A Comparison of Daily Average Consumption (DACON) of Oxycodone and Oxymorphone Long-Acting Oral Tablets

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ABSTRACT

BACKGROUND: The utilization of high-potency opioids is an important component of chronic pain management, and appropriate utilization of these medicines is a common concern of payers. Two of the most commonly prescribed oral long-acting opioids, oxycodone controlled-release (CR) and oxymorphone extended-release (ER), are FDA-approved for twice-daily dosing, which equates to a theoretical average consumption (DACON) of 2 tablets per day. DACON values greater than 2 have budget and policy implications for managed care pharmacists.

OBJECTIVES: To assess from the perspective of the pharmacy benefit decision maker the DACONs of oxycodone CR and oxymorphone ER.

METHODS: The main outcome measure for the analysis was DACON. Pharmacy and medical claims data from a large commercially insured population (i3 InVision Data Mart database) were analyzed to identify patients with at least 1 pharmacy claim for either oxycodone CR or oxymorphone ER from July 1, 2007, to September 30, 2009. After an initial 30-day titration period, all subjects included in the study had 1 or more claims totaling at least a 90-day supply of either study drug during the subsequent 90 days (DACON measurement period). Patients were excluded if there was evidence of a switch from one to the other study opioid during the 90-day measurement period. There were no limitations on the use of other opioids, either short- or long-acting, during either the DACON measurement period or the previous 6 months (baseline period). In addition, patients were excluded if the enrollee was younger than 18 years old, pregnant, did not have continuous insurance coverage for the 6 months before and after the start of the 90-day DACON measurement, or were enrolled in an HMO plan. Bivariate analyses were performed with between-group differences in DACON values assessed using t-tests and Wilcoxon rank sum tests. Patient characteristics including age, sex, geographic location, and baseline Charlson Comorbidity Index (CCI) for each drug group were evaluated descriptively using either the Pearson chi-square test or t-test. Multivariate analyses were conducted using generalized linear models (GLM) to adjust for the observed heterogeneity among patients in the observational database. For the GLMs, the gamma distribution and log link function were chosen to account for non-normal distributions of DACON. Independent variables included study drug, tablet strengths, age, sex, CCI, the maximum days gap between prescription refills during the DACON measurement period, and other opioid medication use. Several sensitivity analyses were conducted to verify all findings.

RESULTS: The final analyses were conducted on 6,567 oxycodone CR patients and 796 oxymorphone ER patients. The unadjusted DACON mean value for the highest strength of oxycodone CR 80 milligrams (mg) was 3.9, compared with 2.9 for oxymorphone ER 40 mg ($P<0.001$); mean DACON values were 3.0 versus 2.4, respectively, for lower strengths ($P<0.001$) and 3.1 versus 2.5 for all strengths ($P<0.001$). After adjusting for age, sex, CCI, maximum gap days, and other opioid medication use, a risk-adjusted mean difference in DACON remained, with oxycodone CR patients receiving on average 0.6 tablets more per day than those dispensed oxymorphone ER

($P<0.001$). The direction, magnitude, and statistical significance of these differences were essentially unchanged in sensitivity analyses.

CONCLUSIONS: On average during a 90-day time period, patients taking oxymorphone ER consumed 0.6 fewer tablets per day than did patients taking oxycodone CR. Further research is necessary to see if this difference amounts to cost savings for health plans that provide prescription reimbursement for patients with chronic pain syndromes.

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What is already known about this subject

- Daily average consumption (DACON), the term often used to describe the average number of dosage units dispensed per day, has been studied for several chronic diseases using retrospective analyses of administrative claims data. Two DACON analyses have been performed for long-acting opioids using prescription claims databases, one for patients with lower back pain and another in a California Medicaid population.
- In an observational study of commercially insured patients with lower back pain, Berner et al. (2011) reported that DACON for the maximum strength tablet of oxycodone controlled-release (CR) 80 mg was 3.9 tablets per day, which was significantly higher than the DACON of 2.9 for equipotent oxymorphone extended-release (ER) maximum strength tablet of 40 mg ($P<0.001$).
- In the study of the California Medicaid pharmacy claims by Malkin et al. (2002), the mean number of oxycodone CR tablets per day across all strengths was 3.4.

What this study adds

- This study assessed utilization patterns in a large, managed care, commercially insured sample and calculated DACON for subjects taking oxycodone CR (n=6,567) versus those taking oxymorphone ER (n=796).
- The unadjusted DACON mean value for the highest strength of oxycodone CR 80 mg was 3.9, compared with 2.9 for oxymorphone ER 40 mg ($P<0.001$); mean DACON values were 3.0 versus 2.4, respectively, for lower strengths ($P<0.001$) and 3.1 versus 2.5 for all strengths ($P<0.001$).
- After adjusting for potential confounders, a risk-adjusted mean difference in DACON remained, with oxycodone CR patients receiving on average 0.6 tablets more per day than those dispensed oxymorphone ER ($P<0.001$).

Opioid analgesics are indicated for moderate to severe pain and are an important component of chronic pain management. In the United States in 2009, 62% of outpatient prescriptions for long-acting opioid (LAO) analgesics were used for musculoskeletal conditions and injuries, 14% for headaches and nerve pain, and 11% for pain associated with neoplastic disease.[1] LAOs represented approximately 9% of all U.S. outpatient opioid prescriptions in 2009.[1] The global market for all opioids was $9.6 billion in 2008 and is expected to grow to almost $12 billion by 2018.[1-4] Commercial and government payers have identified this class of medicines as an opportunity for cost and quality management to curb inappropriate utilization with step-therapy, quantity limits, and prior authorization programs. These programs have focused on the management of chronic pain with LAOs.[5-7]

Two commonly used, oral, branded LAOs are OxyContin (oxycodone controlled-release [CR]) and Opana ER (oxymorphone extended-release). Unpublished data suggest that these 2 products had prescription shares of 86.4% and 11.4%, respectively, in the branded LAO market as of October 2010.[8] In assessments of the utilization of these 2 products, it may be helpful to consider daily average consumption (DACON), the term often used to describe the average number of dosage units dispensed per day based on claims data. The term has been used in association with the treatment of chronic diseases, such as diabetes,[9] hypertension,[10] and arthritis.[11] Both oxycodone CR and oxymorphone ER are U.S. Food and Drug Administration (FDA)-approved for twice-daily dosing,[12,13] which equates to a theoretical DACON of 2 tablets per day. DACON values greater than 2 have budget and policy implications for managed care pharmacists.

A study by Malkin et al. (2002) compared pharmacy claims for oxycodone CR and fentanyl transdermal patches with dose administration guidelines in each manufacturer's prescribing information.[14] For all dosage strengths of oxycodone CR, the average number of tablets supplied per day was 3.4, ranging from 2.9 for the 10 milligram (mg) tablets to 5.2 for the 80 mg tablets. This analysis measured all pharmacy claims for these medications regardless of the number of claims for each patient. As such, the selection criteria did not include a requirement for chronic use.

A recent retrospective analysis of administrative claims data for commercially insured patients, conducted by Berner et al. (2011), compared the DACON of oxycodone CR and oxymorphone ER in patients with lower-back pain.[15] DACON was 3.2 tablets per day for all strengths of oxycodone CR, compared with 2.7 tablets per day for all strengths of oxymorphone ER ($P<0.01$). DACON for the maximum strength tablet of oxycodone CR 80 mg was 3.9 tablets per day, which was significantly higher than the DACON of 2.9 for equipotent oxymorphone ER maximum strength tablet of 40 mg ($P<0.01$). Berner et al. estimated that if a health plan were to substitute

oxymorphone ER 40 mg tablets for oxycodone CR 80 mg tablets in the 688 patients in their analysis, the monthly cost difference would be $217,985 based on the DACON difference, assuming per tablet wholesale acquisition costs (WAC) of $10.96 and $10.83, respectively.

Since these drugs are indicated for moderate to severe pain regardless of etiology[14,15] and most managed care pharmacists do not have access to or include diagnostic codes in their drug utilization evaluations, a broader analysis using information readily available to managed care professionals might be more relevant to payers than a disease-specific analysis.
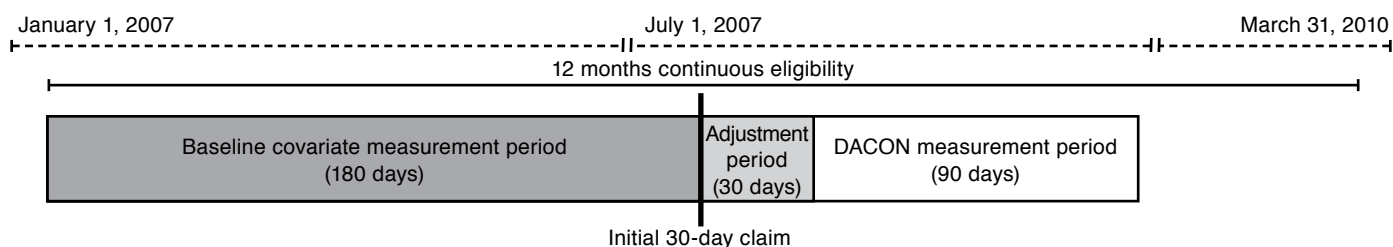
■ Methods
Study Scope

We conducted a retrospective analysis of a database from United Healthcare, a large U.S. managed health care plan. The study data were gathered from a commercially insured population using the i3 InVision Data Mart database (Ingenix, Eden Prairie, MN). The database consists of aggregated medical and pharmacy claims for more than 20 million members during the study period. This database was chosen because both oxycodone CR and oxymorphone ER were subject to the same formulary tier status and quantity limits, (i.e., tier 3 coverage without prior authorization and equal quantity limits of 124 tablets per month). The study period encompassed dates of service from January 1, 2007, to March 31, 2010, in order to collect data for a sufficient number of patients with claims for the 2 study LAOs and provide a 6-month roll-in and a 6-month roll-out period to demonstrate continuous health plan coverage. The database consists of de-identified integrated records from outpatient, inpatient, pharmacy claims, lab result records, and enrollment data sets. Because all records were de-identified, Institutional Review Board approval for the study was not sought.

Sample Selection and Characteristics

The objective of the study was to measure DACON for each study drug (oxycodone CR or oxymorphone ER) for the treatment of chronic pain in usual practice. In the prescription drug claims data, there is no specific identification as to whether a prescription for a study drug was filled for treatment of an acute episode of pain or chronic pain. Accordingly, the days supplied for each prescription were used to infer whether treatment was for acute pain (generally less than 15 days supplied) or chronic pain (30 or more days supplied).

Given that the focus of the study was on the use of opioids for chronic pain, the beginning of a treatment episode for chronic pain was defined as the first instance of a 30-day supply of the patient's initial opioid therapy, identified using pharmacy claims with dates of service from July 1, 2007, to September 30, 2009 (Figure 1). The 30-day supply requirement could be satisfied by either an initial pharmacy claim with 30

January 1, 2007   July 1, 2007   March 31, 2010

12 months continuous eligibility

Baseline covariate measurement period
(180 days)

Adjustment period (30 days)

DACON measurement period
(90 days)

Initial 30-day claim

DACON = daily average consumption.

days supplied, or by multiple pharmacy claims for the initial opioid therapy with less than 30 days supplied, each closely proximate in time, such that the sum of the days supplied was at least 25 over the first 30 days after the date of the initial study drug fill. Patients were included if gap(s) between pharmacy claims were 5 days or less during the 30-day adjustment period. From the database, 26,921 oxycodone CR users and 2,842 oxymorphone ER users satisfied the criteria for chronic opioid use.

An additional sample restriction was that individuals with an initial pharmacy claim for oxycodone CR could not have a subsequent claim for oxymorphone ER (or vice versa) during the 120 days following the date of the initial study drug claim. A total of 29,308 patients satisfied these requirements: 26,721 oxycodone CR users and 2,587 oxymorphone ER users (Figure 2). No sample exclusions relating to the use of opioids, other than the 2 study drugs, were applied. However, the use of short- or long-acting opioids during the 30 days prior to the DACON measurement period was measured and examined in all multivariate analysis.

As shown in Figure 1, DACON was measured during the 90-day period beginning 30 days after the initiation of the study opioid therapy. The rationale for skipping the first 30 days of therapy when measuring DACON was an assumption that potential dosage modifications would be most likely to occur during the initial phase of a new treatment episode for chronic pain therapy. In terms of the measurement of DACON, the most relevant potential modification is a change in the number of units prescribed per day. Because the intent of the study was to measure DACON for "stable" chronic therapy, the first 30 days were excluded from the measurement of DACON. Focusing DACON measurement over a 90-day period is consistent with the current standard of care for chronic pain management according to treatment guidelines.[16,17] All study patients were required to have a cumulative total of at least 90 days supply for the initial study drug on 1 or more claims during the DACON measurement period.

Patients younger than 18 years of age were also excluded, as

were patients who might have been pregnant, identified using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes 633, 640-646, 761, V23.2, V22, V61.5-V61.7, V72.40, or V72.42 in any diagnosis field on the claim. Individuals without continuous insurance coverage for the 6 months before and after the start of the 90-day measurement period were excluded, as were patients enrolled in a health maintenance organization (HMO) because some claims were missing due to capitated arrangements with certain physicians. After all sample inclusion and exclusion criteria were applied, the final study cohort consisted of 6,567 oxycodone CR patients and 796 oxymorphone ER patients (Figure 2). As a sensitivity analysis, we also evaluated a subsample (n = 6,501 oxycodone CR, n = 788 oxymorphone ER) after excluding patients representing the highest 1% of the DACON sample distribution.

Calculation of DACON

The DACON for each patient was calculated by dividing the total number of tablets dispensed during the 90-day DACON measurement period by 90 days. Measurement of total number of tablets dispensed was based on the sum of units supplied on all insurance claims submitted by all pharmacies during the 90-day DACON measurement period. For patients with a pharmacy claim for a study drug during the 90-day DACON measurement period with days supplied extending beyond the end of the DACON measurement period, the total number of tablets for the last pharmacy claim was converted to an average number of tablets per day, with that daily average applied to the number of days between the final pharmacy claim and the end of the 90-day DACON measurement period. For days representing gaps between days supplied within the 90-day DACON period, a daily value of zero (0) units supplied was applied. For example, if a patient filled a 30-day prescription on day 1 of the DACON measurement period, and then filled another 30-day prescription on day 35 of the DACON period, there was a gap of 4 days (days 31 through 34), during which no units were supplied. No sample restriction relating to the

FIGURE 2 Sample Selection Flowchart
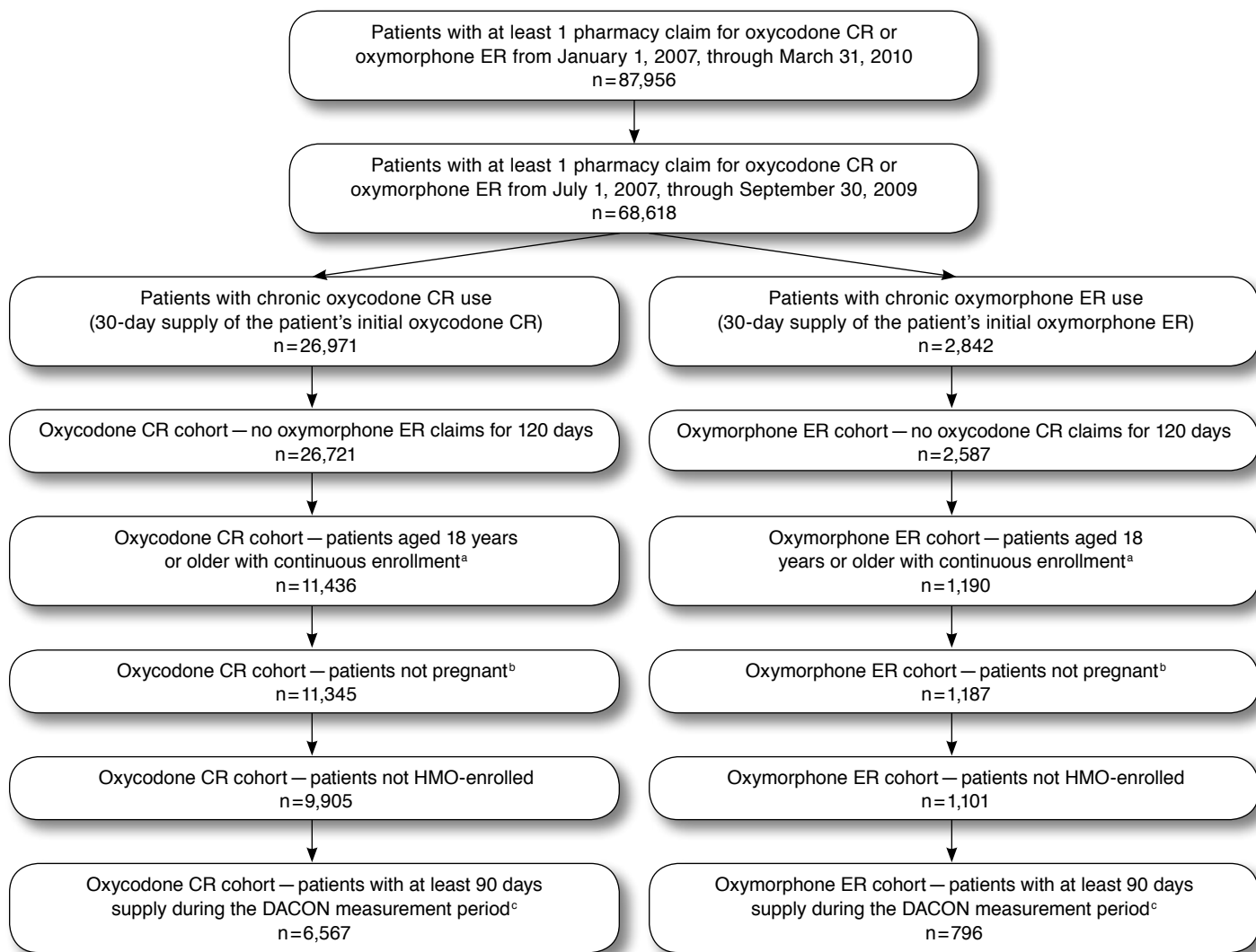
aContinuous enrollment was measured 6 months prior to and after the start of the DACON measurement period.

bPossible pregnancy was identified using International Classification of Diseases, Ninth Revision, Clinical Modification codes 633, 640-646, 761, V23.2, V22, V61.5-V61.7, V72.40, or V72.42 in any diagnosis field on the claim 6 months prior to and after the start of the DACON measurement period.

cIndicates that patient had 1 or more claims with a cumulative days supply totaling at least 90 days during the 90-day DACON measurement period following the 30-day adjustment period.

CR = controlled-release; DACON = daily average consumption; ER = extended-release; HMO = health maintenance organization.

maximum number of gap days allowed was applied, as long as the cumulative days supplied for all pharmacy claims during the DACON period was at least 90 days. However, as part of the sensitivity analysis, DACON results for patients with different frequencies of maximum gap days are reported.

Patients were assigned to dosage strength groups based on the dosage strength on the first day of the DACON measurement period. An equivalent potency assumption for the 2 products was employed to provide potentially more relevant comparisons of DACON within similar dosage strengths. The equivalent potency assumption used a 2:1 (oxycodone CR: oxymorphone ER) dosage conversion ratio, which was derived from a study examining the efficacy and safety of oxymorphone ER compared with placebo, with oxycodone CR as the active control, among patients with low back pain.[18] Both drugs demonstrated similar analgesia that was superior to placebo,

where the relative dose of oxymorphone ER (79.4 mg per day) was approximately one-half that of oxycodone CR (155 mg per day). Thus, we calculated DACON separately for the highest dosage strengths of the 2 drugs (oxycodone CR 80 mg and oxymorphone ER 40 mg) and for all lower dosage strengths (oxycodone CR 60, 40, 30, 20, 15, and 10 mg; oxymorphone ER 30, 20, 15, 10, 7.5, and 5 mg).

Statistical Analysis

Bivariate analyses were performed to illustrate the type of analysis that most managed care pharmacists could replicate using pharmacy claims data alone. Differences in mean (standard deviation [SD]) values of DACON between oxycodone CR and oxymorphone ER were analyzed using t-tests for continuous variables. Since median values are less sensitive than means to outliers, we also calculated medians and Wilcoxon Rank Sum nonparametric tests.[19] Patient variables for age, sex, geographic location, Charlson Comorbidity Index (CCI, a proxy measure for comorbidity that assigns weights for 19 chronic conditions calculated from all diagnosis code fields in patient medical claims in the 6-month baseline period prior to the start of the DACON measurement period[20,21]) other opioid use, and maximum gap days were evaluated descriptively using Pearson chi-square tests for categorical variables and t-tests for continuous variables.

In addition, multivariate analyses were conducted using generalized linear models (GLM) to adjust for the observed heterogeneity among patients in the observational database. The normality assumption was tested by using the Kolmogorov-Smirnov Test. For the GLM model, the gamma distribution and log link function were chosen to account for the non-normal distribution of the dependent variable (DACON). Independent variables included study drug (oxycodone CR vs. oxymorphone ER), the highest strength versus the lower strengths of each drug, age, sex, the number of maximum gap days during the DACON measurement period, and the CCI. Since other opioid analgesic use prior to the DACON measurement period may affect DACON, both short-acting opioid (SAO) and LAO use during the 30 days before the DACON measurement period were also included in the GLM model as independent variables. The variables were (a) the use of 1 or more SAOs; (b) the use of 1 or more LAOs in addition to the study LAO; and (c) the use of both SAOs and LAOs.

The mean values from the GLM models were the estimated marginal means (sometimes called least square means) of the dependent variable (DACON), calculated as predicted values of DACON for each of the 2 study drug groups holding all independent variables at mean values. The estimated marginal SD values were also calculated from the predicted dependent variable using the same method as the marginal means calculation.

The following sensitivity analyses were conducted. First, a subsample excluding the top 1% DACON outliers from each study drug group was analyzed because the means of DACON from the claims databases can be sensitive to extreme outliers.[22] Second, we analyzed a subsample excluding patients with a diagnosis of cancer, measured during the 6-month periods before and after the start of the 90-day DACON measurement period and defined as ICD-9-CM codes 140-208 but including those with nonmelanoma skin cancer (ICD-9-CM code 173) because this type of neoplasm would not be considered as cancer in our definition.[23,24] This analysis was done to reflect utilization by patients managing chronic noncancer pain, a common subset used in pain studies. Third, we calculated DACON results for patients with different frequencies of maximum gap days to determine if differences in the continuity of chronic pain therapy affected DACON measurement. Fourth, we evaluated these populations without cancer in both scenarios: including DACON outliers and excluding outliers. Fifth, we analyzed the cohorts including cancer patients in both scenarios but omitting opioid medication variables including (a) the use of 1 or more SAOs; (b) the use of 1 or more LAOs in addition to the study LAOs; and (c) the use of both SAOs and LAOs. All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina) and an a priori alpha level of 0.05.

■ Results

Demographics

Oxycodone CR users were older than those using oxymorphone ER (mean ages of 49 vs. 47 years, respectively, $P < 0.001$; Table 1). There was no significant difference in sex distribution between the 2 groups; females were 48.3% and 51.8% of the oxycodone CR and oxymorphone ER groups, respectively ($P = 0.065$). There were differences in the regions in which the prescriptions were dispensed. The proportion of patients who had a CCI of 3 or more was higher for oxycodone CR (32.2%) than oxymorphone ER (25.6%, $P < 0.001$). In terms of other opioid use 30 days prior to the DACON measurement period, there were no statistically significant between-group differences in the proportion using SAOs (70.6% vs. 73.0% for oxycodone CR and oxymorphone ER, respectively, $P = 0.163$) or LAOs (13.6% vs. 12.2%, $P = 0.275$). There was no statistically significant between-group difference in the proportion of patients with both at least 1 SAO claim and at least 1 LAO in addition to the study drug (9.5% vs. 7.4%, respectively, $P = 0.058$). In addition, there was no statistically significant between-group difference in the average maximum gap days during the DACON measurement period for oxycodone CR users and oxymorphone ER users (3.1 days vs. 2.9 days, respectively, $P = 0.343$).

Bivariate Analyses of DACON

In the entire sample, (including the top 1% DACON outliers),

TABLE 1 Demographic Characteristics of the Study Sample, All Patients Including Top 1% DACON Outliers

Demographic Variable	Oxycodone CR (n = 6,567)		Oxymorphone ER (n = 796)		P Value[a]
Age (years) mean [SD]	49.3	[11.9]	47.1	[10.9]	< 0.001
Maximum gap days mean [SD]	3.1	[5.7]	2.9	[5.6]	0.343
	n	**%**	**n**	**%**	
Sex					0.065
Female	3,172	48.3%	412	51.8%	
Male	3,395	51.7%	384	48.2%	
Region[b]					< 0.001
Northeast	625	9.5%	56	7.0%	
Midwest	1,423	21.7%	185	23.2%	
South	3,091	47.1%	426	53.5%	
West	1,427	21.7%	129	16.2%	
Charlson Comorbidity Index, 6-month baseline period					< 0.001
0	2,040	31.1%	254	31.9%	
1	561	8.5%	83	10.4%	
2	1,852	28.2%	255	32.0%	
3 or more	2,114	32.2%	204	25.6%	
At least 1 SAO in the 30 days prior to the DACON measurement period	4,637	70.6%	581	73.0%	0.163
At least 1 LAO in addition to study drug in the 30 days prior to the DACON measurement period	892	13.6%	97	12.2%	0.275
Both at least 1 SAO and at least 1 LAO in addition to study drug in the 30 days prior to the DACON measurement period	622	9.5%	59	7.4%	0.058

[a]Pearson chi-square tests for categorical variables (sex, region, CCI category, and use of LAOs and SAOs) and t tests for continuous variables (age, maximum gap days).
[b]Region data were missing for 1 study subject.

CCI = Charlson Comorbidity Index; CR = controlled-release; DACON = daily average consumption; ER = extended-release; LAO = long-acting opioid; SAO = short-acting opioid, SD = standard deviation.

the unadjusted DACON mean value for the highest strength of oxycodone CR was 3.9 tablets compared with 2.9 tablets for oxymorphone ER (P < 0.001), 3.0 versus 2.4 for lower strengths (P < 0.001), and 3.1 versus 2.5 for all strengths (P < 0.001; Table 2a). For all dosage strengths, the difference in median DACONs was 0.7 tablet (P < 0.001), which was consistent with the difference in means of 0.6 tablet (P < 0.001). When excluding the top 1% DACON outliers (DACON range of 9.7 to 33.0 for oxycodone CR and 6.5 to 10.4 for oxymorphone ER), there was again a statistically significant difference in DACON means overall and at the higher and lower strengths (0.6, 0.9, and 0.5 tablet, respectively, all P < 0.001; Table 2b). Over all dosage strengths after excluding outliers, the differences in median and mean DACONs were again 0.7 and 0.6 tablet, respectively (P < 0.001).

In analyses stratified by continuity of therapy during the DACON measurement period, among the 48.3% (n = 3,181) of oxycodone CR patients and 47.9% (n = 381) of oxymorphone ER patients with no gap in days supplied during the DACON measurement period, mean DACON was 3.4 tablets for oxycodone CR and 2.7 tablets for oxymorphone ER, for a difference of 0.7 tablets per day (P < 0.001; Table 2c). The median DACON was 3.1 tablets for oxycodone CR and 2.2 tablets for oxymorphone ER, for a difference of 0.9 tablets per day (P < 0.001). Among

the 33.9% (n = 2,226) of oxycodone CR patients and 37.2% (n = 296) of oxymorphone ER patients with 1-5 day maximum gaps in days supplied during the DACON period, the differences in mean and median DACONs were 0.6 and 0.7 units, respectively. Finally, among the remaining 17.7% (n = 1,160) of oxycodone CR patients and 14.9% (n = 119) of oxymorphone ER patients with a maximum gap of more than 5 days supplied during the DACON period, the differences in mean and median DACONs were 0.6 and 0.3 units, respectively. Thus, DACON differences were larger among patients with no gap in daily supply compared with patients with gaps. DACON differences for every maximum gap day category were statistically significant (P < 0.001).

Multivariate Analyses

After adjusting in GLMs for age, sex, comorbidities, highest strength versus lower strengths, maximum gap days, and concurrent SAO and LAO use during the 30 days prior to the measurement period, a statistically significant risk-adjusted mean difference in DACON remained, with oxycodone CR patients receiving on average 0.6 tablets more per day than those dispensed oxymorphone ER (P < 0.001; Table 3). The same results were obtained when DACON outliers were excluded from the analysis and when variables relating to the extent of maximum

TABLE 2 Bivariate Analyses of DACON by Study Drug

	Oxycodone CR				Oxymorphone ER				Difference in Means	T Test P Value	Difference in Medians	Wilcoxon Rank Sum Test P Value
	n	Mean	Median	SD	n	Mean	Median	SD				
2a. Strength, all patients												
Highest[a]	930	3.9	3.2	2.4	114	2.9	2.3	1.5	1.0	< 0.001	0.9	< 0.001
Lower[a]	5,637	3.0	2.7	1.6	682	2.4	2.1	1.0	0.6	< 0.001	0.6	< 0.001
Overall	6,567	3.1	2.8	1.8	796	2.5	2.1	1.1	0.6	< 0.001	0.7	< 0.001
2b. Strength, excluding 1% DACON outliers[b]												
Highest[a]	902	3.6	3.2	1.5	110	2.7	2.2	1.1	0.9	< 0.001	1.0	< 0.001
Lower[a]	5,599	2.9	2.7	1.4	678	2.4	2.1	0.9	0.5	< 0.001	0.6	< 0.001
Overall	6,501	3.0	2.8	1.4	788	2.5	2.1	0.9	0.6	< 0.001	0.7	< 0.001
2c. Maximum gap days, all patients												
No gap	3,181	3.4	3.1	1.9	381	2.7	2.2	1.2	0.7	< 0.001	0.9	< 0.001
1-5 days	2,226	3.0	2.7	1.5	296	2.4	2.0	0.9	0.6	< 0.001	0.7	< 0.001
More than 5 days	1,160	2.8	2.3	1.7	119	2.2	2.0	1.0	0.6	< 0.001	0.3	< 0.001

[a]Highest dosage strength = oxycodone CR 80 mg; oxymorphone ER 40 mg. Lower dosage strengths = oxycodone CR 60, 40, 30, 20, 15, and 10 mg; oxymorphone ER 30, 20, 15, 10, 7.5, and 5 mg.
[b]The range of DACON values in the top 1% was 9.7 to 33.0 for oxycodone CR and 6.5 to 10.4 for oxymorphone ER.
CR = controlled-release; DACON = daily average consumption; ER = extended-release; mg = milligram; SD = standard deviation.

TABLE 3 Estimated Marginal Means Calculated from Generalized Linear Models[a]

Strength	Oxycodone CR			Oxymorphone ER			Difference in Means	T Test P Value
	n	Mean[b]	SD[b]	n	Mean[b]	SD[b]		
3a. All patients, including DACON outliers								
Highest[c]	930	3.9	0.5	114	3.1	0.5	0.7	< 0.001
Lower[c]	5,637	3.0	0.4	682	2.4	0.3	0.6	< 0.001
Overall	6,567	3.1	0.4	796	2.5	0.3	0.6	< 0.001
3b. Excluding 1% DACON outliers[d]								
Highest[c]	902	3.6	0.5	110	2.9	0.5	0.6	< 0.001
Lower[c]	5,599	2.9	0.4	678	2.4	0.3	0.5	< 0.001
Overall	6,501	3.0	0.4	788	2.5	0.3	0.6[e]	< 0.001

[a]Estimated marginal means were calculated from generalized linear models, adjusted by age, sex, comorbidities, maximum gap days, and other opioid use.
[b]The mean values from the GLMs were the estimated marginal means of the dependent variables from each study drug, holding all independent variables at mean values. The estimated marginal SD values were also calculated from the predicted dependent variable.
[c]Highest dosage strength = oxycodone CR 80 mg; oxymorphone ER 40 mg. Lower dosage strengths = oxycodone CR 60, 40, 30, 20, 15, and 10 mg; oxymorphone ER 30, 20, 15, 10, 7.5, and 5 mg.
[d]The range of DACON values in the top 1% was 9.7 to 33.0 for oxycodone CR and 6.5 to 10.4 for oxymorphone ER.
[e]Rounded from 0.56.
CR = controlled-release; DACON = daily average consumption; ER = extended-release; GLM = generalized linear model; mg = milligram; SD = standard deviation.

gaps in days supplied were added as independent variables.

Details of the GLMs are shown in the Appendix. Drug selection (oxycodone CR vs. oxymorphone ER), highest strength versus lower strengths, and the use of other long-acting and short-acting opioids 30 days prior to the DACON measurement period were statistically significant at $P < 0.001$. The results indicated that patients taking oxycodone CR were likely to utilize more tablets compared with the oxymorphone ER patients. The results also confirmed that higher tablet strengths were associated with higher DACON. Use of SAOs and use of other LAOs in addition to the study drug 30 days prior to the obser-

vation period were positively associated with the magnitude of DACON. When excluding the outliers, only the use of additional LAOs was associated with higher DACON ($P < 0.001$). The direction, magnitude, and statistical significance of these differences were essentially unchanged in the sensitivity analyses conducted.

Sensitivity Analyses

After excluding patients with a diagnosis of cancer, GLM results showed that patients taking oxycodone CR were more likely to utilize more tablets compared with the oxymorphone ER

patients ($P < 0.001$) The results also confirmed that higher tablet strengths were associated with higher DACON. Additional sensitivity analyses were conducted, including the removal of 1% DACON outliers. All of these GLM analyses yielded results similar in magnitude to the differences observed in the bivariate analyses, with all statistical differences remaining ($P < 0.001$).

■ Discussion

The use of LAOs for moderate to severe chronic pain associated with cancer and nonmalignant conditions continues to increase and represents a significant cost for payers. It is expected to be a $12 billion global market by 2018 even with the anticipated introduction of several generic versions by that time.[3] If the average number of tablets paid per day is significantly different among various products as DACON would indicate, payers could develop strategies to prefer the lower-cost agent.

Across all of the statistical analyses performed in the present study, a consistent and robust finding is that DACON is higher for patients using oxycodone CR compared with those using oxymorphone ER. Specifically, over all dosage strengths, mean DACON is approximately 0.6 units higher and median DACON is approximately 0.7 units higher for oxycodone CR than for oxymorphone ER ($P < 0.001$). The differences in mean and median DACON were greater among patients using the highest dosage strength for each drug (1.0 and 0.9 units, respectively, $P < 0.001$). The estimated difference in mean DACON over all dosage strengths remained the same after adjusting for differences between oxycodone CR and oxymorphone ER users in terms of age, sex, comorbidities, maximum gap days, and other opioid use.

These results are consistent with those of the study by Malkin et al., which found that the DACON for all strengths of oxycodone CR was 3.4 and that higher strengths were associated with higher DACON values, ranging from 2.9 for the 10 mg tablets to 5.2 for the 80 mg tablets.[14] In the work by Berner et al., similar DACON differences were observed, including a DACON of 3.9 for the oxycodone CR 80 mg tablet and 2.9 for the oxymorphone ER 40 mg tablet. In addition, Berner et al. calculated the cost implications of DACON differences for these equipotent doses of oxycodone CR and oxymorphone ER using WACs, estimating an average additional cost of $10.56 per day per patient for oxycodone CR 80 mg.[15]

The present study expanded the measurement of daily average use of oxycodone CR and oxymorphone ER to include all patients on chronic therapy with these medications, not just those patients with a medical claim for a specific diagnosis, such as low back pain. We did not include a cost analysis because that had already been estimated using WAC in the study by Berner et al.[15] In addition, manufacturer rebate information, which might significantly affect net cost to the payer, is not available in the I3 database.

Limitations

First, a key limitation of the DACON analysis presented in this study is that it relies exclusively on claims data. Accordingly, it is not possible to determine if higher DACON among oxycodone CR users is clinically appropriate. For example, some unmeasured patient characteristics more prevalent among oxycodone CR users could be associated with a therapeutic need for more frequent dosing. Second, it also is not possible to ascertain whether all tablets supplied were actually used by patients. For example, if a physician changed the prescribed dose for either study drug, the patient could have discarded any remaining supply for the previously prescribed dose. However, from the perspective of managed care pharmacy, an important consideration in drug benefit management is that each tablet supplied resulted in a cost to the plan. Third, this study did not include an analysis of patient diagnosis. Since different pain syndromes might require different doses of opioid analgesics, DACON values might vary between the 2 cohorts. Fourth, managed care organizations commonly impose quantity limits in an attempt to manage overuse and abuse of LAOs. Although most health plans represented in this database imposed a maximum quantity limit of 124 tablets per pharmacy claim for LOAs, the top 1% of DACON values had a range of 9.7 to 33.0 for oxycodone CR and 6.5 to 10.4 for oxymorphone ER.

■ Conclusions

This study can serve as a benchmark for prescription benefit managers to compare DACON values for LAOs in their prescription claims. DACON analyses are simple yet effective tools to gain an understanding of overall utilization.

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APPENDIX Generalized Linear Model Regressions

Variables[a]	GLM 1 (All Patients)			GLM 2 (Excluding Top 1% DACON Outliers)		
	Coefficient	Standard Error	P Value	Coefficient	Standard Error	P Value
Constant	1.209	0.024	<0.001	1.057	0.022	<0.0001
Oxycodone CR	0.209	0.016	<0.001	0.202	0.015	<0.0001
All lower strengths	−0.227	0.015	<0.001	−0.174	0.014	<0.0001
Years deviation from mean age	−0.001	0.001	0.229	0.000	0.001	0.566
Female	−0.011	0.010	0.265	−0.005	0.009	0.579
CCI=1	0.017	0.020	0.398	−0.003	0.019	0.892
CCI=2	0.002	0.014	0.877	−0.014	0.013	0.280
CCI=3 or more	0.006	0.015	0.679	−0.009	0.014	0.508
Having at least 1 SAO in the 30 days prior to the DACON measurement period	−0.123	0.012	<0.001	−0.005	0.011	0.662
Having at least 1 LAO in addition to study drug in the 30 days prior to the DACON measurement period	0.188	0.027	<0.001	0.307	0.025	<0.0001
Having both at least 1 SAO and at least LAO in addition to the study drug in the 30 days prior to the DACON measurement period	0.107	0.032	0.001	−0.012	0.030	0.697
Maximum gap days	−0.014	0.001	<0.001	−0.013	0.001	<0.0001
Log likelihood	−11,918.6			−11,054.8		
Pearson chi-square	1,914.4			1,314.7		
Kolmogorov-Smirnov	<0.01			<0.01		
Number of patients	7,363			7,289		

[a]Reference cases: oxymorphone ER, male, highest strength, CCI=0, no other opioid use.

CCI=Charlson Comorbidity Index; CR=controlled-release; DACON=daily average consumption; ER=extended-release; GLM=generalized linear model; LAO=long-acting opioid; SAO=short-acting opioid.