (16.3)	488 (14)	1088 (16)	9439 (16.0)	1232 (19.1)
Unknown	912 (1.4)	46 (1.3)	158 (2.3)	847 (1.4)	65 (1.0)
Insurance type, N (%)					
POS	4762 (7.3)	267 (7.7)	407 (6)	4255 (7.2)	507 (7.9)
HMO	5957 (9.1)	339 (9.8)	569 (8.4)	5255 (8.9)	702 (10.9)
PPO	35,874 (54.7)	1994 (57.4)	3841 (56.6)	32,801 (55.5)	3073 (47.8)
Comprehensive	12,907 (19.7)	516 (14.8)	1293 (19.1)	11,207 (19.0)	1700 (26.4)
Others or missing ^a	6030 (9.2)	359 (10.3)	673 (9.9)	5577 (9.4)	453 (7.0)
CCI, N (%)					
0	38,530 (58.8)	2044 (58.8)	3773 (55.6)	35,123 (59.4)	3407 (52.9)
1	15,212 (23.2)	821 (23.6)	1628 (24)	13,609 (23.0)	1603 (24.9)
2	7258 (11.1)	378 (10.9)	858 (12.6)	6445 (10.9)	813 (12.6)
3+	4530 (6.9)	232 (6.7)	524 (7.7)	3918 (6.6)	612 (9.5)
5 Most Common Comorbidities, N (%)					
Diabetes	11,769 (18.0)	623 (17.9)	1297 (19.1)	10,600 (17.9)	1169 (18.2)
COPD	9643 (14.7)	549 (15.8)	1047 (15.4)	8560 (14.5)	1083 (16.8)
Malignancy (including leukemia and lymphoma)	4872 (7.4)	239 (6.9)	497 (7.3)	4310 (7.3)	562 (8.7)
Cerebrovascular disease	4335 (6.6)	214 (6.2)	488 (7.2)	3716 (6.3)	619 (9.6)
Rheumatologic disease ^b	3720 (5.7)	202 (5.8)	470 (6.9)	3345 (5.7)	375 (5.8)

Notes: ^aThe "other" insurance category includes (exclusive provider organization, consumer-driven health plan, high deductible health plan). ^bRheumatologic disease included rheumatoid arthritis or other rheumatology conditions the patient had in addition to OA.

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization; CCI, Charlson Comorbidity Index.

Table 2 Medication Use 1 Year Prior to Index Celecoxib Use, by Treatment or Dosing Pattern

Variable Description	All	Persistence/Switch Analysis			Average Daily Dose Analysis		
	Incident Celecoxib Cohort (N= 65,530)	Switched to Generic NSAID (N= 3475)	Persistent on Celecoxib (N= 6783)	P Value	Standard Dose (N= 59,095)	Under-Dose (N= 6435)	P Value
Medication use, N (%)							
Gastroprotective	20,964 (32)	1099 (31.6)	2461 (36.3)	<0.001	18,723 (31.7)	2241 (34.8)	<0.001
PPI	19,400 (29.6)	1013 (29.2)	2287 (33.7)	<0.001	17,335 (29.3)	2065 (32.1)	<0.001
H2 blockers	2252 (3.4)	133 (3.8)	259 (3.8)	0.982	2000 (3.4)	252 (3.9)	0.026
Non-NSAIDs	41,685 (63.6)	2464 (70.9)	4265 (62.9)	<0.001	37,580 (63.6)	4105 (63.8)	0.752
Non-selective NSAIDs	31,882 (48.7)	2483 (71.5)	3474 (51.2)	<0.001	28,893 (48.9)	2989 (46.4)	<0.001

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

respectively, $P < 0.001$), but use was the same among standard and under-dose patients (both 64%). Pre-index non-selective NSAID use was higher in switchers compared with persistent patients (72% vs 51%, $P < 0.001$), and among standard versus under-dose patients (49% vs 47%, respectively, $P < 0.001$). Pre-index GI and CV clinical events were more common in persistent versus switchers to generic NSAIDs (GI: 26% vs 23%; CV: 61% vs 58%). There was a higher percentage of under-dose patients with GI, CV and renal pre-index disorders relative to standard dose patients NSAIDs (GI: 26% vs 23%; CV: 61% vs 57%; renal: 6% vs 4%).

In the cohorts persistent on celecoxib or switched from celecoxib to generic NSAIDs, with the exception of celecoxib MPR (pre-match and post-match, $P < 0.001$), patient characteristics that had been significant pre-propensity score matching (all $P < 0.001$) became non-significant after matching (age, $P = 0.356$; region, $P = 0.804$; payer, $P = 0.861$; CCI, $P = 0.250$; pre-index OA-related inpatient costs, $P = 0.854$; pre-index OA-related outpatient costs, $P = 0.743$; pre-index OA-related drugs costs, $P = 0.676$; any GI event, $P = 0.370$; CV event, $P = 0.317$; renal event, $P = 0.366$; and musculoskeletal and neuropathic pain event, $P = 0.860$).

Similarly, in the cohort of standard versus under-dose, with the exception of GI event occurrence (pre-match $P = 0.023$; post-match $P = 0.015$), patient characteristics that had been significant pre-propensity score matching (all $P < 0.001$) became non-significant after matching (age, $P = 0.957$; region, $P = 0.189$; payer, $P = 0.714$; sex, $P = 0.324$; CCI, $P = 0.261$; Pre-index OA-related inpatient costs, $P = 0.334$; Pre-index OA-related outpatient costs, $P = 0.879$; and celecoxib MPR, $P = 0.616$).

Treatment Discontinuation

Median time to celecoxib discontinuation was longer in standard dose patients compared with under-dose patients (3.0 months vs 2.8 months). By the end of the first year of follow-up 86% of patients had switched or discontinued treatment, and 90% by the end of follow-up. Only 44% of patients were fully adherent (defined as celecoxib MPR ≥ 0.8). Patients who switched from celecoxib to a generic NSAID were less adherent than patients persistent on celecoxib (79% vs 93%, $P < 0.001$). Adherence was significantly higher in the standard relative to under-dose patients (44% vs 41%, $P < 0.001$).

Healthcare Resource Utilization and Costs

In a matched cohort of patients persistent on celecoxib or switched from celecoxib to generic NSAIDs (matched persistence/switch cohort), patients who switched had significantly higher all-cause HCRU (hospital admissions, length of stays, ER visits, and office visits) PPY versus persistent patients. In a matched cohort of standard and under-dose patients (dose-matched cohort), under-dose patients had significantly higher hospital admissions, length of stay, and ER visits PPY than standard dose patients (Table 3).

Mean total all-cause costs in the incident celecoxib cohort were \$23,607 (SD \$46,071) PPY, and the bulk of costs were due to outpatient (45%) and inpatient (35%) care. In the matched persistence/switch cohort, patients who were persistent had significantly lower mean total costs (\$20,378 vs \$23,949, $P < 0.001$). Mean inpatient and outpatient costs were significantly higher in switched versus persistent patients (both $P < 0.001$), while mean drug costs were significantly lower ($P < 0.001$). In the dose-matched cohort, under-dose patients had significantly

Table 3 Mean All-Cause HCRU During Follow-Up by Treatment or Dosing Pattern

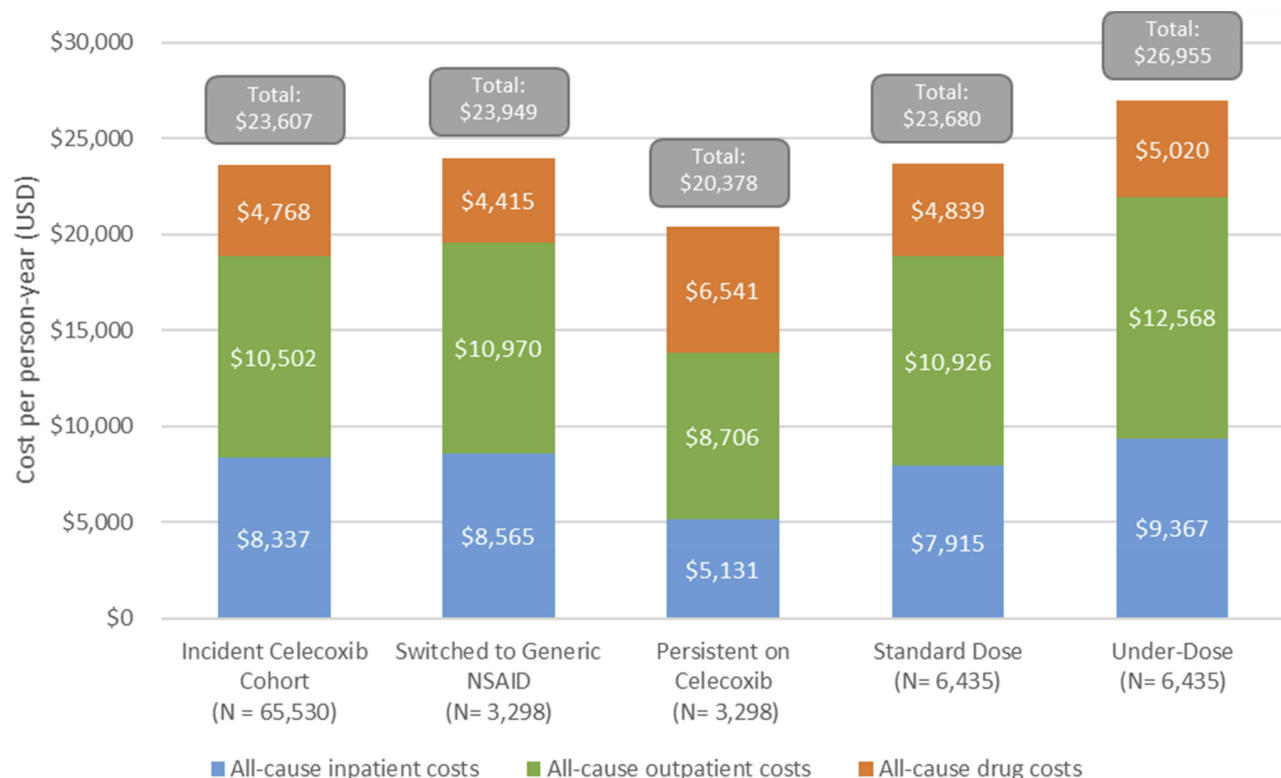
Specific HCRU, Mean (SD)	All	Persistence/Switch Analysis			Average Daily Dose Analysis		
	Incident Celecoxib Cohort (N= 65,530)	Switched to Generic NSAID (N= 3298)	Persistent on Celecoxib (N= 3298)	P Value	Standard Dose (N= 6435)	Under-Dose (N= 6435)	P Value
Hospital admission	0.29 (0.59)	0.31 (0.61)	0.18 (0.56)	<0.001	0.30 (0.60)	0.36 (0.69)	<0.001
Length of stay	1.17 (4.14)	1.28 (4.14)	0.63 (2.89)	<0.001	1.20 (3.61)	1.63 (5.41)	<0.001
ER visit	0.01 (0.13)	0.02 (0.12)	0.01 (0.09)	<0.001	0.01 (0.13)	0.02 (0.16)	0.021
Office visit	17.87 (15.06)	18.71 (15.16)	16.44 (15.5)	<0.001	18.29 (15.13)	18.21 (15.52)	0.763

Abbreviations: HCRU, health care resource use; ER, emergency room.

higher mean total all-cause costs than standard dose patients (\$26,955 vs \$23,680, $P < 0.001$). Inpatient and outpatient mean costs were significantly higher in under-dose compared with standard dose patients ($P=0.003$ and $P<0.001$, respectively) (Figure 3).

In the full incident celecoxib cohort, mean total OA-related costs were \$5969 (SD \$13,585) PPY, and 62% of OA costs were due to inpatient visits. In the matched persistence/switch cohort, persistent patient had numerically higher, although not significant, mean total OA-related

costs (\$5910 vs \$5755 PPY, $P=0.626$). Switched patients had significantly higher mean inpatient and outpatient costs ($P<0.001$, $P=0.001$, respectively), and persistent patients had significantly higher mean drug costs ($P<0.001$). Standard dose patient in the dose-matched cohort had numerically higher mean total OA costs than under-dose patients, but the difference was not significant (\$5698 vs \$5523, $P=0.441$); mean drug costs were significantly higher in standard compared with under-dose patients (\$1382 vs \$1248, $P<0.001$) (Figure 4).

**Figure 3** Mean all-cause costs per person-year in full cohort, matched persistent/switched cohort, and dose-matched cohort.

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug.

Predictors of Celecoxib Persistence and Dosing

Patients that switched to a generic NSAID versus those persistent on celecoxib were younger (<45 years old, $P<0.001$) and had higher pre-index OA-related inpatient ($>\$2000$ vs $\leq\$1000$, $P<0.001$), outpatient ($>\$750$ vs $\leq\$200$, $P=0.022$), and drug costs ($\$50$ vs $\leq\$50$, $P<0.001$). Additionally, switchers were less likely to be fully adherent ($P<0.001$), and less likely to have GI ($P<0.001$), renal ($P=0.018$), or CV ($P<0.001$) clinical events prior to switch or discontinuation (data not shown).

For dosing predictors, patients newly treated with celecoxib were more likely to be under-dose if they were ≥ 65 years old, female, and had a higher CCI (all, $P<0.001$). Under-dose patients had lower pre-index OA-related inpatient costs ($>\$10,000$ vs $\leq\$10,000$, $P<0.001$) and OA-related outpatient costs ($\$200$ – 750 vs $\leq\$200$, $P=0.019$). Adherence was significantly lower in under-dose patients compared with standard dose patients when ($P<0.001$) (data not shown).

Discussion

This study provides insight into treatment patterns of OA patients newly treated with celecoxib. Of incident (new)

celecoxib users, 10% were persistent on celecoxib, 5% switched to a generic NSAID, and 1% switched to a branded NSAID. Over 90% of patients received a standard dose of celecoxib, 200 mg per day. Relative to patients persistent on celecoxib, patients who switched to a generic NSAID were younger, less likely to have clinical events prior to switch or discontinuation (i.e., GI, CV, or renal clinical events), had higher cost for OA-related care prior to starting celecoxib, and were less adherent. Additionally, compared with patients receiving a standard dose of celecoxib, under-dose patients were more likely to be older, had lower costs for OA related care prior to starting celecoxib, and were less adherent. Regardless of dose, the median time to treatment discontinuation or switch was 3 months, and 86% of patients had discontinued or switched from celecoxib 1 year after the index prescription.

OA-related costs were between \$5000 and \$6000 per patient year (PPY), within the range of previously reported costs (\$5000–\$7000 per patient year),^{24–26} and were higher in persistent celecoxib patients compared with those who switched to a generic NSAID. However, over 45% of OA-related costs for persistent patients were drug-related versus only 19% in patients that switched to NSAIDs. Persistent

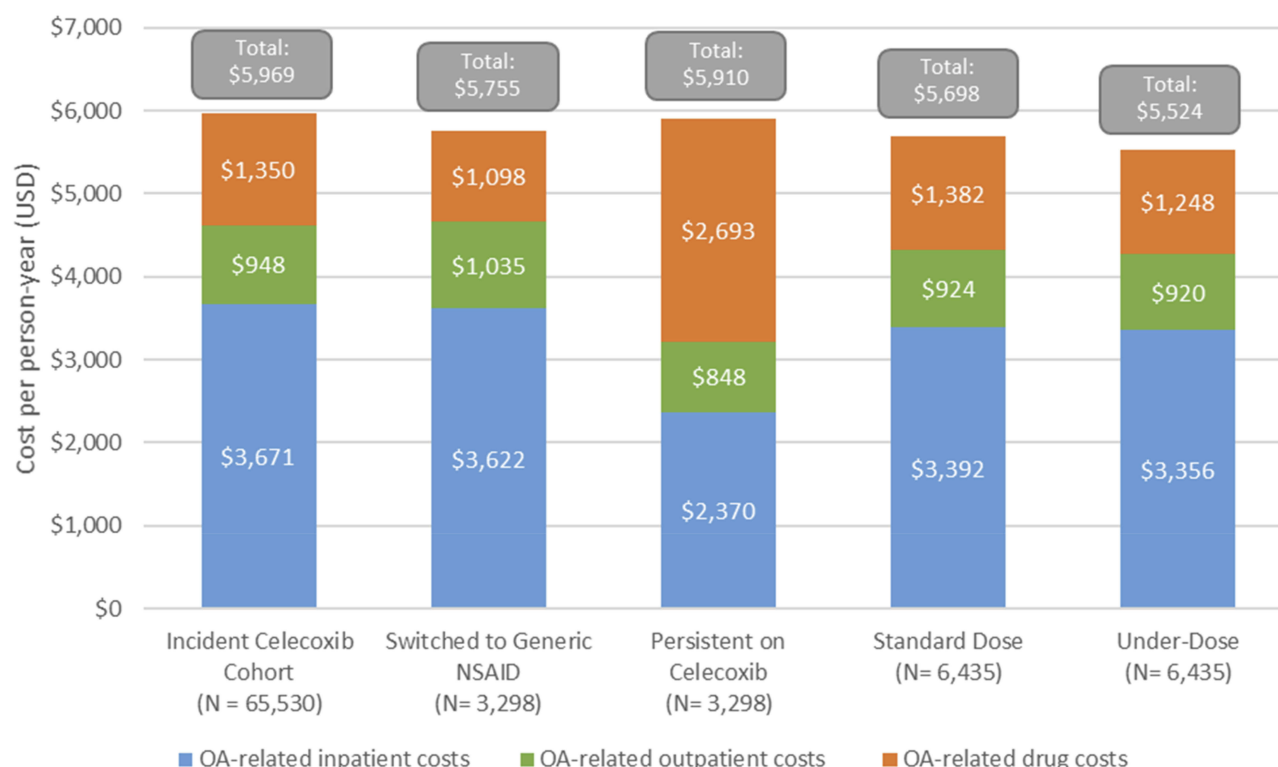


Figure 4 Mean OA-related costs per person-year in full cohort, matched persistent/switched cohort, and dose-matched cohort.

Abbreviations: OA, osteoarthritis; NSAID, nonsteroidal anti-inflammatory drug.

patients had lower OA-related inpatient and outpatient costs per patient year compared with patients who switched to a generic NSAID. This trend was repeated with all-cause costs; persistent patients had higher drug costs but lower inpatient and outpatient costs than patients that switched to a generic NSAID. Patients who were persistent also had lower all-cause HCRU, which also explains the lower inpatient and outpatient costs. Our findings are similar to a recent systematic review which showed celecoxib treated OA patients had lower medical costs, relative to patients treated with non-selective NSAIDs alone or in combination with gastroprotective agents.²⁷

Under-dose patients had higher HCRU (not including office visits) and all-cause costs than patients that received a standard dose of celecoxib, but slightly lower OA-related costs than standard dose patients, likely driven by lower drug costs. In our study, under-dose patients were older, had higher comorbidities, and had experienced more pre-index clinical events, inferring that they were a sicker population. Assuming that the under-dose population was less healthy (due to high number of comorbidities, age, pre-index clinical events, and possibly other latent disease characteristics that cannot be captured in claims database), it is possible they used a lower dose of celecoxib due to apprehension of adverse events associated with celecoxib use. Additionally, if the under-dose patients were sicker with non-OA ailments, the occurrence of higher all-cause costs and lower OA-related costs, is not surprising.

Despite the fact that patients who switched from celecoxib to a generic NSAID were less likely to experience clinical events, they had appeared to have more health problems (i.e., a significantly higher number of hospitalizations, length of stay, ER visits, and office visits) than patients that were persistent. It is possible that switchers were a harder to treat the population with many non-OA ailments, and that treatment switch was due to treatment inefficacy or adverse event. Also, the fact that the switchers had a significantly higher number of office visits which could be related to the fact they sought out different treatments for their OA or had other chronic conditions.

To our knowledge, this is the first real-world analysis of the economic impact of both persistence and dosing with celecoxib. Limiting exposure time or under-dosing of celecoxib in real-world environments may be driven by clinical safety perceptions. Switching from celecoxib to generic NSAIDs and under-dosing, as seen in our study, appears to increase all-cause HCRU and costs. These economic findings are driven by clinical outcomes, particularly the

occurrence of adverse events. Both the CONDOR trial and the GI-REASONS study (a prospective randomized open-blinded end-point design) found that celecoxib use resulted in fewer upper and/or lower GI-related events, than non-selective NSAIDs.^{6,8} A previous meta-analysis of randomized controlled trials found that the risk for cardiovascular events was similar for patients treated with COX-2 inhibitors and other NSAIDs, but higher than treatment with a placebo.⁷

Recent evidence from the landmark PRECISION trial found that major toxicity such as cardiovascular events (e.g., cardiovascular-related death, myocardial infarction, stroke), clinically relevant renal and gastrointestinal events, and GI-related iron deficiency anemia, were lower with celecoxib compared with ibuprofen or naproxen.^{9,10} Even though PRECISION trial patients had moderate to high risk of cardiovascular disease, the study found that standard doses of celecoxib (mean 209mg/day) for a mean duration of 20 months was non-inferior to ibuprofen or naproxen with regard to CV safety, and the risk of GI and renal events were significantly lower with celecoxib.⁶⁻⁹ This new safety data helps support our real-world findings of lower HCRU and costs for patients that are persistent on celecoxib and receive a standard dose versus under-dose.

Our study is not without limitations. The database used does not capture over-the-counter medication use. In our analysis, number of prescriptions filled was a proxy for medication use and does not reflect if the patient took the medication as prescribed. Additionally, we cannot be sure of the causal relationship between outcomes (e.g., treatment discontinuation, emergent AEs, HCRU) and medications received, due to confounding and unobserved factors, such as disease severity or comorbidities. Finally, use of a database does not provide insight into lifestyles changes or non-pharmacological interventions tried by patients, which may have impacted celecoxib use.

Conclusion

In this real-world study of incident branded celecoxib users, 10% were under-dose based on average daily dose and 90% either switched from celecoxib to a generic NSAID or discontinued treatment. Patients that switched from branded celecoxib to a generic NSAID or received an under-dose of branded celecoxib had higher average overall HCRU and costs. OA-related inpatient and outpatient cost savings may offset the higher drug cost in celecoxib for those persistent patients.

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Author Contributions

All authors contributed to conception, design, data analysis or critical review/interpretation of the data analysis, drafting or critically revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

Jennifer Stephens and Courtney Johnson are employees of Pharmerit International who were paid consultants to Pfizer in connection with this study and development of the manuscript. Christopher Walker, Ahmed Shelbaya, and Joseph C. Cappelleri are employees and stockholders of Pfizer. The authors report no other conflicts of interest in this work.

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