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Comparative Out-of-Hospital Mortality of Long-Acting Opioids Prescribed for Non-Cancer Pain: A Retrospective Cohort Study

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Abstract

Purpose—Despite significant growth of opioid prescriptions, only limited data are available regarding the comparative safety of long-acting opioids for chronic non-cancer pain. Recent data suggest that transdermal fentanyl and oxycodone CR may have greater toxicity than morphine SR in patients with non-cancer pain. Thus, we compared the risk of out-of-hospital deaths in patients with non-cancer pain filling prescriptions for transdermal fentanyl or oxycodone CR with that for morphine SR.

Methods—We conducted a retrospective cohort study in 50,658 patients enrolled in Tennessee Medicaid who filled prescriptions for transdermal fentanyl (n=8,717), oxycodone CR (n=14,118), or morphine SR (n=27,823) between 1999 and 2011. We excluded individuals with cancer or other life-threatening diagnoses and used propensity scores to adjust for multiple potential confounders. The primary outcome was out-of-hospital mortality.

Results—During 44,385 person-years of follow-up, 689 patients died. The out-of-hospital mortality rate among all study subjects was 155/10,000 patient-years. Contrary to earlier data suggesting greater risk, mortality was not significantly different in patients filling prescriptions for transdermal fentanyl compared to morphine SR (adjusted HR=0.96, 95% C.I.: 0.77–1.21); moreover, patients filling prescriptions for oxycodone CR had lower mortality risk compared to those filling prescriptions for morphine SR (adjusted HR=0.79, 95% C.I. 0.66–0.95).

Conclusion—In the study population, long-acting opioids for non-cancer pain were associated with high out-of-hospital mortality rates. We found comparable out-of-hospital mortality risks associated with transdermal fentanyl and morphine SR. The risk of out-of-hospital death for oxycodone CR was lower than that for morphine SR.

Keywords

opioids; morphine; oxycodone; fentanyl; mortality

The increased use of opioid analgesic drugs has been accompanied by a corresponding increase in the number of deaths and hospitalizations attributed to opioid toxicity in the U.S.

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^{1,2} Between 1999 and 2008, opioid sales, opioid-related death rates, and hospitalization for opioid toxicity tripled;³ despite growing awareness, recent reports by the Centers for Disease Control and Prevention (CDC) indicate that opioid-related death rates remain high.⁴ In the U.S., opioid overdoses account for at least 16,000 deaths annually,⁵ and for every death attributed to opioid toxicity, there are approximately 10 hospital admissions.⁶ In 2011, the Drug Abuse Warning Network reported 20,034 and 151,218 visits to U.S. emergency rooms involving fentanyl and oxycodone products, respectively.⁷ Medical personnel have raised similar concerns regarding increasing use and potential toxicity of opioids in Europe and Canada.^{8,9}

Despite these trends, prescriptions for long-acting opioids treating chronic non-cancer pain have continued to increase over the past two decades.^{10,11} Amidst larger concerns about opioid safety, scholars and government institutions have issued alerts and recommendations regarding two opioids with specific administration—transdermal fentanyl and oxycodone CR—indicating that these drugs may pose greater risks for toxicity compared to more established long-acting opioids, such as morphine SR.^{7,12} the preferred long-acting opioid for severe pain by U.S. practitioners¹³ and a prototypical mu opioid agonist.¹⁴

Risks for overdose among transdermal fentanyl users most plausibly are related to its route of administration and pharmacodynamics, which produce significant inter-individual variability. Factors such as body surface area and temperature can influence the clearance and variability of transdermal absorption of fentanyl.^{15,16} Furthermore, fentanyl is one hundred times more potent than morphine, and the transdermal patches release the drug for two to three days, with variable bioavailability.¹⁶

Ecological studies have raised questions regarding the safety of oxycodone CR. After a Canadian province added long-acting oxycodone to formularies, an initial report found markedly increased opioid-related mortality.¹² Follow-up reports showed a 264% increased risk of drug overdose deaths attributed to oxycodone between 2003 and 2009.¹⁷ Another study found that the risk of death for oxycodone users was more than twice that of comparable hydrocodone users.¹⁸ However, it is not clear whether or not these findings reflect a secular trend of increasing prescriptions or if they are due to differences in relative opioid doses.

Despite these concerns about the safety of transdermal fentanyl and oxycodone CR, we are unaware of direct comparisons of these drugs with other long-acting opioids in patients with non-cancer pain. Indeed, a panel of experts has called for more research on the comparative benefits and harms of different opioids.¹⁹ Thus, we conducted a retrospective cohort study to compare the relative mortality in users of transdermal fentanyl and oxycodone CR with that for morphine SR.

Patients and Methods

This retrospective cohort study included persons aged 30 to 74 years who filled prescriptions for transdermal fentanyl, oxycodone CR, or morphine SR between 1/1/1999 and 12/31/2011.

The Vanderbilt University institutional review board approved the study and waived the need for informed consent.

Cohort

We used data from Tennessee Medicaid (TennCare) to assemble the study cohort. TennCare is an expanded version of the joint federal-state Medicaid program that finances medical care for qualifying low-income persons.^{20,21} The TennCare data are contained in several different files, including the enrollment file, medical encounters, filled prescriptions, inpatient admissions, outpatient visits, and other types of care. A unique recipient number identifies enrollees in all files. TennCare files are linked to other state databases, including that of computerized death certificates and an “all payers” hospital discharge database.²¹

Patients entered the cohort on the date of filling their first prescription for transdermal fentanyl, oxycodone CR, or morphine SR. To improve the study capacity to identify deaths related to opioids and thus reduce the potential for confounding, we aimed to study out-of-hospital deaths in patients in whom such deaths should be infrequent otherwise. Therefore, to decrease the likelihood of deaths related to terminal illness, the cohort excluded patients 75 years of age or older, those with cancer and other life-threatening diseases, and nursing home residents. Patients in the hospital could not enter the cohort until 30 days after discharge, because deaths during this period could be related to reasons related to the hospitalization. We excluded persons with recorded evidence of substance abuse, given the increased risk for drug overdose unrelated to therapeutic use.

Use of opioid and dose equivalences

We studied the long-acting opioid analgesics transdermal fentanyl and oxycodone CR with morphine SR as the comparator. We excluded patients taking methadone or buprenorphine, which are often markers for substance abuse disorder treatment. Our calculations for opioid dose-equivalences were based upon a previously published study of chronic opioid therapy for non-cancer pain in adults.²²

Opioid indication

We assigned a single indication (the probable reason for which the opioid was prescribed) for each prescription. We used an algorithm that prioritized temporal proximity to the prescription fill date, type of medical care (primary over secondary diagnoses), and the specific indication in the following order: back pain, other musculoskeletal/soft tissue pain, abdominal pain, headache, other neurological pain, infection, trauma, dental procedures, and other procedures.

Follow-up

Patients entered the cohort on the date of filling their first prescription for transdermal fentanyl, oxycodone CR, or morphine SR. Follow-up ended on the first of the following dates: (1) the end of the study—12/31/2011; (2) last day of Medicaid enrollment or transition to a category without full pharmacy benefits; (3) failure to meet the study inclusion criteria; (4) day of death; or (5) meeting the exclusion criteria, as listed above. We

excluded person-time during the 30 days following hospitalization to reduce the likelihood of including deaths unrelated to the use of opioids.

End-points

The primary study endpoint was death occurring outside of hospital during study follow-up.

These deaths were further classified as: (1) unintentional opioid toxicity deaths—the definition of which has a positive predictive value (PPV) of >90%,²³ and (2) other deaths—defined as death not attributed to the use of opioids.

Statistical analysis

We used proportional hazard regression models to estimate the hazard ratios (HR) for transdermal fentanyl and oxycodone SR use compared to morphine SR use. The HRs were adjusted for potential differences among the groups using propensity scores that included 145 covariates such as demographic variables, calendar time, opioid indication, use of other opioids, cardiovascular medications and diagnoses, psychiatric medications and diagnoses, respiratory conditions, musculoskeletal diseases, indicators of frailty, other comorbidities, and medical care utilization (Appendix, table 1). Because concurrent use of benzodiazepines is associated with a higher risk of overdose death, we included this variable in the propensity scores. We estimated two different propensity scores (one for fentanyl and one for oxycodone) using morphine SR as reference. The first one calculated the probability of assignment to transdermal fentanyl, and the second one calculated the probability of assignment to oxycodone SR given the same set of 145 covariates. To assess the performance of the propensity scores, we compared the distribution of the study variables after inverse probability of treatment weighting (Appendix tables 2–5). To avoid the inclusion of patients whose treatment was effectively predetermined, we trimmed subjects whose propensity scores were less than the 1st or greater than the 99th percentiles.

To adjust for potential confounders, we used stratified proportional hazard models with the strata defined by propensity score deciles. These models included drug exposure as time-dependent covariates; eight models included study opioid dose (in estimated morphine equivalent mg/d) as an additional covariate. To assess for robustness of the results, we performed three sensitivity analyses. First, we calculated hazard ratios for propensity score-matched observations. Second, we conducted analyses restricted to 365 days of follow-up. Third, to examine whether drug abuse affected the relationship between the study drugs and mortality differentially, we conducted a sensitivity analysis in which follow-up was not censored for codes indicating substance abuse. All analyses were completed using STATA 13.1 (StataCorp LP, College Station, TX). All p-values are two sided.

Results

Of 50,658 patients who filled prescriptions for long-acting opioids for non-cancer pain, 8,717 filled a prescription for transdermal fentanyl, 14,118 for oxycodone CR, and 27,823 for morphine SR. Patients were predominantly female and Caucasian. The majority were disabled; back pain and other musculoskeletal conditions were the most common indications for prescription of long-acting opioids. Although the calculated median daily dose for

oxycodone CR patients was greater than that for morphine SR (120 mg vs 90 mg), demographic characteristics, comorbidities, and use of other medications were distributed similarly among the three study groups. The three groups also had similar rates of medical care utilization measured as hospital stay in the previous year and emergency room and inpatient encounters due to overdose in the previous year (Table 1).

There were 689 out-of-hospital deaths during 44,385 person-years of follow-up, and the all-cause mortality rate was 155 per 10,000 patient-years. Table 2 presents the risk of death during current use of transdermal fentanyl and morphine SR, by type of death. Unadjusted mortality rates were similar in both groups and the propensity score-adjusted all-cause mortality was not significantly different in patients using transdermal fentanyl (aHR=0.96, 95% C.I.: 0.77–1.21) compared to those receiving morphine SR.

Table 3 presents the risk of death during current use of oxycodone CR and morphine SR, by type of death. Unadjusted mortality rates were higher in patients filling prescriptions for morphine SR and the propensity score-adjusted all-cause mortality was 21% lower in patients filling oxycodone CR (aHR=0.79, 95% C.I. 0.66–0.95) than in those filling prescriptions for morphine SR.

We found no significant differences in the risk of death from non-opioid related causes among fentanyl and morphine SR users (aHR=1.09, 95% C.I. = 0.85–1.41) (Table 2) or among those taking oxycodone or morphine SR (aHR=0.89, 95% C.I. = 0.72–1.10) (Table 3).

Sensitivity analyses that included propensity score-matched cohorts and restriction to the first 365 days of observation gave similar results (Table 4). An analysis restricting the outcome to deaths from unintentional opioid toxicity/overdose also showed lower risk in patients using oxycodone CR (aHR=0.60, 95% C.I. = 0.38–0.94) compared to morphine SR.

Similar results were obtained when analyses were restricted to the first year of drug exposure and the mortality rates were very similar in a sensitivity analysis in which follow-up did not end due to codes indicating addiction. (Appendix Table 6).

As a check on the dose-equivalents for study opioids, two models did not include opioid doses (Tables 2 and 3). In these analyses, the HRs for oxycodone remained less than one but they were no longer statistically significant.

Discussion

Our study generated three main findings: 1) the use of long-acting opioids in study patients with non-cancer pain was associated with high rates of out-of-hospital mortality; this rate contrasts with the out-of-hospital death rate of 108/10,000 person-years in a cohort of similar patients with non-cancer chronic pain and similar demographic characteristics that filled prescriptions for analgesic anticonvulsants or low-dose cyclic antidepressants;²⁴ 2) there was no increased mortality risk associated with prescriptions of transdermal fentanyl or oxycodone CR compared to morphine SR; 3) there was a small, but statistically significant,

decreased risk of out-of-hospital death in patients prescribed oxycodone CR compared to morphine SR.

Our first finding is consistent with other studies that have documented high mortality rates associated with opioid use. A cohort study in Denmark on patients filling prescriptions for opioids for long-term use reported an all-cause mortality rate of 320/10,000 person-years.²⁵ Similarly, a study in patients from the Department of Veterans Affairs (VA) receiving prescriptions for methadone and long-acting morphine reported mortality rates between 200 and 1,300 per 10,000 person-years (although this study did not exclude patients with cancer or deaths that occurred in hospital).²⁶

Our second finding was surprising. In contrast to our hypothesis, out-of-hospital mortality rates associated with the use of transdermal fentanyl and oxycodone CR were not higher than those in patients using morphine SR. One explanation may be that our study focused on the mortality risk associated with therapeutic use by excluding patients with previous evidence of substance abuse, whereas in other ecologic studies, a significant number of deaths attributed to fentanyl and oxycodone CR use are related to abuse (rather than therapeutic use).²⁷ Alternately, this finding may indicate that dose—rather than other pharmacologic variables—may be the main determinant of opioid toxicity; equivalent doses of either fentanyl or morphine confer similar risks.

Our third finding was that patients prescribed long-acting oxycodone had lower mortality rates than those prescribed morphine SR. Although these results coincided with those reported in a smaller study in Oregon,²⁸ we observed a smaller difference between the two mortality rates. This finding could reflect better safety for oxycodone CR; however, other reasons should be considered. Pharmacokinetic differences between the study drugs potentially could explain the reduced risk of death for oxycodone. The accumulation of the active metabolites of morphine in patients with renal impairment, particular M6G, could increase the risk of morphine toxicity.²⁹ Although this would suggest risk should also be lower with fentanyl, it could have continued to be delivered even when the patient became sedated, unless the patch was removed, thus increasing risk by another mechanism. However, the fact that oxycodone and its metabolites also accumulate in patients with renal impairment³⁰ argues against this explanation.

Another potential explanation relates to the accuracy of widely accepted conversion factors for opioid doses that equate 20mg of oxycodone to 30mg of morphine. In the study cohort, the median prescribed dose for oxycodone CR was 80 mg/day, which equates to 120 mg morphine-equivalents, which was greater than the 90 mg/day for morphine SR. Only after statistically adjusting for this higher dose of oxycodone did the mortality difference between the two opioids become significant.

The rates of opioid diversion may have differed among the three study opioids, resulting in differential exposure misclassification. Although we sought to reduce such misclassification by excluding patients with any recorded evidence of drug abuse, some diversion of opioids may have occurred. Given the study data, it was not possible to estimate the extent of such diversion.

Three important concerns pertinent to all pharmacoepidemiologic studies should be considered: misclassification, confounding, and power. We excluded patients with potentially terminal conditions and those with a history of drug abuse to minimize the risk of misclassification resulting from deaths unrelated to the therapeutic use of opioids. We took several steps to minimize potential confounding. First, we performed a careful selection of an extensive number of potential covariates. Second, we used propensity scores for adjustments.³¹ Third, we performed sensitivity analyses including propensity score matched results and analyses restricted to the first 365 days of observation; all yielded similar results. Fourth, we conducted an analysis of the risk of death classified as “other deaths,” for which, as expected, there were no statistical differences between the three opioids. Nevertheless, residual confounding is possible. To address power concerns, the study included a large defined population followed for several years.

There were several other potential limitations. The study was restricted to patients enrolled in the TennCare program, and Tennessee is among the states with the highest rates of opioid prescriptions in the U.S.³² Thus, the findings may not be generalizable to other populations. We restricted the study to three long-acting opioids commonly prescribed in routine clinical practice, but whose relative safety has been questioned; therefore, the findings may not be generalizable to short-acting forms of these opioids. We did not directly compare oxycodone and fentanyl because the a priori protocol specified comparisons of fentanyl and oxycodone with morphine, the most commonly prescribed long-acting opioid for non-cancer pain. Oxycodone is metabolized by both CYP3A4 and CYP2D6. Although the propensity score did not include a variable for concurrent use of CYP2D6 inhibitors, it did include indicators of current use of the antidepressants fluoxetine and paroxetine, the most commonly prescribed 2D6 inhibitors in the study population. We did account for use of short-acting opioids, but did not include their doses in the propensity score because these drugs, when used with long-acting opioids, often are taken as needed for breakthrough pain. Finally, while we sought to exclude patients filling prescriptions for methadone, it is possible that some could have received it through the Medication-Assisted Treatment program for opioid dependence disorder. Further, we could not estimate rates of drug diversion; thus we cannot exclude differential rates on drug diversion among study drug users. However, by excluding patients and person-time with recorded evidence of substance abuse, we decreased the likelihood of this source of misclassification.

In conclusion, a cohort of patients with no evidence of life-threatening illness and non-cancer pain treated with long-acting opioids had high rates of out-of-hospital mortality. We did not find evidence that the risk of out-of-hospital death associated with transdermal fentanyl or oxycodone CR was higher than that for morphine SR. There was a statistically significant, but small decrease in the risk of out-of-hospital mortality in patients who filled a prescription for oxycodone CR compared to those who filled a prescription for morphine SR.

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Table 1

Baseline characteristics of the cohort

	Fentanyl	Oxycodone CR	Morphine SR
Cohort members, N	8,717	14,118	27,823
Study opioid prescriptions during follow-up, N	103,485	228,408	338,928
Year of prescription, median (IQR)	2004 ('03-'05)	2004 ('02-'05)	2005 ('03-'07)
Age, years, median (IQR)	50 (42–58)	48 (42–56)	48 (42–55)
Female	67.7%	53.9%	59.6%
White	85.3%	85.7%	84.6%
Medicaid enrollment disabled	67.9%	70.7%	68.8%
<i>Study opioid prescription characteristics</i>			
Opioid indication			
Back pain	76.5%	78.2%	80.7%
Other musculoskeletal pain	12.9%	11.8%	10.7%
Other pain: soft tissue, abdominal, or neurologic	1.8%	1.4%	1.3%
Acute pain related to medical/dental procedure, trauma, or infection	2.8%	2.9%	2.4%
No indication recorded	6.1%	5.7%	4.9%
Dose per day (morphine-equivalents), mg, median (IQR)	100 (50–150)	120 (60–180)	90 (50–120)
Non-study opioids, current use	77.7%	71.3%	73.4%
<i>Psychotropic medications</i>			
Benzodiazepine	42.7%	45.3%	35.3%
Cyclic antidepressant	10.3%	9.0%	9.6%
SSRI or other antidepressant	39.7%	29.5%	30.7%
Antipsychotic, %	9.0%	5.6%	7.6%
<i>Cardiovascular medications</i>			
Digoxin	3.1%	2.7%	2.0%
Loop diuretic	26.7%	22.2%	20.9%
Insulin	10.1%	8.2%	8.6%
Oral hypoglycemic	17.7%	16.8%	15.8%
<i>Musculoskeletal medications</i>			
NSAID/coxib	24.1%	22.3%	21.3%
Musculoskeletal relaxant	35.2%	35.8%	36.0%
Corticosteroid, systemic	2.5%	2.1%	2.1%
<i>Respiratory medications and diagnoses</i>			
Beta agonist	10.7%	11.0%	10.5%
Other bronchodilator	4.4%	4.1%	3.9%
COPD	24.5%	21.8%	23.0%
Asthma	11.1%	10.3%	10.9%
Home oxygen	9.7%	7.4%	9.1%
<i>Medical care utilization</i>			

	Fentanyl	Oxycodone CR	Morphine SR
Hospital stay past year	17.2%	15.0%	14.2%
Overdose ED/inpatient past year	4.8%	3.1%	3.2%

IQR= interquartile range

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Table 2

Risk of death during current use of transdermal fentanyl and morphine SR, by type of death. HR denotes hazard ratio, CI denotes 95% confidence interval

	Fentanyl (5,957 person-yrs)	Morphine SR (22,686 person-yrs)	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	Adjusted HR** (95% CI)
Rate/10,000 person-yrs (N deaths)					
All deaths	169.5 (101)	160.5 (364)	1.04 (0.84–1.30)	1.01 (0.81–1.27)	0.96 (0.77–1.21)
Unintentional opioid overdose	25.2 (15)	33.9 (77)	0.72 (0.42–1.24)	0.81 (0.47–1.41)	0.77 (0.44–1.34)
Other deaths	141.0 (84)	115.0 (261)	1.20 (0.94–1.53)	1.15 (0.89–1.47)	1.09 (0.85–1.41)

* Adjusted for propensity scores (by deciles)

** Adjusted for propensity scores (by deciles) and morphine equivalent dose

Table 3

Risk of death during current use of oxycodone CR and morphine SR, by type of death. HR denotes hazard ratio, CI denotes 95% confidence interval

	Oxycodone CR (14,423 person-yrs) <i>Rate/10,000 person-yrs (N deaths)</i>	Morphine SR (22,686 person-yrs)	<i>Unadjusted HR (95% CI)</i>	<i>Adjusted HR* (95% CI)</i>	<i>Adjusted HR** (95% CI)</i>
All deaths	135.9 (196)	160.5 (364)	0.88 (0.84–1.30)	0.88 (0.73–1.05)	0.79 (0.66–0.95)
Unintentional opioid overdose	20.8 (30)	33.9 (77)	0.62 (0.41–0.94)	0.71 (0.46–1.10)	0.60 (0.38–0.94)
Other deaths	109.5 (158)	115.0 (261)	0.99 (0.81–1.20)	0.98 (0.80–1.20)	0.89 (0.72–1.10)

* Adjusted for propensity scores (by deciles)

** Adjusted for propensity scores (by deciles) and morphine equivalent dose

Table 4

Sensitivity analyses

	Fentanyl vs Morphine SR		Oxycodone SR vs Morphine SR	
	HR	95% CI	HR	95% CI
All deaths				
Propensity score matched	1.04	0.84–1.30	0.70	0.41–1.19
Restricted to first year *	1.19	0.92–1.53	0.77	0.61–0.98
Restricted to first year **	1.10	0.85–1.42	0.68	0.54–0.87
Opioid related deaths				
Propensity score matched	0.71	0.41–1.21	0.63	0.42–0.94
Restricted to first year *	0.95	0.52–1.76	0.67	0.38–1.17
Restricted to first year **	0.86	0.47–1.59	0.53	0.30–0.94
Other deaths				
Propensity score matched	1.20	0.94–1.53	0.99	0.81–1.20
Restricted to first year *	1.34	1.01–1.79	0.84	0.64–1.10
Restricted to first year **	1.25	0.94–1.67	0.76	0.57–1.00

* Adjusted for propensity scores (by deciles)

** Adjusted for propensity scores (by deciles) and morphine equivalent dose

Appendix Table 1

List of variables in the propensity score.

1. Age_at_t0
2. Sex
3. Race
4. Calendar year
5. Calendar month
6. Enrolled: aged
7. Uninsured
8. Enrolled: disabled
9. SMSA
10. Use of concurrent CYP3A4 inhibitor
11. Use of ACE inhibitor
12. Use of ARB
13. Use of anticoagulants
14. Use of antiarrhythmics
15. Use of aspirin
16. Use of beta-blockers
17. Use of calcium channel blockers
18. Use of loop diuretics
19. Use of other diuretics
20. Use of insulin
21. Use of oral hypoglycemic drugs
22. Use of statins
23. Use of fibrates
24. Use of nitrates
25. Use of other antihypertensives
26. Use of drugs for peripheral vascular disease
27. Use of other platelet inhibitors
28. New prescription for cardiovascular drugs
29. Angina
30. Revascularization/acute myocardial infarction
31. Oth_CHD
32. Mitral valve disease
33. Other_valve disease
34. Atrial fibrillation
35. Other_arrhythmia
36. CHF
37. CVA
38. TIA

39. Other cerebrovascular disease
40. Peripheral vascular disease
41. Diabetes
42. Severe diabetes
43. Hypertension
44. Malignant hypertension
45. Hyperlipidemia
46. DVT/PE
47. Chronic renal disease
48. Other renal disease
49. Other cardiovascular disease
50. Obesity
51. Morbid obesity
52. Smoking
53. New CV diagnosis
54. Schizophrenia
55. Bipolar disorder
56. Major depression
57. Other mood disorder
58. OCD/ADHD
59. Sleep disorder
60. Panic disorder
61. Anxiety
62. Personality disorder
63. Stress adjustment
64. Alcohol
65. Somatic disorder
66. Organic sex disorder
67. Other psychiatric disorder
68. Psychiatric symptoms
69. Self-injury
70. Current use of tricyclics
71. New use of tricyclics
72. Chronic use of tricyclics
73. Current use of SSRIs
74. New use of SSRIs
75. Chronic use of SSRIs
76. Current use of other antidepressants
77. New use of other antidepressants
78. Chronic use of other antidepressants

79. Current use of antipsychotics
80. Chronic use of antipsychotics
81. New use of antipsychotics
82. Current use of benzodiazepines
83. Chronic use of benzodiazepines
84. New use of benzodiazepines
85. Use of other gaba-agonists
86. Hydroxyzine
87. Any anxiolytic
88. Medications for OCD/ADHD
89. Current mood stabilizer
90. Chronic mood stabilizer
91. New mood stabilizer
92. Seizure
93. Migraine
94. Parkinson/movement disorder
95. Anticonvulsants
96. Gabapentin
97. Current use of antiparkinson drugs
98. Autoimmune diseases
99. Inflammatory arthropathies
100. Osteoarthritis
101. Injury unintentional
102. Injury, intentional
103. Current use of DMARD
104. Current use of corticosteroids
105. Muscle relaxants
106. NSAIDs
107. Other non-narcotic pain medications
108. Other_sd_rx
109. Beta_agonist
110. Other bronchodilators
111. Estrogen
112. GI drugs
113. Any oral contraceptives
114. Antibiotics
115. Inpatient CV hospitalization
116. CV inpatient hospitalization, number of days
117. Other inpatient hospitalization

118. Other inpatient hospitalization, number of days
119. Injury, inpatient
120. Injury, ED visit
121. Poison, ED visit or hospitalization
122. Injury,_outpatient
123. Poison, outpatient
124. Any hospitalization
125. Unintentional fall
126. Wheelchair
127. Incontinence, any
128. Malnutrition
129. COPD
130. Asthma
131. Pneumonia
132. Other respiratory infections
133. Use of CPAP
134. Home O2
135. Delirium
136. Opioid indication
137. Any injury
138. Any poisoning
139. Non-study opioid use in prior year (days of supply)
140. Non-study opioid use prior month (days of supply)
141. Non-study opioid use prior, month (remaining days of supply)
142. Nonstudy opioid prior yr high dose
143. Nonstudy opioid prior month, high dose
144. Nonstudy opioid prior month remaining high dose
145. Nonstudy_opioid prior_month high

Appendix Table 2

Propensity-score-matched cohort characteristics Fentanyl vs Morphine SR.

	Fentanyl n=102,089	Morphine SR n=102,089
Age, years, median (inter-quartile range)	48 (41–56)	48 (42–55)
Female	67.4%	67.0%
White	85.3%	85.3%
Medicaid enrollment disabled	68.1%	68.0%
Study opioid prescription characteristics		
Opioid indication		
Back pain	76.8%	76.8%
Other musculoskeletal pain	12.8%	12.7%
Other chronic pain: soft tissue, abdominal, or neurologic	1.7%	1.7%
Acute pain related to medical/dental procedure, trauma, or infection	2.7%	2.8%
No indication recorded	6.0%	5.9%
Non-study opioids, current use	77.6%	77.6%
Psychotropic medications		
Benzodiazepine	42.6%	42.5%
Cyclic antidepressant	10.3%	10.3%
SSRI	39.4%	39.4%
Antipsychotic	10.1%	10.2%
Cardiovascular medications		
Digoxin	3.0%	2.8%
Loop diuretic	26.3%	26.1%
Insulin	10.0%	10.1%
Oral hypoglycemic	17.6%	17.5%
Musculoskeletal medications		
NSAID/coxib	63.0%	63.3%
Musculoskeletal relaxant	64.3%	63.7%
Corticosteroid, systemic	2.5%	2.5%
Respiratory medications and diagnoses		
Beta agonist	10.7%	10.4%
Other bronchodilator	4.3%	4.2%
COPD	24.3%	24.0%
Asthma	11.1%	11.1%
Home oxygen	9.5%	9.4%
Medical care utilization		
Hospital stay past year	17.0%	17.0%
Overdose ED/inpatient past year	4.6%	4.6%

Appendix Table 3

Propensity-score-matched cohort characteristics: Oxycodone vs Morphine SR

	Oxycodone(n=203,819)	Morphine SR (n=203,819)
Age, years, median (inter-quartile range)	48 (42–56)	48 (42–55)
Female	55.1%	55.4%
White	85.6%	85.7%
Medicaid enrollment disabled	70.1%	69.8%
Study opioid prescription characteristics		
Opioid indication		
Back pain	79%	79.1%
Other musculoskeletal pain	11.6%	11.5%
Other chronic pain: soft tissue, abdominal, or neurologic	1.4%	1.4%
Acute pain related to medical/dental procedure, trauma, or infection	2.7%	2.7%
No indication recorded	5.3%	5.3%
Non-study opioids, current use	71.3%	71.9%
Psychotropic medications		
Benzodiazepine	43.3%	43.3%
Cyclic antidepressant	4.9%	5.0%
SSRI	30.2%	30.3%
Antipsychotic	6.1%	6.1%
Cardiovascular medications		
Digoxin	2.5%	2.3%
Loop diuretic	22.1%	22.2%
Insulin	8.2%	8.3%
Oral hypoglycemic	16.4%	16.4%
Musculoskeletal medications		
NSAID/coxib	22.6%	22.1%
Musculoskeletal relaxant	36.1%	36.0%
Corticosteroid, systemic	2.1%	2.2%
Respiratory medications and diagnoses		
Beta agonist	2.2%	2.4%
Other bronchodilator	4.1%	4.1%
COPD	22.1%	22.2%
Asthma	10.4%	10.5%
Home oxygen	7.7%	7.8%
Medical care utilization		
Hospital stay past year	14.8%	14.8%
Overdose ED/inpatient past year	3.1%	3.1%

Appendix Table 4

Inversed probability weighted cohort characteristics Fentanyl vs Morphine SR.

	Fentanyl(n=103,485)	Morphine SR (n=338,928)
Age, years, median (inter-quartile range)		
Female	61.6%	61.5%
White	84.8%	84.8%
Medicaid enrollment disabled	68.5%	68.6%
Study opioid prescription characteristics		
Opioid indication		
Back pain	79.6%	79.7%
Other musculoskeletal pain	11.2%	11.2%
Other chronic pain: soft tissue, abdominal, or neurologic	1.5%	1.5%
Acute pain related to medical/dental procedure, trauma, or infection	2.5%	2.5%
No indication recorded	5.2%	5.2%
Non-study opioids, current use	74.7%	74.5%
Psychotropic medications		
Benzodiazepine	37.1%	37.0%
Cyclic antidepressant	9.6%	9.8%
SSRI	33.1%	32.8%
Antipsychotic	7.7%	7.9%
Cardiovascular medications		
Digoxin		
Loop diuretic	22.2%	22.2%
Insulin	9.0%	9.0%
Oral hypoglycemic	15.9%	16.2%
Musculoskeletal medications		
NSAID/coxib	21.6%	21.9%
Musculoskeletal relaxant	35.3%	36.0%
Corticosteroid, systemic	2.1%	2.2%
Respiratory medications and diagnoses		
Beta agonist	10.3%	10.5%
Other bronchodilator	4.1%	4.0%
COPD	22.8%	23.3%
Asthma	10.7%	10.9%
Home oxygen	8.8%	9.2%
Medical care utilization		
Hospital stay past year	15.0%	14.9%
Overdose ED/inpatient past year	3.7%	3.6%

Appendix Table 5

Inversed probability weighted cohort characteristics: Oxycodone vs Morphine SR

	Oxycodone SR (n=228,408)	Morphine SR (n=338,928)
Age, years, median (inter-quartile range)		
Female	57.6%	57.4%
White	85.4%	85.1%
Medicaid enrollment disabled	69.6%	69.6%
Study opioid prescription characteristics		
Opioid indication		
Back pain	79.9%	79.6%
Other musculoskeletal pain	11.1%	11.2%
Other chronic pain: soft tissue, abdominal, or neurologic	1.4%	1.4%
Acute pain related to medical/dental procedure, trauma, or infection	2.6%	2.6%
No indication recorded	5.1%	5.2%
Non-study opioids, current use	72.6%	72.7%
Psychotropic medications		
Benzodiazepine	37.1%	37.0%
Cyclic antidepressant	9.5%	9.4%
SSRI	30.0%	30.2%
Antipsychotic	6.7%	6.8%
Cardiovascular medications		
Digoxin		
Loop diuretic	21.9%	21.6%
Insulin	8.3%	8.4%
Oral hypoglycemic	15.9%	16.2%
Musculoskeletal medications		
NSAID/coxib	22.2%	21.4%
Musculoskeletal relaxant	35.8%	35.8%
Corticosteroid, systemic	2.1%	2.1%
Respiratory medications and diagnoses		
Beta agonist	10.8%	10.7%
Other bronchodilator	4.1%	4.0%
COPD	22.6%	22.5%
Asthma	10.6%	10.6%
Home oxygen	8.5%	8.5%
Medical care utilization		
Hospital stay past year	14.6%	14.5%
Overdose ED/inpatient past year	3.2%	3.2%

Appendix Table 6

Mortality rates among patients filling prescriptions for fentanyl, oxycodone CR and morphine SR. Sensitivity analysis with follow-up not censored for drug addiction/abuse

	Fentanyl (6,051 person-yrs)	Oxycodone CR (14,823 person-yrs)	Morphine SR (24,534 person-yrs)
All deaths	103	200	407
Rate (deaths/10,000 person years)	170.2	134.9	165.9