

Patient-Reported Utilization Patterns of Fentanyl Transdermal System and Oxycodone Hydrochloride Controlled-Release Among Patients With Chronic Nonmalignant Pain

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ABSTRACT

BACKGROUND: Although use of long-acting opioid analgesics has increased for chronic nonmalignant pain management, little is known about patient-reported utilization patterns.

OBJECTIVE: To assess patient-reported utilization patterns of fentanyl transdermal system and oxycodone hydrochloride (HCl) controlled-release among patients with chronic nonmalignant pain and to compare these patterns to standard dose administration guidelines recommended in the manufacturers' prescribing information (PI).

METHODS: Cross-sectional, observational, multicenter study of English-speaking patients who were seeking chronic nonmalignant pain management from 6 outpatient pain clinics. The inclusion criteria for the study were (1) diagnosis of chronic nonmalignant pain, (2) prescription for and current use of either transdermal fentanyl or oxycodone HCl controlled-release, and (3) duration of use for either transdermal fentanyl or oxycodone HCl controlled-release of at least 6 weeks. Patients completed either an oxycodone HCl controlled-release or transdermal fentanyl utilization questionnaire. A conversion table was used to standardize opioid analgesic doses from transdermal fentanyl or oxycodone HCl controlled-release to daily oral morphine equivalents. The principal outcome measures were the average interval between oxycodone HCl controlled-release administrations, the number of days the current transdermal fentanyl patch would be worn, and the percentage of oxycodone HCl controlled-release and transdermal fentanyl patients whose administration frequency exceeded the standard recommendation in the manufacturer's PI (every 12 hours for oxycodone HCl controlled-release or every 72 hours for transdermal fentanyl). Other outcome measures included the number of oxycodone HCl controlled-release tablets per administration, the daily dose of long-acting opioid, the duration of adequate pain relief, and the difference in daily oral morphine equivalents between transdermal fentanyl and oxycodone HCl controlled-release patients, after adjusting in a multivariate regression model for demographic and clinical characteristics.

RESULTS: A total of 690 patients were enrolled in this study; 437 (63.4%) received oxycodone HCl controlled-release and 253 (36.6%) received transdermal fentanyl. Oxycodone HCl controlled-release patients reported taking a median of 1 tablet 3 times per day or a median of 3 tablets per day. A mean of 1.6 tablets per administration and 4.6 tablets per day were taken. The average interval between administrations of oxycodone HCl controlled-release was 7.8 hours, and the median daily dose was 80.0 mg (mean 155.6 mg). Among oxycodone HCl controlled-release patients, 17.5% had an average interval between administrations of 12 or more hours, whereas 1.9% reported the duration of pain relief as 12 or more hours. Transdermal fentanyl patients reported wearing the patch, on average, for 2.5 days (median 2.5), and 41.2% reported wearing the patch for at least 3 days, whereas 14.1% reported the duration of pain relief as at least 3 days. The median daily dosage strength of transdermal fentanyl was 75.0 mcg/hour. In the multivariate regression analysis, oxycodone HCl controlled-release patients had, on average, roughly 22 mg additional oral morphine equivalents per day relative to transdermal fentanyl patients (not statistically significant); the probability that oxycodone HCl controlled-release patients had higher oral morphine equivalents was 82.6%, which suggests a trend toward higher oral morphine equivalents per day in the oxycodone HCl controlled-release group.

CONCLUSION: Transdermal fentanyl and oxycodone HCl controlled-release both appear to be used by patients in a manner that is inconsistent with the standard recommendation in the manufacturers' PI; however, the difference between patient-reported utilization and the PI recommendation is more pronounced with oxycodone HCl controlled-release.

KEYWORDS: Opioid analgesics, Fentanyl transdermal system, Oxycodone HCl controlled-release, Patient-reported utilization, Chronic nonmalignant pain

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Unrelieved pain due to chronic, nonmalignant conditions affects between 8% and 30% of adults and imposes a substantial economic burden on society.¹ Although use of opioid analgesics has increased for chronic nonmalignant pain management,^{2,3} little is known about patient-reported utilization patterns for long-acting opioids. To date, most studies have evaluated prescribing patterns using either health insurance claims data, pharmacy data, or medical chart review,^{4,5} which do not reflect actual patient consumption. For example, a recent study by Malkin et al.⁵ used a large Medicaid claims database to describe patterns of care among patients receiving fentanyl transdermal system (Duragesic, Janssen Pharmaceutica Products, L.P., Titusville, New Jersey) or oxycodone hydrochloride (HCl) controlled-release (OxyContin, Purdue Pharma L.P., Norwalk, Connecticut) for chronic nonmalignant or malignant pain. These investigators found that if one oxycodone HCl controlled-release tablet was taken at each administration, the number of oxycodone HCl controlled-release administrations per day exceeded the manufacturers' prescribing recommendation by 70%.

A limitation of the results reported by Malkin et al. was the inability to determine how many oxycodone HCl controlled-release tablets were taken at each administration because this information was not included in the claims database. The standard recommendation in the manufacturers' prescribing information (PI) for oxycodone HCl controlled-release indicates that some patients may benefit from asymmetric dosing (a different dose given in the morning than in the evening), tailored to the pattern of pain.⁶ As such, a total of 3 tablets per day could still be dosed every 12 hours (for example, 1 tablet in the morning and 2 tablets in the evening). In addition, pharmacy claims databases provide information about medications dispensed, as opposed to the actual daily intake of the medications.

To address these limitations, a cross-sectional, observational, multicenter, patient-reported utilization study was conducted to assess the actual daily intake of transdermal fentanyl and oxycodone HCl controlled-release by patients with chronic nonmalignant pain. We chose these 2 long-acting opioids because they are the most commonly used long-acting opioids to treat chronic nonmalignant pain.³ We focused on chronic nonmalignant pain because long-acting opioids have been used with increasing frequency over the last few years for nonmalignant pain, such as chronic low back pain.³ Transdermal fentanyl provides continuous, controlled systemic delivery of fentanyl for up to 72 hours through a rectangular transparent patch, which is available in 4 dosage strengths: 25 mcg/hour, 50 mcg/hour, 75 mcg/hour, and 100 mcg/hour.⁶ Oxycodone HCl controlled-release is supplied

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FIGURE 1 Selected Patient Survey Questions

Oxycodone Hydrochloride Controlled-Release

1. We are interested in knowing **when** during the day you take OxyContin and how many pills you take at each time. Please tell us at **what time(s)** you take your OxyContin pain medication on a typical day and the **number of pills** you take at each time. Please fill in the number of pills in the box above the time(s) you take your pills. For example, if you take 1 OxyContin pill at 7:30 AM, and 2 OxyContin pills at 8 PM, you would complete this question as follows:

Example:

1										2																									
6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	Mid-	1	2	3	4	5	6											
AM						Noon						PM						Mid-						night						AM					

Now please tell us at what time(s) and how many OxyContin pills you take at each time:

6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	Mid-	1	2	3	4	5	6											
AM						Noon						PM						Mid-						night						AM					

FIGURE 2 Selected Patient Survey Questions

Fentanyl Transdermal System

1. We would like to know what day you **put on** your Duragesic patch that you are wearing now. Please put an "X" in the box under the day you put on this patch. Put the "X" either in the box on the left for *before* 12 noon or in the box on the right for *after* 12 noon under the appropriate day.

Sunday		Monday		Tuesday		Wednesday		Thursday		Friday		Saturday	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12 Noon		12 Noon		12 Noon		12 Noon		12 Noon		12 Noon		12 Noon	

2. We would like to know what day you **expect to change** your patch. Please put an "X" in the box under the day you **will change** this patch. Put the "X" in the box on the left for *before* 12 noon or in the box on the right for *after* 12 noon under the appropriate day.

Sunday		Monday		Tuesday		Wednesday		Thursday		Friday		Saturday	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12 Noon		12 Noon		12 Noon		12 Noon		12 Noon		12 Noon		12 Noon	

in 20 mg, 40 mg, 60 mg, and 80 mg tablet strengths for oral administration.⁶ The 160 mg dosage formulation of oxycodone HCl controlled-release was not made available until July 2000 and was later withdrawn from the market. The manufacturer's PI recommends that oxycodone HCl controlled-release tablets should be taken every 12 hours (every-12 hour) and that it is most appropriate to increase the every-12 hour dose, not the administration frequency.⁶ The standard recommendation in the manufacturer's PI for transdermal fentanyl indicates that the majority of patients are adequately maintained with transdermal fentanyl administered every 72 hours but that a small number of patients may not achieve adequate analgesia using the 72-hour adminis-

tration interval and may require administration every 48 hours. The PI recommendation further indicates that an increase in the transdermal fentanyl dose should be evaluated before changing the dosing interval in order to maintain patients on a 72-hour administration regimen.⁶

We administered a patient-reported utilization survey to assess real-world patterns of care among patients receiving these 2 medications for chronic nonmalignant pain and compared these patterns to the standard dose administration guidelines recommended in the manufacturers' PI. We hypothesized that both oxycodone HCl controlled-release and transdermal fentanyl are used by patients in a manner that is inconsistent with the standard recommendation in the manufacturers' PI but that the difference between patient-reported utilization and the PI recommendation would be greater with oxycodone HCl controlled-release.

Methods

Study Design

A cross-sectional, observational, multicenter study was conducted of English-speaking patients who were seeking chronic nonmalignant pain management across 6 outpatient pain clinics. In order to be eligible for the study, patients must have been (1) diagnosed with chronic nonmalignant pain, (2) prescribed and currently using either transdermal fentanyl or oxycodone HCl controlled-release, and (3) on transdermal fentanyl or oxycodone HCl controlled-release for at least 6 weeks. Patients were ineligible to participate if they (1) were currently taking both transdermal fentanyl and oxycodone HCl controlled-release, (2) were currently participating or had been participating in a trial of an investigational drug within the last 30 days, or (3) would not sign informed consent to participate in this study. Institutional Review Board approval for the study was obtained for all sites. Written informed consent was obtained from all enrolled patients.

Each site was asked to enroll patients in a 2 to 1 ratio of oxycodone HCl controlled-release patients to transdermal fentanyl patients because we anticipated that this would reflect current prescription patterns.² Trained study coordinators reported the patient's visit date, age, gender, date first prescribed oxycodone HCl controlled-release or transdermal fentanyl, and diagnosis on the inclusion/exclusion and demographic case-report form. Duration on medication was computed as the visit date minus the date first prescribed oxycodone HCl controlled-release or transdermal fentanyl. The site coordinators also completed a medication case-report form specifying the prescribed dose of oxycodone HCl controlled-release or transdermal fentanyl as well as use of supplemental prescription pain medications.

Because we collected data on patients who either were using oxycodone HCl controlled-release or transdermal fentanyl, the drugs' different routes of administration (that is, oral versus transdermal, respectively) and different standard recommendations in the manufacturers' PI (that is, every 12 hours versus every 72 hours, respectively) required that we develop separate utilization questions for each patient group. Enrolled patients, therefore,

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completed either an oxycodone HCl controlled-release or transdermal fentanyl patient questionnaire during their follow-up visits once they had been established on their medications. The patient questionnaires, which required roughly 10 minutes to complete, assessed patterns of utilization from the patient's perspective, including frequency of use and duration of adequate pain relief (see Figures 1 and 2 for selected survey questions). The oxycodone HCl controlled-release utilization questions included the times when patients took their tablets on a typical day and the number of tablets taken at each time. The transdermal fentanyl utilization questions included when patients applied the patch and when they expected to change the current patch.

The principal outcome measures were the average interval between oxycodone HCl controlled-release administrations, the number of days the current transdermal fentanyl patch will be worn, and the percentage of oxycodone HCl controlled-release and transdermal fentanyl patients whose administration frequency exceeded the standard recommendation in the respective manufacturer's PI (that is, every 12 hours for oxycodone HCl controlled-release and every 72 hours for transdermal fentanyl). Other outcome measures included the number of oxycodone HCl controlled-release tablets per administration, the daily dose of long-acting opioid, the duration of adequate pain relief, and the difference in daily oral morphine equivalents between transdermal fentanyl and oxycodone HCl controlled-release patients, after adjusting in a multivariate regression model for demographic and clinical characteristics.

Statistical Methods

Morphine is considered the reference standard for comparing other opioid analgesics.^{7,8} Due to the 2 different routes of administration, we converted daily-prescribed doses of transdermal fentanyl and oxycodone HCl controlled-release to a common metric—oral morphine equivalents—given that there is a pharmacologic basis for converting fentanyl and oxycodone (a derivative of morphine) to oral morphine equivalents.⁹ The dose conversion algorithms are presented in Table 1.⁶ Because the manufacturer's PI for transdermal fentanyl provides a range of oral morphine equivalents,⁶ in the “base-case” analysis, the average of the range for each dosage strength of transdermal fentanyl was used to calculate daily oral morphine equivalents. In addition, sensitivity analyses were conducted by varying the oral morphine equivalents for each strength of transdermal fentanyl between the low and high values.

Demographic and clinical characteristics were evaluated using either *t* tests or Mann-Whitney U tests, as appropriate, for continuous variables and chi-square tests for categorical variables. Both means and medians were reported when the variable distributions were skewed. We also examined the duration of pain relief among transdermal fentanyl patients who expected to wear their current patches for at least 3 days and among oxycodone HCl controlled-release patients who administered every 12 or more hours. In addition, the number of oxycodone HCl controlled-release

TABLE 1 Dose Conversions to Oral Morphine Equivalents

Medication	Oral Morphine Equivalents (mg)*
Oxycodone HCl controlled-release	
1 mg	2
Fentanyl transdermal system†	
25 mcg/hour patch	45, 89, 134
50 mcg/hour patch	135, 179, 224
75 mcg/hour patch	225, 269, 314
100 mcg/hour patch	315, 359, 404

* For example, a person taking 2 oxycodone HCl controlled-release 80 mg tablets daily would equal 320 mg oral morphine equivalents daily (2 tablets x 80 mg x 2). A person wearing a 25 mcg/hour patch and a 100 mcg/hour patch daily would equal 448 mg oral morphine equivalents daily (89 mg + 359 mg) when using the middle values (average transdermal dose) tabulated above.

† The fentanyl transdermal system prescribing information provides a range of oral morphine equivalents for each dosage strength of fentanyl transdermal system. Therefore, we used the average of the range (for example, 89 mg for a 25 mcg/hour patch) in the base-case analysis and conducted sensitivity analyses using the low and high values.

tablets per administration was calculated at the patient level. The difference between daily opioid load from transdermal fentanyl or oxycodone HCl controlled-release was examined using the Mann-Whitney U test.

Finally, in multivariate analyses using base-case (average transdermal dose) values for transdermal fentanyl, the difference in daily opioid load from oxycodone HCl controlled-release relative to transdermal fentanyl was examined, after adjusting for age, gender, and clinical characteristics that differed significantly between groups. Because the dependent variable—oral morphine equivalents—was skewed, a nonparametric “bootstrapping” approach was used to estimate the mean difference in daily oral morphine equivalents from oxycodone HCl controlled-release compared to transdermal fentanyl. Bootstrapping involves “resampling” the data many times (that is, repetitive computations) to generate an empirical estimate of the entire sampling distribution.¹⁰ The nonparametric bootstrapping procedure was used to develop a 95% confidence interval (CI) around the mean difference in daily oral morphine equivalents between groups. This was accomplished by drawing 1,000 random resamples of size 437 from the original oxycodone HCl controlled-release sample and size 253 from the original transdermal fentanyl sample, with replacement.¹⁰ In each resample, we calculated the group means and the difference and selected the 26th and 975th rank-ordered values of the observed distributions to define the 95% CI. The 95% CI contains the true value with a probability of 95%. This nonparametric approach also permitted estimation of the probability that the daily oral morphine equivalents from oxycodone HCl controlled-release exceeded the daily oral morphine equivalents from transdermal fentanyl. All statistical analyses were performed using version 8.0 of the Statistical Applications Software of the SAS Institute (Cary, North Carolina).

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TABLE 2 Demographic and Clinical Characteristics*

Characteristic	Oxycodone HCl Controlled-Release (N=437)	Fentanyl Transdermal System (N=253)	P Value†
Age, years			0.0723
Mean (SD)	45.7 (11.0)	47.5 (10.9)	
Gender, %			0.0034
Male	45.3	34.0	
Female	54.7	66.0	
Duration on medication,‡ weeks			<0.0001
Mean (SD)	69.0 (54.3)	50.9 (54.5)	
Median	54.0	31.4	
Diagnosis, %			0.5074
Abdominal pain	2.8	5.5	
Back and neck pain	57.9	58.5	
Muscle pain	8.5	6.7	
Joint pain	4.1	4.0	
Arthritis pain	4.4	3.6	
Generalized pain	5.5	6.7	
Neuropathic pain	7.8	8.7	
Other§	9.2	6.3	
Use of supplemental prescription pain medications, %	71.6	87.0	<0.0001

* Reported by site coordinators based on review of medical charts.

† T test for normally distributed continuous variables, Mann-Whitney U test for skewed continuous variables, and chi-square test for categorical variables.

‡ Oxycodone HCl controlled-release, N=434; fentanyl transdermal system, N=251. Duration on medication for the remaining 5 patients exceeded 6 weeks, but the actual duration was not known.

§ Includes limb pain, connective tissue pain (other than joint pain), head pain/headache, thoracic pain, other pain/unknown diagnoses.

Results

Between August 2001 and January 2002, 691 patients were enrolled in the study; 438 (63.4%) were oxycodone HCl controlled-release patients and 253 (36.6 %) were transdermal fentanyl patients. One oxycodone HCl controlled-release patient who was on medication for only 4 weeks was inadvertently enrolled in the study and was excluded from all analyses. Therefore, the analyses included a total of 690 patients (437 oxycodone HCl controlled-release patients and 253 transdermal fentanyl patients).

Gender, duration on medication, and use of supplemental prescription pain medications differed significantly between the transdermal fentanyl and oxycodone HCl controlled-release patient groups, whereas age and diagnosis did not differ between groups (Table 2). The average age was 46.4 years and the most

common diagnosis was back and neck pain (58.1%). Among patients who received transdermal fentanyl, 34.0% were male and 87.0% used supplemental prescription pain medications; among patients who received oxycodone HCl controlled-release, 45.3% were male and 71.6% used supplemental prescription pain medication ($P=0.0034$ and $P<0.0001$, respectively). Patients in the transdermal fentanyl group were on this medication for a shorter duration than patients in the oxycodone HCl controlled-release group (median 31.4 and 54.0 weeks, respectively; $P<0.0001$) (Table 2).

Oxycodone HCl controlled-release patients reported taking a median of 1 tablet 3 times per day or a median of 3 tablets per day (Table 3). A mean of 1.6 tablets per administration and 4.6 tablets per day were taken. The average interval between administrations of oxycodone HCl controlled-release was 7.8 hours and the median daily dose was 80.0 mg (mean 155.6 mg). Among oxycodone HCl controlled-release patients, 17.5% had an average interval between administrations of 12 or more hours and 1.9% reported the duration of pain relief as 12 or more hours. The single largest group of oxycodone HCl controlled-release patients ($n=184$; 42.7%) reported adequate pain relief lasting at least 4 hours but less than 6 hours; roughly 15% of patients ($n=65$) reported adequate pain relief lasting less than 4 hours (Table 3).

Among transdermal fentanyl patients, 88.5% were wearing 1 patch, 9.5% were wearing 2 patches, and 2.0% were wearing 3 or 4 patches (Table 4). Transdermal fentanyl patients reported wearing the patch, on average, for 2.5 days (median 2.5) and 41.2% reported wearing the patch for at least 3 days, whereas 14.1% reported the duration of pain relief as at least 3 days. The single largest group of transdermal fentanyl patients ($n=142$; 57.3%) reported adequate pain relief lasting at least 2 days but less than 3 days. The median daily dosage strength of transdermal fentanyl was 75.0 mcg/hour (Table 4).

Table 1 provides the dose conversion algorithms for oral morphine equivalents per day from transdermal fentanyl and oxycodone HCl controlled-release. In the bivariate (unadjusted) analysis using the transdermal fentanyl base-case (average transdermal dose) values (Table 5), transdermal fentanyl patients had significantly higher oral morphine equivalents per day relative to oxycodone HCl controlled-release patients (medians—transdermal fentanyl: 269 mg, oxycodone HCl controlled-release: 160 mg; $P=0.0010$); the inferences were similar when using the high dosage morphine equivalents for transdermal fentanyl ($P<0.0001$). In the sensitivity analysis using the low dosage strength of transdermal fentanyl, there was no significant difference in daily oral morphine equivalents between medications (Table 5).

In the multivariate regression analysis (Table 6), after adjusting for age, gender, duration on medication, and use of supplemental prescription pain medications, oxycodone HCl controlled-release patients had, on average, roughly 22 mg additional oral morphine equivalents per day relative to transdermal fentanyl patients

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(based on average transdermal dose values). Although this difference in daily oral morphine equivalents was not statistically significant, the results suggest a trend toward higher oral morphine equivalents per day in the oxycodone HCl controlled-release group. The probability that oxycodone HCl controlled-release patients had higher oral morphine equivalents was 82.6%, after adjusting for age, gender, duration on medication, and use of supplemental prescription pain medications, which also suggests a trend toward higher oral morphine equivalents per day in the oxycodone HCl controlled-release group. Referring to Table 6, women had significantly lower oral morphine equivalents than men (approximately 89 mg lower, on average; $P=0.0011$). For every month on long-acting opioid medication, patients had roughly 5 mg additional oral morphine equivalents per day ($P<0.0001$). With every 10 years of age, patients had 6 fewer oral morphine equivalents per day, although this trend was not significantly associated with daily oral morphine equivalents from transdermal fentanyl or oxycodone HCl controlled-release. Similarly, there was a nonsignificant trend where patients who were taking supplemental prescription pain medications were taking higher doses (50.7 mg additional oral morphine equivalents per day, on average) of these long-acting opioids (relative to patients who were not taking supplemental prescription pain medications).

Discussion

In this study, we administered a patient-reported utilization survey to assess actual patterns of care among patients receiving oxycodone HCl controlled-release or transdermal fentanyl for chronic nonmalignant pain. This patient-reported utilization survey demonstrated that transdermal fentanyl and oxycodone HCl controlled-release both appear to be used by patients in a manner that is inconsistent with standard recommendations in the manufacturers' PI; however, the difference between patient-reported utilization (average interval between oxycodone HCl controlled-release administrations or number of days the current transdermal fentanyl patch will be worn) and the standard recommendations in the manufacturers' PI is more pronounced with oxycodone HCl controlled-release.

Among oxycodone HCl controlled-release patients, 17.5% had an average interval between administrations of 12 or more hours (Table 3), whereas 41.2% of transdermal fentanyl patients reported wearing the patch for at least 3 days (Table 4). The standard recommendation in the manufacturer's PI indicates that oxycodone HCl controlled-release tablets should be taken every 12 hours and that it is most appropriate to increase the every-12 hour dose, not the administration frequency.⁶ The standard recommendation in the manufacturer's PI for transdermal fentanyl indicates that the majority of patients are adequately maintained with transdermal fentanyl administered every 72 hours, but that a small number of patients may not achieve adequate analgesia using the 72-hour administration interval and may require administration every 48 hours. The PI further indi-

TABLE 3 Oxycodone HCl Controlled-Release Patient-Reported Utilization

Oxycodone HCl Controlled-Release (N=437)	Value
Number of tablets per day*	
Mean (SD)	4.6 (4.0)
Median	3.0
Number of administrations per day†	
Mean (SD)	3.0 (1.0)
Median	3.0
Number of tablets per administration*	
Mean (SD)	1.6 (1.2)
Median	1.0
Average interval between administrations,‡ hours	
Mean (SD)	7.8 (2.8)
Median	7.0
Percent ≥12 hours	17.5
Daily dose, mg	
Mean (SD)	155.6 (218.7)
Median	80.0
Duration of adequate pain relief§, n (%)	
Less than 4 hours	65 (15.1)
At least 4 hours but less than 6 hours	184 (42.7)
At least 6 hours but less than 8 hours	116 (26.9)
At least 8 hours but less than 10 hours	39 (9.1)
At least 10 hours but less than 12 hours	19 (4.4)
12 or more hours	8 (1.9)

* N=426. Eleven patients did not report the number of tablets per day. The number of tablets per administration was calculated as the number of tablets per day divided by the number of administrations per day.

† N=432. Five patients did not report the number of administrations per day.

‡ N=423. Fourteen patients did not report the average interval between administrations.

§ N=431. Six patients did not report the duration of adequate pain relief.

cates that an increase in the transdermal fentanyl dose should be evaluated before changing the dosing interval in order to maintain patients on a 72-hour administration regimen.⁶

The results of the current study are consistent with those reported by Malkin et al.⁵ based on a claims database analysis using California Medicaid (Medi-Cal) data. The current survey demonstrated that the average interval between administrations of oxycodone HCl controlled-release tablets was 7.8 hours (median of 1 tablet per administration, 3 administrations per day, and 3 tablets per day; Table 3), whereas transdermal fentanyl patients reported wearing their patch an average of 2.5 days (Table 4).

In the current study, the number of oxycodone HCl controlled-release administrations per day exceeded the recommended amount by 50% ([3 administrations per day—recommended use]/recommended use, where recommended use equals 2 administrations per day), whereas the number of transdermal fentanyl patches applied exceeded the manufacturers' prescribed recommendation by 17% ([2.5 days patch will be worn—recommended use]/recommended use, where recommended use equals 3 days). Malkin et al.⁵ found that nonmalignant patients in the transdermal fentanyl group were wearing their patch an average of

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TABLE 4 Fentanyl Transdermal System Patient-Reported Utilization

Fentanyl Transdermal System (N=253)	Value
Number of patches worn, n (%)	
1	224 (88.5)
2	24 (9.5)
3	4 (1.6)
4	1 (0.4)
Number of days <i>current</i> patch will be worn*	
Mean (SD)	2.5 (0.6)
Median	2.5
Percent ≥ 3 days	41.2
Daily dose, mcg/hour	
Median	75.0
Duration of adequate pain relief†, n (%)	
Less than 1 day	10 (4.0)
At least 1 day but less than 2 days	61 (24.6)
At least 2 days but less than 3 days	142 (57.3)
At least 3 days but less than 4 days	35 (14.1)
4 or more days	0 (0.0)

* N=228. Twenty-five patients did not report the number of days the current patch will be worn.

† N=248. Five patients did not report the duration of adequate pain relief.

TABLE 5 Oral Morphine Equivalents per Day From Oxycodone HCl Controlled-Release and Fentanyl Transdermal System (Base-Case and Sensitivity Analysis)

Medication	Oral Morphine Equivalents (mg)			
	N	Mean	Median	P Value*
Oxycodone HCl controlled-release	437	311.3	160.0	
Fentanyl transdermal system				
Base case	253	264.9	269.0	0.0010†
Low	253	214.9	225.0	0.1635
High	253	316.2	314.0	<0.0001†

* Fentanyl transdermal system base case, low, and high compared to oxycodone HCl controlled-release using the Mann-Whitney U test. The base-case analysis uses the average transdermal dose for fentanyl transdermal system.

† In this unadjusted analysis, fentanyl transdermal system patients had significantly higher median oral morphine equivalents per day.

2.2 days, whereas oxycodone HCl controlled-release patients were taking an average of 3.5 tablets per day. Using these Medi-Cal data for nonmalignant patients, we calculated that, if 1 oxycodone HCl controlled-release tablet was taken at each administration (which is consistent with the median of 1 tablet per administration in the current study), then the number of oxycodone HCl controlled-release administrations per day (3.5 administrations per day)

exceeded the recommended amount by 75% ($[3.5-2]/2$), whereas the number of transdermal fentanyl patches prescribed exceeded the manufacturers' prescribing recommendation by 27% based on 1 patch every 2.2 days ($[2.2-3]/3$).

The current patient-reported utilization study demonstrated that both oxycodone HCl controlled-release and transdermal fentanyl exceeded the manufacturers' prescribed recommendation by less than that calculated using Medi-Cal data from Malkin et al.⁵ Nevertheless, the difference between patient-reported utilization (average interval between oxycodone HCl controlled-release administrations or number of days the current transdermal fentanyl patch will be worn) and the standard recommendations in the manufacturers' PI remains more pronounced with oxycodone HCl controlled-release. Malkin et al. used Medicaid data from 1 state, whereas the current study included patients from 6 states without regard to insurance status, suggesting that the results reported herein may be more generalizable than those reported by Malkin et al. Further, the results of the current study reflect patient-reported consumption, whereas the results from Malkin et al. reflect medications dispensed.

We searched the PreMEDLINE, MEDLINE, HealthSTAR/OVID, Embase, Current Contents, IMS R&D Focus, and Adis R&D Insight databases (January 1994 to July 2002) using the search terms "utilization" or "prescribing patterns" or "prescriptions" or "claims analysis" or "insurance claims" coupled with "Duragesic," "transdermal fentanyl," "OxyContin," "oxycodone," "analgesia," "analgesic," or "opioid." Based on this literature search, to our knowledge, this is the first cross-sectional, multicenter study describing patient-reported utilization patterns of transdermal fentanyl and oxycodone HCl controlled-release for chronic nonmalignant pain. Through this literature search, however, we identified 1 medical chart review study that compared only the initial dosage of transdermal fentanyl to the standard recommendation in the manufacturer's PI in 32 patients hospitalized during 1993.¹¹ We also identified 2 other patient-utilization surveys for chronic nonmalignant pain, but these studies provided no information about dosages and administration intervals for comparison with the standard recommendation in the manufacturer's PI; the first survey identified characteristics of patients treated with various opioids versus those not treated with opioids,¹² and the second survey reported the degree of pain relief and tolerance among patients using various opioids.¹³

The results of our survey suggest that some patients may have either inadequate pain relief or need to take their pain medication more frequently than PI administration recommendations because the duration of pain relief is not adequate with the current dosing frequency. Among oxycodone HCl controlled-release patients, 1.9% reported the duration of pain relief as 12 or more hours (Table 3). The single largest group of oxycodone HCl controlled-release patients (n=184; 42.7%) reported adequate pain relief lasting at least 4 hours but less than 6 hours and 15.1% (n=65) reported pain relief lasting less than 4 hours (Table 3). Among

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transdermal fentanyl patients, 14.1% reported the duration of pain relief as at least 3 days (Table 4). The single largest group of transdermal fentanyl patients (n=142; 57.3%) reported adequate pain relief lasting at least 2 days but less than 3 days (Table 4).

Further, the standard recommendations in the manufacturers' PI for transdermal fentanyl and oxycodone HCl controlled-release indicate that some patients may require periodic supplemental doses of short-acting analgesics for "breakthrough pain."⁶ The current study suggests that use of supplemental prescription pain medication may be more common than previously thought. Overall, approximately 77% of patients in the current study used supplemental prescription pain medications. Similarly, Cramer et al. reported that 74.7% of 1,543 nursing home residents received adjunctive pharmacotherapy primarily for nonmalignant pain.¹⁴ There was a high rate of rescue medication use with both drugs—71.6% for oxycodone HCl controlled-release and 87.0% for transdermal fentanyl (Table 2)—indicating that the majority of these patients still required short-acting opioids to help control breakthrough pain, in lieu of increasing the long-acting opioid dose. Given that physicians at the 6 sites were experienced pain specialists, they may have been more aggressive in controlling pain than others, such as primary care physicians.

It is difficult to speculate why more patients on transdermal fentanyl were taking supplemental prescription pain medication; the difference in use of supplemental prescription pain medication between the 2 patient groups may not be clinically significant. Our results also suggest that patients who were taking supplemental prescription pain medications were taking higher doses of oxycodone HCl controlled-release or transdermal fentanyl, which is consistent with what one might expect, given that these were chronic pain patients who were using opioids for an extended period of time.

The current study found that with every additional month on medication, patients had, on average, roughly 5 additional oral morphine equivalents per day from transdermal fentanyl or oxycodone HCl controlled-release. The increased utilization per additional month of 5 morphine equivalents per day is of unclear clinical significance. It may represent tolerance or another mechanism. Tolerance, defined as the need for increasing doses of opioids to maintain a defined effect such as analgesia, is not unusual during chronic opioid therapy.¹⁵ Progressively higher dosages may be required due to disease progression or pharmacological tolerance. Other investigators also have reported dose escalation in patients being treated for chronic nonmalignant pain.^{13,16}

Limitations

Several limitations merit explanation. First, this survey was administered to patients with chronic nonmalignant pain referred to clinics that specialize in pain management. As such, the results of this study may not be generalizable to either malignant pain patients or patients who seek medical care in other settings. By definition, chronic pain patients have more intractable, difficult-to-treat pain.

TABLE 6 Difference in Oral Morphine Equivalents per Day Between Oxycodone HCl Controlled-Release and Fentanyl Transdermal System: Multivariate Regression Analysis (N=690)*

Variable	Oral Morphine Equivalents (mg)		
	Mean	95% CI	P Value
Medication			
Oxycodone HCl controlled-release	21.8	(-24.9, 71.6)†	0.4144
fentanyl transdermal system (reference)			
Age, years	-0.6	(-2.7, 1.5)	0.5013
Gender			
Female	-88.9	(-147.2, -30.6)	0.0011
Male (reference)			
Duration on medication, weeks	1.3	(0.7, 2.0)	<0.0001
Supplemental prescription pain medications			
Yes	50.7	(-9.6, 107.6)	0.1134
No (reference)			

* Using base-case (average transdermal dose) values for fentanyl transdermal system. Up to 3 oxycodone HCl controlled-release patients and 2 transdermal fentanyl patients could have been excluded from a bootstrap regression resample due to missing values for duration on medication.

† Probability that oxycodone HCl controlled-release has higher oral morphine equivalents was 82.6%, after adjusting for age, gender, duration on medication, and use of supplemental prescription pain medications. This result suggests a trend toward higher oral morphine equivalents per day in the oxycodone HCl controlled-release group.

The dosage of oxycodone HCl controlled-release and transdermal fentanyl, therefore, is expected to be greater in patients seen in chronic pain clinics. The number of such patients likely will grow over the next decades due to changing demographics, combined with improved medical technology, improved health care delivery, and increased patient awareness about the "right to be pain free."

Second, we did not calculate the total daily opioid load (long-acting plus supplemental prescription pain medications) because the use of supplemental prescription pain medications was not a statistically significant confounder in the multivariate regression analysis (Table 6).

Third, we did not conduct subgroup analyses by diagnosis to assess whether patients had different administration patterns depending on their diagnosis. Nevertheless, because the distribution of diagnoses did not differ across patient groups ($P=0.5074$; Table 2), diagnosis would not be considered a confounding factor for the observed administration patterns. We do, however, expect that the variability in the outcome measures (for example, average interval between oxycodone HCl controlled-release administrations or number of days the current transdermal fentanyl patch will be worn) is, in part, attributable to the different etiologies and pain levels.

Fourth, the oxycodone HCl controlled-release patient questionnaire (Figure 1) was designed for patients to report administration

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times based on 2-hour intervals (rather than hourly). Similarly, the transdermal fentanyl patient questionnaire (Figure 2) was designed for patients to report when they put their patch on and expected to change the patch based on 12-hour increments (for example, put the patch on Tuesday morning and change the patch Thursday afternoon). Although the design of these particular questions introduced some imprecision, they were designed in this fashion to decrease the burden on the patients completing the surveys.

Lastly, although patient-reported data offer many advantages relative to claims data,¹⁷ patient-reported data may be subject to recall bias¹⁸; however, given that the patients in this study were reporting about medications they currently were taking, we expect that the magnitude of recall bias should have been minimal. On the other hand, the data abstracted from medical charts (for example, prescribed dose and use of supplemental prescription pain medication) may have been subject to inaccurate data abstraction; again, we anticipate that inaccurate abstraction would have been minimal because site coordinators were trained prior to data abstraction.

The current patient-reported utilization survey reported measures of utilization such as mean number of tablets per administration, interval between administrations, and percentage of patients who reported administering more frequently than is recommended in the manufacturers' PI. On the other hand, Malkin et al. reported measures of utilization such as mean number of transdermal fentanyl patches or oxycodone HCl controlled-release tablets per day, mean cost per month, and percentage by which the administrations per day exceed the standard recommendations in the manufacturers' PI.⁵ A recent editorial in the *Journal of Managed Care Pharmacy* emphasized that reporting multiple measures of utilization provides assistance to readers when interpreting the results and judging the validity of the conclusions.¹⁹ Despite the different measures of utilization used in the current study versus those reported by Malkin et al., the findings are consistent, thereby supporting the validity of the authors' conclusions.

Conclusion

This patient-reported utilization survey demonstrated that transdermal fentanyl and oxycodone HCl controlled-release both appear to be used by patients in a manner that is inconsistent with the standard recommendations in the manufacturers' PI. However, the difference between patient-reported utilization (that is, average interval between oxycodone HCl controlled-release administrations or number of days the current transdermal fentanyl patch will be worn) and the standard recommendations in the manufacturers' PI (that is, every 12 hours for oxycodone HCl controlled-release and every 72 hours for transdermal fentanyl) is more pronounced with oxycodone HCl controlled-release. Among oxycodone HCl controlled-release patients, only about 18% of patients were observed to exhibit every-12 hour administration patterns (Table 3), whereas about 41% of transdermal fentanyl patients reported wearing the patch for at least 3 days

(Table 4). These results underscore the need to better understand the reasons for increasing the dosing frequency for both oxycodone HCl controlled-release and transdermal fentanyl above their respective manufacturers' PI recommendations.

Further, this study will help inform physicians and managed care organizations about the actual frequency of dosing of these long-acting opioids in a chronic nonmalignant pain setting. Lastly, these results offer insights into, and recognition of, real-world prescribing patterns and suggest that a pharmacoeconomic evaluation based solely on the PI dosing recommendations may lead to an inaccurate assessment of the true costs of these agents.

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Ackerman served as principal author of the study. Study concept and design were contributed primarily by Ackerman, Mordin and Schein. Ackerman, Mordin, Reblando, and Xu had full access to the data and accept full responsibility for the integrity of the data and the data analysis. Ackerman, Mordin, Reblando, Xu, Schein, Vallow, and Brennan analyzed and interpreted the data, and Ackerman provided statistical expertise. Drafting of the manuscript was the work of Ackerman and its critical revision was the work of Ackerman, Mordin, Reblando, Xu, Schein, Vallow, and Brennan.

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