Daily Average Consumption of 2 Long-Acting Opioids: An Interrupted Time Series Analysis

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Background: Oxycodone controlled release (CR) and oxymorphone extended release (ER) are frequently prescribed long-acting opioids, which are approved for twice-daily dosing. The US Food and Drug Administration approved a reformulated crush-resistant version of oxycodone CR in April 2010.

Objective: To compare the daily average consumption (DACION) for oxycodone CR and for oxymorphone ER before and after the introduction of the reformulated, crush-resistant version of oxycodone CR.

Methods: This was a retrospective claims database analysis using pharmacy claims from the MarketScan database for the period from January 2010 through March 2011. The interrupted time series analysis was used to evaluate the impact of the introduction of reformulated oxycodone CR on the DACON of the 2 drugs—oxycodone CR and oxymorphone ER. The source of the databases included private-sector health data from more than 150 medium and large employers. All prescription claims containing oxycodone CR and oxymorphone ER dispensed to members from January 1, 2010, to March 31, 2011, were included in the analysis. Prescription claims containing duplicate National Drug Codes, missing member identification, invalid quantities or inaccurate days supply of either drug, and DACON values of <1 and >500 were removed.

Results: The database yielded 483,063 prescription claims for oxycodone CR and oxymorphone ER from January 1, 2010, to March 31, 2011. The final sample consisted of 411,404 oxycodone CR prescriptions (traditional and reformulated) dispensed to 85,150 members and 62,656 oxymorphone ER prescriptions dispensed to 11,931 members. Before the introduction of reformulated oxycodone CR, DACON values for the highest strength available for each of the 2 drugs were 0.51 tablets higher for oxycodone CR than for oxymorphone ER, with mean DACON values of 3.5 for oxycodone CR and 3.0 for oxymorphone ER (P < .001). The differences of mean DACON between the 2 drugs for all lower strengths were 0.46 tablets, with mean DACON values of 2.7 for oxycodone CR and 2.3 for oxymorphone ER (P < .001). After the introduction of the new formulation, the difference in mean DACON between the 2 drugs was slightly lower: 0.45 tablets for the highest-strength and 0.40 tablets for the lower-strength pairs. Regression analyses showed that the immediate and overall impact of the reformulation of oxycodone CR on the DACON of oxycodone CR was minimal, whereas no changes were seen in the DACON of oxymorphone ER. The estimated DACON for oxycodone CR decreased by 0.1 tablets, or 3.7% (P < .001), 6 months after the new formulation was introduced.

Conclusion: The mean DACON was 0.4 tablets per day higher for oxycodone CR compared with oxymorphone ER for all dosage strengths for the entire study period. After the introduction of the reformulated oxycodone CR, the DACON for this drug was slightly mitigated; however, there was a minimal impact on the mean differences between oxycodone CR and oxymorphone ER.

Disclosures are at end of text.
Chronic pain is experienced by more than one third of the US population. Regardless of disease etiology or individual characteristics, chronic pain is debilitating and has a profound impact on emotional and physical functioning. For chronic pain, which is characterized as pain lasting 3 or more months, opioid analgesics are considered part of a multifaceted strategy to manage moderate-to-severe pain for a number of conditions involving the musculoskeletal system (eg, osteoarthritis, low back pain), neurologic system (eg, diabetic neuropathy, spinal cord pain), and for pain associated with neoplastic disease.

Two long-acting opioid analgesics, oxycodone controlled release (CR; OxyContin) and oxymorphone extended release (ER; Opana), are often prescribed to reduce the intensity of moderate-to-severe noncancer pain. However, the usefulness of long-acting opioids in chronic noncancer pain has been scrutinized, because of their adverse effects (eg, nausea and constipation) and the association with illicit drug behaviors, ranging from drug abuse, illegal distribution, and drug product tampering. In addition, a prospective study confirmed that some patients with chronic pain may require more frequent dosing of sustained-release opioids beyond the doses recommended by the manufacturer. Despite concerns over long-term analgesic use, multiple expert panels have concluded that long-term opioid therapy can be effective for carefully selected and monitored patients with chronic noncancer pain.

To encourage proper use, new drug formulations are designed to improve pharmacotherapy either by reducing the dosing frequency or by hindering potential misuse and abuse. In August 2010, the US Food and Drug Administration (FDA) approved a newly formulated crush-resistant version of oxycodone CR. The recommended dosing regimen for oxycodone CR, oxymorphone ER, and the reformulated oxycodone CR is 2 tablets daily. Besides the need for product formulations that will provide more consistent and sustained levels of analgesia throughout the recommended dosing interval, the crush-resistant form of oxycodone may present an obstacle to some forms of misuse.

In making pharmaceutical policy decisions, commercial insurers may need to consider utilization patterns in addition to cost. Daily average consumption (DACON) is a readily available measure that is often used to assess drug utilization. DACON has been used in previous studies to examine medication use in patients with arthritis, diabetes, and hypertension. With chronic pain, the utilization of opioid analgesics may be of concern to pharmacy benefit managers and third-party payers who design and manage prescription drug benefit plans. To build on previous research, we wanted to know if differences in the DACON for oxycodone CR compared with oxymorphone ER persist in recent data that include utilization of a reformulated version of oxycodone CR.

Opportunities to investigate changing patterns of opioid use will allow healthcare benefit managers to monitor opioid use with the goal of maintaining tablet utilization within the expected range of 2 tablets daily. Therefore, the purpose of this study was to evaluate the DACON of oxycodone CR and of oxymorphone ER before and after the introduction of the reformulated oxycodone CR. This study provides some insight into the utilization patterns of 2 branded opioid products used in pain management.

Methods
This was a retrospective, interrupted time series analysis of observational data to assess the DACON of oxycodone CR, oxymorphone ER, and reformulated oxycodone CR over time using the prescription claims-level analysis. Pharmacy claims for the 2 drugs from the MarketScan Commercial database (Thomson Reuters, Inc.) were analyzed for patients aged ≥18 years who filled at least one prescription for oxycodone CR or oxymorphone ER from January 1, 2008, to June 30, 2011. A control group of patients who filled oxycodone CR or oxymorphone ER prescriptions at least once before the index date but before approval of the reformulated oxycodone CR (October 1, 2010) were included. The exposure of interest was defined as filling a prescription for the reformulated oxycodone CR 30 days before to 30 days after the index date. The primary outcome was the DACON of oxycodone CR and oxymorphone ER before and after the introduction of reformulated oxycodone CR.
Ann Arbor, MI) were used to evaluate average monthly and weekly DACON values of oxymorphone ER and oxycodone CR. The database contains individual-level healthcare claims, including enrollment, medical, and prescription (outpatient) records from all providers of care. For the most recent 3 years, data were collected from more than 150 large employers (>200 carriers) and more than 20 regional health plans that provide healthcare coverage for more than 30 million lives annually.

The covered lives include active employees, early retirees, COBRA continuance, and their dependents who are insured by large employers and health plans. Insurance coverage was provided under a variety of fee-for-service, preferred provider organizations, and capitated and partially capitated health plans. Data were de-identified and used in accordance with the Health Insurance Portability and Accountability Act (HIPAA). Approval by the institutional review board was not required.

Calculation of Opioid Consumption

We evaluated DACON over time for oxycodone CR and oxymorphone ER (traditional and reformulated) from January 2010 to March 2011. All prescription claims containing oxycodone CR and oxymorphone ER dispensed to members aged 18 to 64 years from January 1, 2010, to March 31, 2011, were included in the calculation of DACON. Prescription claims containing duplicate National Drug Codes, missing member identification, invalid quantities or inaccurate days supply for either drug, and DACON of <1 and >500 tablets were removed.

The DACON for each prescription was calculated by dividing the total tablets dispensed by days supplied, as reflected by these data fields in each submitted prescription claim. Overall monthly and weekly DACON was calculated for all doses combined, the highest-strength dosages (80-mg oxycodone CR and 40-mg oxymorphone ER), and for all lower-strength dosages, respectively (ie, oxycodone CR 10, 20, 30, 40, and 60 mg, and oxymorphone ER 5, 7.5, 10, 20, and 30 mg).

Statistical Analysis

The measurement of DACON over time was interrupted by the introduction of reformulated oxycodone CR. Because the outcome was analyzed with respect to time intervals (ie, weekly), the error terms may be correlated (ie, not independent), thereby violating one of the classic regression assumptions. Therefore, the interrupted time series analysis was used to estimate changes in levels and weekly trends for the mean DACON of oxymorphone ER and oxycodone CR (traditional and reformulated) before and after the introduction of reformulated oxycodone CR. The model is also often referred to as the segmented regression model, which is used to evaluate longitudinal effects (ie, change in intercept and slopes) of interventions, while relaxing the assumption that observations are independent.

The segmented regression model we developed was derived as follows:

\[ Y_t = \beta_0 + \beta_1 \times \text{time}_t + \beta_2 \times \text{intervention}_t + \beta_3 \times \text{time}_t \times \text{intervention}_t + \epsilon_t \]

- \( Y_t \): average DACON in week \( t \)
- \( \text{Time}_t \): a continuous variable for time in weeks at time \( t \) from the first week of January 2010
- \( \text{Intervention}_t \): a dummy variable taking the values of 0 in the preintroduction period (before August or week 31) and 1 after introduction
- \( \beta_0 \): estimates the baseline level of outcomes
- \( \beta_1 \): estimates for the baseline slope of the outcomes to control for secular trends before the introduction
- \( \beta_2 \): estimates the intercept change immediately after the introduction
- \( \beta_3 \): estimates the change in slope of mean DACON after the introduction.

Autocorrelation in error terms of consecutive observations often exist when time is a predictor in the time series regression analysis. To assess the regression models for serial correlation of the time series data, the Durbin-Watson, alternative Durbin-Watson, Breusch-Godfrey LM, and Bartlett’s statistic white noise tests were used.18,19 The Breusch-Pagan test was used to assess heteroscedasticity or the nonconstant variance assumption.19

Serial correlations were adjusted using one of the autoregressive, integrated, moving-average (ARIMA) models. These models are built by finding the best possible weighted average for a single time series, taking into account past observations (autoregressive terms) and past error terms (moving average terms).20 For this study, interrupted time series analysis allowed researchers to control for previous trends in the assessment of DACON and to study the dynamics of change in response to the introduction of reformulated oxycodone CR.21

To ensure a sufficient number of observations for the segmented regression model, we utilized weekly DACON data of 64 weekly intervals in this study: 31 weeks before the intervention and 33 after the intervention, from January 2010 to March 2011. The number of time points in this study exceeds the range of 50 time points suggested in similar segmented regression analyses and achieves an acceptable level of variability of the estimate at each time point.21 Before analysis, outliers were removed using the standard deviation method, such that DACON values whose deviation exceeds 3 standard deviations of the mean were excluded from the analysis.21

A sensitivity analysis was conducted to examine
model stability. The sensitivity analysis used a similar approach to account for the brief transition period after the introduction of reformulated oxycodone CR by excluding the outcome values that occurred during the potential intervention periods of August 2010 and September 2010. Descriptive statistics and overall mean comparison were evaluated using student t-tests. Statistical significance was established for P <.05. SAS version 9.1 (SAS Institute, Inc, Cary, NC) and Stata version 11.2 (StataCorp, College Station, TX) were used for data analysis.

Results

The MarketScan commercial database yielded 483,063 prescription claims for oxycodone CR and oxymorphone ER from January 1, 2010, to March 31, 2011 (Figure 1). After applying the exclusion criteria for age and high D A C O N outliers, the final sample consisted of 411,404 oxycodone CR prescriptions (traditional and reformulated) dispensed to 85,150 members and 62,656 oxymorphone ER prescriptions dispensed to 11,931 members. Of the total members, 51% were women with the mean age of 48.5 years.

Over the 15-month observation period, the overall mean D A C O N values for all dosage strengths were approximately 0.4 tablets per day higher for oxycodone CR than for oxymorphone ER, with means of 2.9 for oxycodone CR and 2.5 for oxymorphone ER (Figure 2). Reformulated oxycodone CR accounted for approximately 50% of oxycodone CR tablets dispensed in September 2010, 1 month after its introduction. The proportion of reformulated oxycodone CR relative to all oxycodone CR tablets steadily increased from 50% to 95% by the end of the study period (Figure 3).

Overall mean D A C O N values for the 2 drugs over the observation period were relatively stable, ranging from 2.8 to 2.9 tablets per day for oxycodone CR and 2.4 to 2.5 tablets per day for oxymorphone ER, respectively (Figure 2). During the observation period before the introduction of the new formulation, D A C O N values for the highest strength were 0.51 tablets higher for oxycodone CR than for oxymorphone ER, with a mean D A C O N of 3.5 for oxycodone CR and 3.0 for oxymorphone ER (P <.001; Figure 4). After the introduction of the new formulation, the difference in mean D A C O N values between reformulated oxycodone CR and oxymorphone ER decreased slightly to 0.45 tablets per day for the highest-strength pairs (ie, mean D A C O N, 3.5 for oxycodone CR vs 3.0 for oxymorphone ER; P <.001).

The differences of mean D A C O N for all lower strengths between oxycodone CR and oxymorphone ER were 0.46 tablets per day before the introduction of the new formulation, with mean D A C O N values of 2.7 and 2.3 tablets (P <.001) for oxycodone CR and oxymorphone ER, respectively (Figure 4). After the introduction of the new formulation, the difference in mean D A C O N values between the 2 drugs was 0.40 tablets per day, with a mean D A C O N of 2.7 for oxycodone CR and 2.3 for oxymorphone ER (P <.001).

Interrupted Time Series Results

Figure 2 shows the actual and predicted values of weekly D A C O N trends for oxycodone CR and oxymorphone ER over time using the interrupted time
Figure 2  Actual and Predicted Trend Values of Overall DACON for Oxycodone CR and Oxymorphone ER from the Interrupted Time Series Models, January 2010-March 2011

CR indicates controlled release; DACON, daily average consumption; ER, extended release.

Figure 3  Tablets per 1000 Beneficiaries of Oxycodone CR and Oxymorphone ER, January 2010-March 2011

CR indicates controlled release; ER, extended release.

Figure 4  Mean DACON by Strength Before and After Introduction of New Formulation of Oxycodone CR

*Mean differences by each pair were all significant (P < .001). CR indicates controlled release; DACON, daily average consumption; ER, extended release.
series models. Before the introduction of reformulated oxycodone CR, there was no significant week-to-week impact in the mean DACON for oxycodone CR and oxymorphone ER ($P = .956$ and $P = .878$, respectively; Table 1). Immediately after the introduction of the new formulation, the estimated mean DACON for oxycodone CR dropped slightly, by 0.05 tablets weekly. Throughout the study period, there was neither immediate change nor any weekly change in oxymorphone ER’s DACON as a result of the introduction of oxycodone CR.

In terms of changes in trends for the mean DACON after the introduction of oxycodone CR, the weekly trends for oxycodone CR slightly decreased, by 0.003 tablets weekly (0.01 tablets per month). Because the absolute change in weekly DACON was minimal, we compared the overall change by combining the immediate and trend effects for the estimated DACON 6 months after the introduction of the new formulation, with the outcomes as if that introduction had not occurred.

The models showed that the average DACON for oxycodone CR decreased by 0.11 tablets or 3.7% ($P < .001$) 6 months after the new formulation was introduced compared with the DACON level before the introduction (Table 2).

When analyzing the data by strength, the average DACON for the 80-mg (highest strength) oxycodone CR 6 months after the introduction increased slightly by 0.07 tablets or 2.1% ($P = .003$), whereas the DACON for the lower strengths decreased by 0.09 tablets or 3.4% ($P < .001$).

Sensitivity analyses were conducted by excluding the outcome values that occurred during the potential intervention period of August and September 2010. The results (not shown) indicate that the introduction of reformulated oxycodone CR had a slight, mitigating effect on DACON; however, there was no significant change in DACON over time. In addition, there was no significant change in DACON for oxymorphone ER associated with the introduction of the newly formulated oxycodone CR.

**Discussion**

To evaluate the impact on utilization, differences in DACON were assessed between traditional oxycodone CR and oxymorphone ER before and after the introduction of the reformulated oxycodone CR. Results from the interrupted time series analyses and sensitivity analyses revealed that the impact on DACON associated with the introduction of reformulated oxycodone CR was minimal, whereas there was no impact on oxymorphone ER’s DACON. The models estimated that the average DACON for oxycodone CR decreased by 0.1 tablets, or 3.7%, 6 months after the new formulation was introduced ($P < .001$).

In addition, differences in mean DACON between oxycodone CR and oxymorphone ER were quite stable before and after the introduction of reformulated oxycodone CR.
Throughout the 15-month study period, the overall D A C O N was higher for oxycodone CR (traditional or reformulated) compared with oxymorphone ER, by 0.4 to 0.5 tablets per day for all dosage strengths. For a subgroup analysis by strength, the differences of mean D A C O N between oxycodone CR and oxymorphone ER slightly decreased to 0.45 tablets for the highest strength and 0.4 tablets for lower strengths after the introduction of the new formulation.

Findings from this study provide additional information when D A C O N is considered for oxycodone CR (traditional and reformulated) across all tablet strengths compared with oxymorphone ER.

These results are consistent with previous research in this area. For example, there is evidence from other studies to support a higher D A C O N with oxycodone CR compared with oxymorphone ER. Malkin and colleagues found that the D A C O N for all strengths of oxycodone CR was 3.4 and that higher strengths were associated with a higher D A C O N value, ranging from 2.9 for the 10-mg tablets to 5.2 for the 80-mg tablets.\(^24\)

In another study by Berner and colleagues, a retrospective analysis of administrative claims data for commercially insured patients was conducted to compare the D A C O N of oxycodone CR and oxymorphone ER in patients with low back pain.\(^3\) Again, the D A C O N was higher for the maximum-strength tablets of oxycodone CR 80 mg, which were 3.9 tablets per day and significantly higher than the D A C O N of 2.9 for an equipotent oxymorphone ER maximum-strength tablet of 40 mg (P <.01).\(^3\) The investigators estimated that if oxymorphone ER 40-mg tablets were substituted for oxycodone CR 80-mg tablets in the 688 patients in their analysis of a health plan with 32,325 patients having at least 1 prescription for oxycodone CR or oxymorphone ER, the monthly cost difference would be $217,985 based on the D A C O N difference, assuming per-tablet wholesale acquisition costs of $10.83 and $10.93, respectively.\(^25\)

Given the consistent patterns in D A C O N for these drugs, pharmaceutical policymakers may want to consider these results in related decisions.

Findings from this study provide additional information when D A C O N is considered for oxycodone CR (traditional and reformulated) across all tablet strengths compared with oxymorphone ER. A notable finding is the continued difference in D A C O N between oxycodone CR and oxymorphone ER, both before and after introduction of the reformulated oxycodone CR. Considering the potential for dose escalation during long-term opioid use\(^26\), the consistent D A C O N values observed throughout the 15-month study period suggest that current dosing schedules were not altered in response to the introduction of reformulated oxycodone CR.

Interrupted time series analysis is useful when changes over time are interrupted by events, such as the introduction of reformulated oxycodone CR in this study. However, longitudinal designs can be influenced by events outside the control of researchers. Therefore, a sensitivity analysis was performed to assess model robustness. The concordance of results through the transition period of reformulated oxycodone CR indicates that our findings will provide decision makers with a valid assessment of the D A C O N for this population.

Although the D A C O N provides an accurate assessment of drug utilization, with long-term opioid use there may be some members who either fail to achieve adequate analgesic effects despite reaching the maximum tablet strength for frequently prescribed opioids or may experience analgesic tolerance if more frequent dosing is necessary.\(^27\)

Realizing that it may be difficult to distinguish analgesic tolerance from potential drug abuse, especially if members are requesting traditional oxycodone CR over...
reformulated oxycodone CR, health professionals should be cognizant of and recognize that changes in utilization may reflect inappropriate drug use. It is, therefore, essential to follow the guidelines for opioid use to ensure that these drugs are used judiciously in the management of chronic noncancer pain, especially for patients who require higher doses of opioids, have issues with drug abuse, or who report numerous comorbid conditions.26,29

**Limitations**

There are certain caveats associated with the use of claims data. First, it was not possible to examine whether patients were actually using the medications examined in this database. Thus, it was not possible to determine if changes in pain intensity required patients to alter the dose or dosing frequency of opioids for medical emergencies or procedures.

Second, it was not possible to determine if prescribers changed medications in response to oxycodone CR or to oxymorphone ER failures, or changed the dosing schedule to accommodate other medication use or additional diagnoses. For these reasons, it was not possible to control for patient-initiated self-management of pain.

Third, although the calculations of DACON were statistically robust, as observed from sensitivity analyses, additional changes in utilization could occur from inappropriate use of opioids.

Fourth, a common limitation about the claims database is that there is no diagnosis code entered on prescription claims; this study was based on prescription claims, not patients. Therefore, information related to diagnosis codes is not provided in this study.

Finally, because claims databases do not contain data regarding pain severity, it was not possible to evaluate whether one population suffered from more severe pain. To monitor opioid use, managed care plans often place quantity limits on long-acting opioids. Although the patterns of drug use examined in this study were relatively stable over time, it is important to continue monitoring changes in long-acting utilization of these opioids.

**Conclusion**

In this study, the introduction of a crush-resistant oxycodone CR very slightly lowered the DACON for that drug; however, the change was minimal. Therefore, this research supports the notion that differences in DACON are more likely a result of differences in the oxycodone and oxymorphone molecules and not the effects of oxycodone CR reformulation.

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**References**

MEDICAL/PHARMACY DIRECTORS: Long-acting opioids are continuing to get more attention as a result of several factors. Both long- and short-acting opioids have strong brand recognition among opioid users and nonusers alike. There is no shortage of media coverage around diversion, misuse, and abuse of opioids. Many payers and pharmacy benefit managers have implemented high utilization clinical programs and auditing initiatives specific to this narcotic class. In addition, several opioid manufacturers are modifying existing mechanisms or introducing new release mechanisms to decrease the amount of opioid misuse.

Market dynamics have changed within several drug classes over the past couple of years. Several antidepressants and antihypertensives are available as generics. And with the recent introduction of generic atorvastatin, the cholesterol-lowering drug class has also become very accessible in a generic form. During 2012, generics will increase substantially within the atypical antipsychotic class as a result of recent and near-future products losing or about to lose patent protection. Long-acting opioids are moving up the “top paid” list for payers, gaining more attention from large employers as well.

This article reviews the daily average consumption (DACON) of 2 long-acting opioids, namely, oxycodone controlled release (CR) and oxymorphone extended release (ER). DACON was analyzed over a 15-month time frame to evaluate if a reformulated oxycodone CR changed the existing variance of the DACON compared with oxymorphone ER. This analysis shows that the reformulation of oxycodone CR had little impact on the overall DACON of both products, and oxymorphone ER continued to have a similar, but lower, DACON.

Several factors are difficult to assess from this review, including the severity of pain within groups, duration of therapy, or previous trials of other long-acting opioids. DACON may correlate with pharmacokinetic differences, pain management needs, or even misaligned prescribing and/or diversion practices. However, these correlations are difficult to ascertain from a retrospective claims analysis.

Policymakers and payers need to consider DACON when making coverage decisions, but this is only one piece of the decision-making process. Ingredient cost, utilization patterns, generic availability, and, of course, efficacy and safety need to be evaluated, as well as cost. The long-acting opioid class has a variety of available options, including generic alternatives, and the class is expected to continue to expand with new branded products over the next 18 to 24 months.

PATIENTS: Patients now have the opportunity to select from several options, including cost-effective oral and transdermal opioids. No matter the choice, patients must be conscious of adequate pain management needs and out-of-pocket responsibilities.

Other concerns need to be considered as well, such as refill requirements and other, less obvious, unintended consequences associated with misuse or theft of medications.

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