

## Original Investigation

# Rates of Opioid Dispensing and Overdose After Introduction of Abuse-Deterrent Extended-Release Oxycodone and Withdrawal of Propoxyphene

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**IMPORTANCE** In the second half of 2010, abuse-deterrent extended-release oxycodone hydrochloride (OxyContin; Purdue Pharma) was introduced and propoxyphene was withdrawn from the US market. The effect of these pharmaceutical market changes on opioid dispensing and overdose rates is unknown.

**OBJECTIVE** To evaluate the association between 2 temporally proximate changes in the opioid market and opioid dispensing and overdose rates.

**DESIGN, SETTING, AND PARTICIPANTS** Claims from a large national US health insurer were analyzed, using an interrupted time series study design. Participants included an open cohort of 31.3 million commercially insured members aged 18 to 64 years between January 1, 2003, and December 31, 2012, with median follow-up of 20 months (last follow-up, December 31, 2012).

**EXPOSURES** Introduction of abuse-deterrent OxyContin (resistant to crushing or dissolving) on August 9, 2010, and market withdrawal of propoxyphene on November 19, 2010.

**MAIN OUTCOMES AND MEASURES** Standardized opioid dispensing rates and prescription opioid and heroin overdose rates were the primary outcomes. We used segmented regression to analyze changes in outcomes from 30 quarters before to 8 quarters after the 2 interventions.

**RESULTS** Two years after the opioid market changes, total opioid dispensing decreased by 19% from the expected rate (absolute change, -32.2 mg morphine-equivalent dose per member per quarter [95% CI, -38.1 to -26.3]). By opioid subtype, the absolute change in dispensing by milligrams of morphine-equivalent dose per member per quarter at 2 years was -11.3 (95% CI, -12.4 to -10.1) for extended-release oxycodone, 3.26 (95% CI, 1.40 to 5.12) for other long-acting opioids, -8.19 (95% CI, -9.30 to -7.08) for propoxyphene, and -16.2 (95% CI, -18.8 to -13.5) for other immediate-release opioids. Two years after the market changes, the estimated overdose rate attributed to prescription opioids decreased by 20% (absolute change, -1.10 per 100 000 members per quarter [95% CI, -1.47 to -0.74]), but heroin overdose increased by 23% (absolute change, 0.26 per 100 000 members per quarter [95% CI, -0.01 to 0.53]).

**CONCLUSIONS AND RELEVANCE** Opioid dispensing and prescription opioid overdoses decreased substantially after 2 major changes in the pharmaceutical market in late 2010. Pharmaceutical market interventions may have value in combatting the prescription opioid overdose epidemic, but heroin overdose rates continue to increase. Complementary strategies to identify and treat opioid abuse and addiction are urgently needed.

*JAMA Intern Med.* doi:10.1001/jamainternmed.2015.0914  
Published online April 20, 2015.

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Prescription opioid overdose deaths quadrupled in parallel with prescription opioid sales in the United States between 1999 and 2010.<sup>1,2</sup> A strong spatial association has also been demonstrated between prescription opioid supply and prescription opioid overdose mortality at the state level.<sup>3</sup> Such associations suggest that supply-based interventions could effectively combat the opioid overdose epidemic. However, some experts<sup>4,5</sup> have hypothesized that reduced prescription opioid supplies may lead individuals already addicted to opioids to substitute alternative prescription opioids or heroin. Two different changes in the pharmaceutical market occurred in late 2010: introduction of abuse-deterrent OxyContin and withdrawal of propoxyphene (both the napsylate and hydrochloride formulations).

Abuse-deterrent opioid formulations with physical or pharmacologic deterrents to tampering have been proposed<sup>6,7</sup> as part of a comprehensive strategy to combat opioid misuse, abuse, and overdose. OxyContin, an extended-release formulation of oxycodone hydrochloride containing higher doses than immediate-release oxycodone, was introduced in 1995 and soon became a drug of choice among individuals with substance use disorders.<sup>8</sup> Although one could abuse extended-release oxycodone by swallowing as intended a whole tablet, crushing the tablets and then ingesting, snorting, or injecting them was a simple mechanism used to bypass the extended-release mechanism and attain a quicker, more intense “high.” An abuse-deterrent OxyContin formulation resistant to crushing and dissolving was introduced on August 9, 2010.

Propoxyphene was approved by the US Food and Drug Administration in 1957 for treatment of pain; however, it was demonstrated to be a weak opioid agonist with efficacy comparable to that of aspirin.<sup>9</sup> Reports of propoxyphene abuse were noted soon after its introduction<sup>10</sup>; by 1977, it was the second leading agent in prescription drug-induced deaths.<sup>11</sup> In 2010, 8% of US residents older than 12 years reported lifetime nonmedical use of codeine or propoxyphene—a percentage second only to that of hydrocodone bitartrate.<sup>12</sup> On a per-prescription basis, propoxyphene was shown<sup>13</sup> to have higher rates of overdose deaths compared with tramadol hydrochloride and codeine phosphate, other weak opioid agonists. In response to emerging data about cardiac toxic effects, propoxyphene was voluntarily withdrawn from the US market on November 19, 2010.<sup>14</sup>

Numerous studies have investigated the impact of abuse-deterrent OxyContin demonstrating decreased prescribing of extended-release oxycodone,<sup>15-18</sup> a decrease in abuse or overdose specific to extended-release oxycodone,<sup>16,17,19-22</sup> and a possible increase in the abuse of alternative prescription opioids<sup>16,21-23</sup> or heroin.<sup>16,23</sup> We are not aware of studies considering the effect of propoxyphene withdrawal or the potential effect of these co-occurring interventions on total prescription opioid supply and overdose. Our objective for the present study was to assess the association of these 2 supply-based interventions on prescription opioid dispensing and overdose.

## Methods

### Study Design and Data Source

We used an interrupted time series design to assess the impact of 2 pharmaceutical market interventions—introduction of abuse-deterrent OxyContin in August 2010 and withdrawal of propoxyphene in November 2010—in a cohort of commercially insured patients from January 1, 2003, through December 31, 2012; the final follow-up was December 31, 2012. We used the Optum data, which contains all inpatient, outpatient, and pharmacy claims from a large US health insurer with members in all 50 states. All members had prescription drug coverage and all pharmacy claims are captured. We obtained approval for the study through the Harvard Pilgrim Health Care institutional review board. Waiver of informed consent was granted based on use of a limited data set.

### Patient Selection

We included members aged 18 to 64 years enrolled in a commercial health plan between January 1, 2003, and December 31, 2012. We assessed eligibility on a monthly basis, and patients entered and exited the cohort over the 10-year period on a rolling basis. We identified 31 428 338 members meeting our inclusion criteria and excluded 111 740 of the members (0.4%) owing to missing data.

### Variables of Interest

We assessed reimbursed dispensings for opiate agonists identified by American Hospital Formulary Service classification 28080800 (<http://www.fdbhealth.com/fdb-medknowledge/>). We used the First DataBank drug summary tables to distinguish between generic and brand (OxyContin) non-abuse-deterrent extended-release oxycodone, and abuse-deterrent OxyContin. We identified abuse-deterrent OxyContin using the relevant National Drug Code with a market entry date on or after August 9, 2010, when abuse-deterrent OxyContin was released (<http://www.fdbhealth.com/fdb-medknowledge/>). Other long-acting opioids included extended-release morphine sulfate, hydrocodone bitartrate, hydromorphone hydrochloride, methadone hydrochloride, oxymorphone hydrochloride, tramadol, and transdermal fentanyl patch. We assessed propoxyphene separate from other immediate-release opioids, including codeine, dihydrocodeine bitartrate, meperidine hydrochloride, morphine, oxycodone, hydrocodone, hydromorphone, oxymorphone, levorphanol tartrate, and tramadol. We used established conversion factors to estimate milligrams of morphine-equivalent dose (MED) for each dispensing.<sup>24</sup> We calculated the annual mean out-of-pocket cost per dispensing (copayment plus deductible) for OxyContin to assess changes in insurance coverage for the new formulation.

We identified opioid overdose episodes using emergency department or inpatient claims containing an *International Classification of Diseases, Ninth Revision (ICD-9)* diagnosis code for poisoning due to opioids. Consistent with past studies<sup>5,25,26</sup> using administrative data and consensus recommendations

from the Injury Surveillance Workgroup, we categorized overdose as due to a prescription opioid (*ICD-9* codes 965.00, 965.02, 965.09, E850.1, and E850.2) or heroin (*ICD-9* codes 965.01 and E850.0). Preliminary results of a detailed medical record review validation study<sup>27</sup> found a positive predictive value of 71% for these codes to detect opioid overdose. We defined *opioid overdose episodes* as comprising all claims related to an emergency department visit and/or inpatient admission in which any claim contained an opioid poisoning diagnosis. We classified episodes with fewer than 2 days between the end date of one and the start date of the next event as a single episode. A small number of overdose episodes (1.4%) contained diagnosis codes for poisoning due to both a prescription opioid and heroin; we counted these episodes as both a prescription opioid and heroin overdose.

We used a combination of 2000 US census<sup>28</sup> neighborhood characteristics and surname analysis to characterize race/ethnicity; this approach has been validated and has high positive predictive value (eMethods in the Supplement).<sup>29</sup> For descriptive purposes, we created previously established categorical variables of census block group poverty and educational levels derived from 2000 US census reports.<sup>30,31</sup>

## Statistical Analysis

### Data Analyses

We analyzed outcomes on a quarterly basis and divided the study into 3 periods: preintervention, quarter (Q) 1/2003 to Q2/2010; phase-in period for the 2 interventions, Q3/2010 to Q4/2010; and, postintervention, Q1/2011 to Q4/2012. To control for any changes in cohort characteristics during the course of the study, we standardized all outcomes to the population distribution of Q2/2010 members by age (18-24, 25-34, 35-44, 45-54, and 55-64 years), sex, race/ethnicity, and region. In addition to assessing prescription opioid overdoses as a quarterly rate, we assessed the ratio of prescription opioid overdoses per milligrams of MED dispensed in each quarter.

We used segmented regression to test for changes in each outcome after the formulation change.<sup>32</sup> Regression models included terms for baseline level and trend and terms to estimate the changes in level and trend beginning with the first postintervention quarter (Q1/2011). We excluded the intervention phase-in period (Q3/2010-Q4/2010) from regression analyses. We used a stepwise approach to test and control for autocorrelation, with an initial order of 4 (correlation within 1 year). To improve power to detect significant predictors and avoid inclusion of nonsignificant terms that might bias estimated trends, we removed terms from the segmented regression models with  $P > .20$  using backward elimination. We used 2-tailed tests with  $\alpha = .05$  to determine whether changes in level and/or trend were significant. By visual inspection, we noted that most preintervention and postintervention trends were nonlinear. Models including quadratic terms had a better fit by the Akaike information criterion for all outcomes, so we chose this more conservative approach. We used regression results to estimate the absolute effects and 95% CIs for each outcome at 2 years after the formulation change (Q4/2012) using multivariate delta methods.<sup>33</sup> We used SAS, version 9.3, for analyses (SAS Institute Inc).

### Sensitivity Analyses

We first tested an 8-quarter baseline starting in Q3/2008 to compare baseline and follow-up periods of equal duration and generate a baseline period more proximal to the formulation change that might provide more accurate baseline trend estimates. For this analysis, we used linear terms only because modeling fewer baseline points with a quadratic term could lead to overfitting and unreliable estimates.

Second, preliminary results of a detailed medical record validation study<sup>27</sup> found that the positive predictive value of *ICD-9* codes to identify prescription opioid overdose increased from 71% to 80% if overdoses related to surgical anesthesia were removed. We therefore ran our regression models after eliminating such episodes identified using *ICD-9* procedure codes and found that the absolute reduction in prescription opioid overdose changed by less than 3% (eTable in the Supplement).

## Results

We included 31 316 598 adults with a median enrollment in the insurance carrier of 20 months (interquartile range, 9-39 months), with 7.2 million to 8.3 million enrolled per quarter. The distribution of members by sex, age, educational level, and poverty level was relatively consistent over the course of the study; however, there were small shifts in ethnicity from white to Hispanic/Asian and in region from the Midwest to the South and West (Table 1). We identified 13 816 opioid overdose episodes during the study period: 12 164 of these episodes (88.0%) were due to prescription opioids and 1823 of the episodes (13.2%) were due to heroin.

### Opioid Dispensing Rates

The dispensing rate for all opioids combined increased from an estimated 95.1 to 163 mg MED per member per quarter between Q1/2003 and Q3/2010 (Table 2 and Figure 1A). Immediately following the interventions, the dispensing rate dropped by 14.8 mg MED per member per quarter (95% CI, -19.3 to -10.4) along with a change to a decreasing trend that persisted throughout the 8-quarter postintervention period. In Q4/2012, the dispensing rate was estimated to be 139 mg MED per member, a 19% decrease from the expected rate based on baseline trend (absolute change, -32.2 mg [95% CI, -38.1 to -26.3]).

The dispensing rate for all extended-release oxycodone products (OxyContin plus generic formulations) increased linearly from an estimated 22.9 to 27.7 mg MED per member per quarter from Q1/2003 through Q3/2010 (Table 2 and Figure 1B). In Q1/2011 following the introduction of abuse-deterrent OxyContin, the dispensing rate dropped significantly by 4.56 mg MED per member per quarter (95% CI, -5.91 to -3.21) along with a decreasing trend that slowed over the 8-quarter postformulation change period. Two years after the formulation change, the dispensing rate for extended-release oxycodone decreased 39% from an expected 29.1 mg to 17.8 mg MED per member per quarter (absolute change, -11.3 [95% CI, -12.4 to -10.1]). Comparatively, the estimated dispensing rate for non-

Table 1. Baseline Characteristics of Cohort Members by Quarter<sup>a</sup>

Characteristic	No., Millions (%)					
	Quarter 1					Quarter 4 (2012)
	2003	2005	2007	2009	2011	
No. of members	7.2	7.6	8.1	8.1	7.8	7.7
Male sex	3.6 (49.0)	3.8 (49.1)	3.9 (48.9)	4.0 (49.1)	3.8 (49.3)	3.8 (49.7)
Age, y						
18-24	0.9 (13.0)	1.0 (12.8)	1.0 (13.0)	1.0 (12.8)	1.0 (13.3)	1.0 (13.8)
25-34	1.7 (24.1)	1.7 (22.7)	1.8 (22.1)	1.8 (22.0)	1.7 (21.3)	1.7 (21.6)
35-44	2.0 (27.7)	2.0 (26.6)	2.0 (25.4)	2.0 (24.4)	1.8 (23.3)	1.8 (22.8)
45-54	1.7 (22.8)	1.8 (23.8)	1.9 (24.1)	2.0 (24.3)	1.9 (24.3)	1.8 (23.6)
55-64	0.9 (12.3)	1.1 (14.0)	1.2 (15.4)	1.3 (16.5)	1.4 (17.8)	1.4 (18.3)
Race/ethnicity <sup>b</sup>						
White	5.1 (70.1)	5.3 (69.8)	5.5 (67.9)	5.4 (66.3)	5.2 (66.6)	5.1 (66.5)
Black	0.2 (2.6)	0.2 (2.5)	0.2 (2.4)	0.2 (2.6)	0.2 (2.5)	0.2 (2.4)
Hispanic	0.6 (8.5)	0.7 (9.0)	0.8 (10.5)	0.9 (10.8)	0.8 (10.7)	0.8 (10.7)
Asian	0.2 (3.0)	0.2 (3.2)	0.3 (3.7)	0.4 (4.4)	0.4 (4.5)	0.4 (4.9)
Mixed	1.1 (15.8)	1.2 (15.5)	1.2 (15.5)	1.3 (15.8)	1.2 (15.6)	1.2 (15.5)
Region						
Northeast	0.8 (10.7)	0.8 (10.8)	0.8 (10.4)	0.8 (10.3)	0.8 (10.2)	0.8 (10.1)
Midwest	2.4 (32.9)	2.3 (30.4)	2.2 (27.8)	2.1 (26.0)	2.0 (26.0)	2.1 (27.4)
South	3.1 (43.2)	3.4 (44.1)	3.8 (46.9)	3.9 (48.4)	3.7 (47.6)	3.5 (45.1)
West	1.0 (13.2)	1.1 (14.7)	1.2 (15.0)	1.3 (15.7)	1.3 (16.2)	1.0 (13.2)
Neighborhood educational level <sup>c</sup>						
High	4.4 (60.1)	4.6 (60.2)	4.8 (59.2)	4.8 (59.0)	4.6 (59.7)	4.7 (60.5)
High-middle	1.6 (21.6)	1.7 (21.7)	1.8 (22.0)	1.8 (22.0)	1.7 (21.8)	1.7 (21.5)
Low-middle	1.0 (13.4)	1.0 (13.3)	1.1 (13.8)	1.1 (13.9)	1.1 (13.7)	1.0 (13.2)
Low	0.4 (4.9)	0.4 (4.8)	0.4 (5.0)	0.4 (5.0)	0.4 (4.8)	0.4 (4.7)
Neighborhood poverty level <sup>d</sup>						
Low	3.3 (45.5)	3.5 (45.3)	3.6 (44.2)	3.6 (44.1)	3.5 (44.7)	3.5 (44.8)
Low-middle	1.9 (25.9)	2.0 (26.1)	2.1 (26.0)	2.1 (26.0)	2.0 (25.9)	2.0 (25.8)
High-middle	1.4 (19.2)	1.5 (19.3)	1.6 (20.0)	1.6 (20.1)	1.5 (19.9)	1.5 (19.7)
High	0.7 (9.5)	0.7 (9.3)	0.8 (9.7)	0.8 (9.8)	0.7 (9.5)	0.8 (9.7)

<sup>a</sup> Data are presented for the first quarter of every other year and the final study quarter.

<sup>b</sup> Race/ethnicity data were derived from a combination of geocoded census-block group-level race from the 2000 US Census and surname analysis to identify Asian and Hispanic individuals. Mixed neighborhoods are those that do not meet a 75% threshold for white, black, or Hispanic ethnicity.

<sup>c</sup> Neighborhood educational level was based on geocoded census-block

group-level data from the 2000 US Census. *High* denotes neighborhoods with less than 15%; *high-middle*, 15% to 24.9%; *low-middle*, 25% to 39.9%; and *low*, 40% or more of individuals with less than high-school educational attainment.

<sup>d</sup> Neighborhood poverty was based on geocoded census-block group-level data from the 2000 US Census. *Low* denotes neighborhoods with less than 5%; *low-middle*, 5% to 9.9%; *high-middle*, 10% to 19.9%; and *high*, 20% or more of individuals living below the poverty level.

oxycodone long-acting opioid formulations 2 years after the formulation change was 11% higher than the rate predicted from the baseline trend (absolute change, 3.26 mg MED per member per quarter [95% CI, 1.40 to 5.12]) (Table 2 and Figure 1C).

During the 30-quarter baseline period, the dispensing rate for propoxyphene declined from an estimated 17.6 mg to 12.4 mg MED per member per quarter and then was eliminated from Q1/2011 onward (Table 2 and Figure 1D). In comparison, non-propoxyphene immediate-release opioid dispensing decreased by 16% from the expected rate at 2 years (absolute change, -16.2 mg MED per member per quarter [95% CI, -18.8 to -13.5]) (Table 2 and Figure 1E).

### Subtypes of Extended-Release Oxycodone and Out-of-Pocket Costs

In 2003, all extended-release oxycodone dispensed was OxyContin. Generic extended-release oxycodone was first dispensed in Q2/2004, with the share of dispensing increasing to more than 50% from Q3/2005 through Q1/2008. From Q2/2008 through Q2/2010, the generic share of dispensing dropped to 15% (eFigure 1 in the Supplement). In Q4/2010, the first quarter after the formulation change, 76% of extended-release oxycodone dispensing was the new, abuse-deterrent OxyContin formulation. This share increased to 96% in Q2/2011 and 99% by Q4/2011, indicating rapid decrease in availability of non-abuse-deterrent formulations (eFigure 1 in the Supplement).

Table 2. Segmented Linear Regression Model Results for Change in Outcome After Opioid Market Changes

Characteristic	Model Variable (95% CI)					
	Intercept <sup>a</sup>	Baseline			Change	
		Linear Trend <sup>b</sup>	Quadratic Trend <sup>b</sup>	Level Change <sup>c</sup>	Linear Trend <sup>d</sup>	Quadratic Trend <sup>d</sup>
Opioid dispensing rate, mg MED per member per quarter						
All opioids	95.1 (93.1 to 97.0)	3.27 (2.96 to 3.57)	-0.034 (-0.044 to -0.023)	-14.8 (-19.3 to -10.4)	-2.17 (-2.95 to 1.39)	NA
Extended-release oxycodone	22.9 (22.3 to 23.4)	0.16 (0.13 to 0.19)	NA	-4.56 (-5.91 to -3.21)	-1.35 (-2.03 to -0.67)	0.064 (-0.009 to 0.137)
Other long-acting opioids	19.4 (18.8 to 20.0)	1.52 (1.43 to 1.62)	-0.032 (-0.035 to -0.029)	1.09 (-0.27 to 2.46)	0.27 (0.03 to 0.51)	NA
Propoxyphene	17.6 (17.3 to 18.0)	0.062 (0.005 to 0.118)	-0.008 (-0.010 to -0.006)	-12.2 (-12.9 to -11.4)	0.50 (0.36 to 0.64)	NA
Other immediate-release opioids	35.1 (34.2 to 36.0)	1.54 (1.40 to 1.68)	0.006 (0.001 to 0.010)	NA	-1.01 (-1.96 to -0.05)	-0.13 (-0.24 to -0.01)
Overdose rate, episodes per 100 000 members per quarter						
Prescription opioid	2.90 (2.76 to 3.05)	0.067 (0.057 to 0.074)	NA	NA	-0.14 (-0.18 to -0.09)	NA
Heroin	0.43 (0.33 to 0.53)	-0.017 (-0.031 to -0.003)	0.0009 (0.0005 to 0.0013)	NA	NA	0.0041 (-0.0003 to 0.0085)
Ratio of prescription opioid overdose to total prescription opioid dispensing, episodes per million mg MED per quarter	0.31 (0.30 to 0.33)	-0.005 (-0.007 to -0.002)	0.0002 (0.0001 to 0.0002)	NA	-0.0067 (-0.0133 to -0.0002)	NA

Abbreviations: MED, morphine-equivalent dose; NA, not applicable (*P* value for the model variable >.20).

<sup>a</sup> The intercept is the model estimate for the rate in the first study quarter (Q1/2003).

<sup>b</sup> Baseline linear and quadratic trends describe the trend in overdose rate per quarter in the preformulation change period (Q1/2003-Q2/2010).

<sup>c</sup> Level change is the estimated instantaneous change in overdose rate in the

first postformulation change quarter (Q1/2011) compared with the expected rate based on the baseline trend.

<sup>d</sup> Change in linear and quadratic trends describe the change in trend in the postformulation change period (Q1/2011-Q4/2012). The trend in the postformulation change period is the sum of the baseline trend plus the change in trend.

The out-of-pocket cost for OxyContin increased by \$2.15 per year (95% CI, \$1.82 to \$2.48), reaching a mean of \$42.33 in 2012. We did not detect a change in level (*P* = .71) or trend (*P* = .96) at the time of the 2010 formulation change (eFigure 2 in the Supplement).

### Opioid Overdose Event Rates

Prescription opioid overdoses increased by 66% during the 30-quarter baseline period from an estimated 3.01 to 4.99 per 100 000 members per quarter (Table 2 and Figure 2A). Two years after the interventions, the rate of overdoses due to prescription opioids decreased by 20% from an expected 5.48 to 4.38 per 100 000 members per quarter (absolute change, -1.10 [95% CI, -1.47 to -0.74]). The ratio of prescription opioid overdoses to dispensing of prescription opioids was relatively stable during the baseline period, with a slight increasing trend at the time of the interventions (Table 2 and Figure 2B). Two years after the interventions, there were 0.321 prescription opioid overdoses per million milligram MEDs dispensed compared with the expected value of 0.375 (absolute change, -0.054 [95% CI, -0.104 to -0.003]).

The baseline heroin overdose rate increased from an estimated 0.43 to 0.72 per 100 000 members per quarter, with an accelerating rate of increase in the last half of the baseline period (Table 2 and Figure 2C). Following the interventions,

there was a greater acceleration that was not statistically significant (0.0041 per 100 000 members per quarter<sup>2</sup> [95% CI, -0.0003 to 0.0085]). Two years after the interventions, the heroin overdose rate increased by 23% from an expected 1.15 to 1.41 per 100 000 members per quarter (absolute change, 0.26 [95% CI, -0.01 to 0.53]).

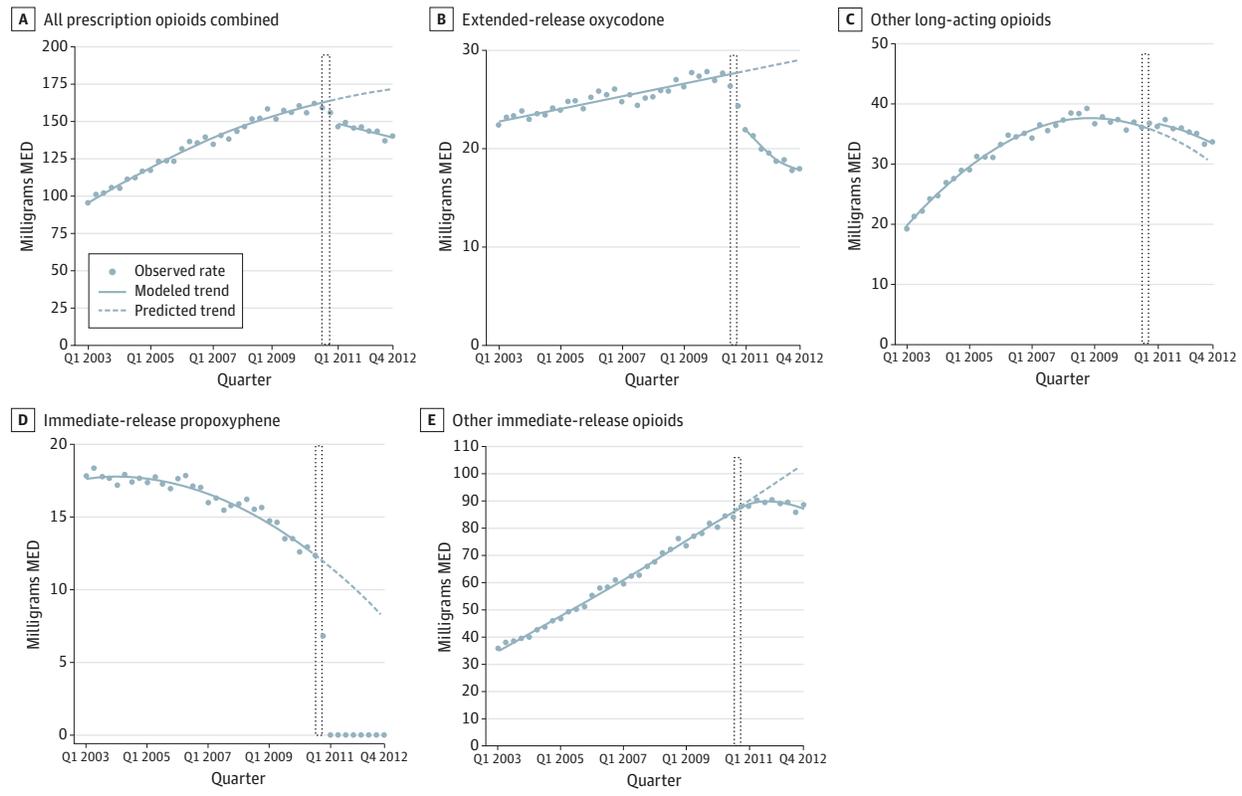
### Sensitivity Analyses

Compared with a 30-quarter baseline period with quadratic modeling, an 8-quarter baseline period with linear modeling produced similar results for opioid dispensing outcomes at 2 years (Table 3). However, for overdose outcomes, the decrease in prescription opioid overdose was diminished (-7% vs -20%), but the estimated increase in heroin overdose was greater (43% vs 23%). Furthermore, the ratio of prescription opioid overdose rate per million milligram MEDs dispensed changed direction from a relative decrease of 14% to an increase of 7%.

### Discussion

The introduction of abuse-deterrent OxyContin and withdrawal of propoxyphene at the end of 2010 were associated with sudden, substantial, and sustained decreases in prescrip-

**Figure 1. Standardized Prescribing Rates and Segmented Regression Results Before and After Introduction of Abuse-Deterrent Extended-Release Oxycodone Hydrochloride and Withdrawal of Propoxyphene**



Extended-release oxycodone hydrochloride (OxyContin and generic products combined), other long-acting opioid formulations, and immediate-release propoxyphene and other opioids. Dashed vertical lines indicate the time of introduction of abuse-deterrent OxyContin (third quarter [Q] of 2010) and withdrawal of propoxyphene (Q4 of 2010). MED indicates morphine-equivalent dose.

tion opioid dispensing. The estimated decrease in opioid dispensing at 2 years would be enough to supply 5 mg of oxycodone each day of Q4/2012 to 5% of the population. The trend in prescription opioid overdose mirrored that of prescription opioid dispensing. Compared with the expected baseline trends, prescription opioid dispensing and overdose decreased by 19% and 20%, respectively, 2 years after the interventions. During the same time frame, we identified a trend toward acceleration of the previously increasing rate of heroin overdose. Extrapolating our estimates at 2 years to the 124 million commercially insured US residents aged 18 to 64 years,<sup>34</sup> there would be 5456 fewer prescription opioid overdoses and 1290 additional heroin overdoses annually.

To our knowledge, this study is the first to demonstrate a reversal in previously unrelenting increases in opioid dispensing on a national scale. The change in dispensing was driven by 3 main trends: absence of propoxyphene dispensing after Q4/2010, a sudden drop and subsequent decreasing trend in dispensing of extended-release oxycodone products, and a flattening of the previously increasing trend in dispensing of non-propoxyphene immediate-release opioids. Although the first trend is consistent with the market withdrawal of a drug, reasons for the general lack of opioid substitution and the medi-

ating mechanism for the changes in dispensing of extended-release oxycodone and other immediate-release opioids are not immediately apparent.

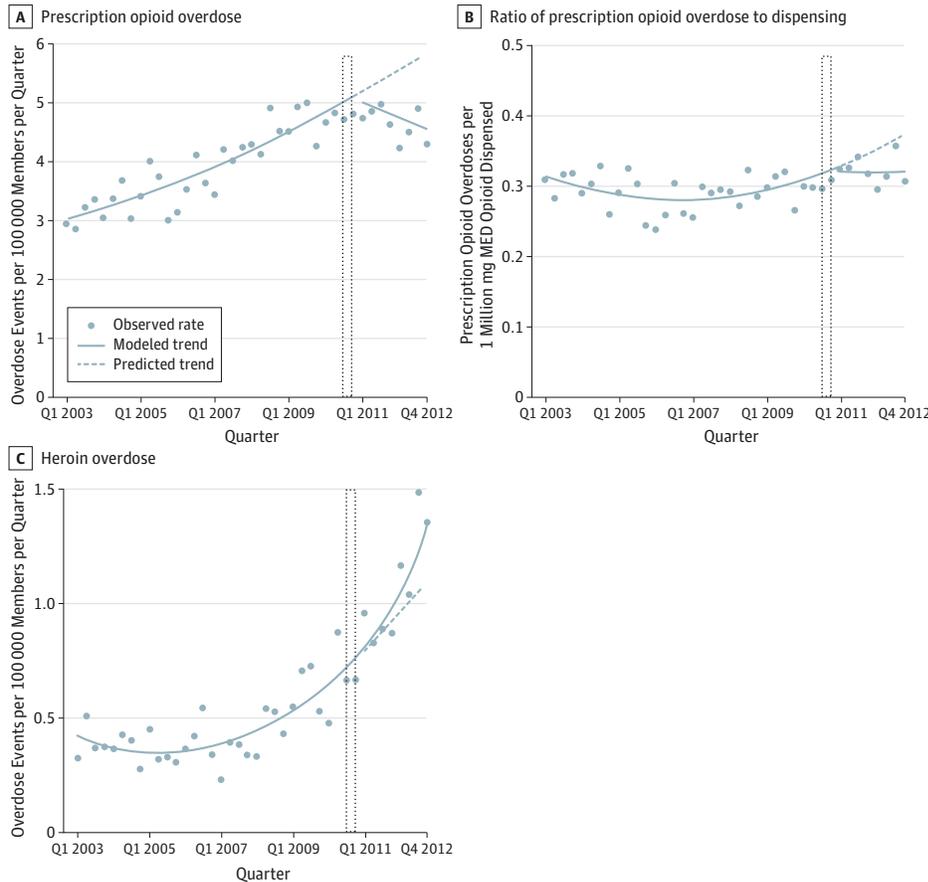
Our finding of a drop in dispensing of extended-release oxycodone is consistent with several studies using data from IMS Health.<sup>15-18</sup> There are many potential explanations for this result. First, generic extended-release oxycodone was withdrawn from the market concurrently with the introduction of abuse-deterrent OxyContin as a result of patent infringement litigation settlements,<sup>15</sup> and this withdrawal could have contributed to reduced dispensing. However, our data support efficient substitution of generic and brand formulations in the preformulation change period, and another study<sup>15</sup> found strong evidence for substitution in the preformulation period. Second, increased patient out-of-pocket cost might have reduced the use of extended-release oxycodone, but we found no such evidence. We cannot rule out formulary changes, but we detected minimal substitution to alternative long-acting or immediate-release opioids. Third, demand from individuals who abused or diverted the non-abuse-deterrent oxycodone formulation might have decreased. Corroborating this hypothesis, one study<sup>18</sup> demonstrated that individuals with a diagnosis of substance use

disorder who were receiving extended-release oxycodone at the time of the formulation change had lower odds of switching to the abuse-deterrent formulation.

Before the introduction of abuse-deterrent OxyContin and withdrawal of propoxyphene, dispensing of nonpropoxy-

phene immediate-release opioids was increasing at a steady rate; afterward, the trend shifted downward and became nearly flat. This finding is surprising since we expected switching to alternative immediate-release opioids. During the past decade, there have been numerous public health efforts de-

**Figure 2. Standardized Overdose Rates and Segmented Regression Results Before and After Opioid Market Changes**



Dashed vertical lines indicate the time of introduction of abuse-deterrent OxyContin (third quarter [Q] of 2010) and withdrawal of propoxyphene (Q4 of 2010). MED indicates morphine-equivalent dose.

**Table 3. Sensitivity Analysis: 30-Quarter Baseline With Quadratic Model vs 8-Quarter Baseline With Linear Model**

Characteristic	Scenario 1: 30-Quarter Baseline, Quadratic Model		Scenario 2: 8-Quarter Baseline, Linear Model	
	Absolute Change (95% CI)	Relative Change, %	Absolute Change (95% CI)	Relative Change, %
Opioid dispensing rate, mg MED per member per quarter				
All opioids	-32.2 (-38.1 to -26.3)	-19	-28.5 (-32.6 to -24.3)	-17
Extended-release oxycodone	-11.3 (-12.4 to -10.1)	-39	-12.3 (-14.5 to -10.2)	-41
Other long-acting opioid	3.26 (1.40 to 5.12)	11	1.18 (-0.22 to 2.58)	4
Propoxyphene	-8.19 (-9.30 to -7.08)	-100	-7.84 (-8.51 to -7.18)	-100
Other immediate-release opioid	-16.2 (-18.8 to -13.5)	-16	-11.0 (-17.5 to -4.6)	-11
Overdose rate, episodes per 100 000 members per quarter				
Prescription opioid	-1.10 (-1.47 to -0.74)	-20	-0.34 (-0.50 to -0.17)	-7
Heroin	0.26 (-0.01 to 0.53)	23	0.41 (-0.07 to 0.88)	43
Ratio of prescription opioid overdose to total prescription opioid dispensing, episodes per million mg MED per quarter	-0.054 (-0.105 to -0.003)	-14	0.022 (0.003 to 0.041)	7

Abbreviation: MED, morphine-equivalent dose.

signed to improve the safety of opioid prescribing and reduce diversion, such as revision of prescribing guidelines, state policy changes, and implementation of prescription drug monitoring programs. Although these initiatives were not collectively contemporaneous with the interventions analyzed, they may have affected the dispensing of immediate-release opioids. Further analyses are needed to confirm this finding and understand the mechanism behind it.

To our knowledge, this is the first study to demonstrate that a decrease in opioid supply is associated with a decrease in overall prescription opioid overdose. We were unable to ascertain the relative effect of the introduction of abuse-deterrent OxyContin compared with the withdrawal of propoxyphene on the change observed in prescription opioid overdose. Detailed studies<sup>35,36</sup> of decedents of prescription opioid overdose have implicated oxycodone more often than propoxyphene. However, data suggest that misuse of widely available weaker opioids, such as propoxyphene, may precede OxyContin misuse.<sup>37</sup>

The ratio of prescription opioid overdose per milligram of MED dispensed was relatively constant during the 10-year study period. We detected a slight decrease in the ratio after the interventions; however, this finding was reversed in our sensitivity analysis using a shorter baseline period. With the removal of more dangerous opioids from the market, one may have hypothesized that this ratio would decrease owing to improved safety among remaining opioids on average. It remains unknown whether a movement toward potentially safer opioids can affect opioid abuse on a population level.

The rate of heroin overdose was increasing before the interventions that we examined occurred. This increase may be linked to the previously unrelenting increase in prescription opioid abuse because most heroin users misuse prescription opioids prior to initiating heroin use.<sup>38,39</sup> We found a nonstatistically significant increase in the rate of heroin overdose after the interventions. Findings of studies on the effect of use of abuse-deterrent OxyContin on heroin use are mixed. Individuals entering treatment for opioid use disorder reported a near doubling in heroin as the choice of drug to get high 18 months after the formulation change,<sup>23</sup> but a small sample of opioid abusers in rural Kentucky reported no change in heroin use.<sup>40</sup> Heroin-related telephone calls to poison control centers increased 42% after the formulation change.<sup>16</sup> Further studies are needed to understand the causes of the worsening heroin epidemic.

Our study has strengths that add to the accumulating evidence about the association between prescription opioid prescribing and overdose. Our sample of approximately 31 million persons represents a significant proportion of the US population aged 18 to 64 years. We used 7.5 years of data prior to the formulation change to identify and control for baseline trends in each of our outcomes. Finally, the use of a defined cohort allowed adjustment for changing denominator characteristics when calculating event rates.

Our study has several limitations. We were unable to identify the source of prescription opioids for individuals who overdosed, and many individuals who misuse opioids

do not obtain them directly from physician prescriptions.<sup>41</sup> However, the interventions were time limited, changed the underlying trend, and could reasonably be expected to have affected the cohort studied without changing its composition. These points suggest that an interrupted times series design using aggregate level outcomes is valid.<sup>42</sup> Our analysis included overdoses treated in emergency departments and hospitals and thus does not capture some events, including fatalities. Differences in the rates of seeking treatment might generate differential misclassification between heroin vs prescription opioid overdoses. However, analyzing trends in heroin and prescription opioid overdoses separately should not lead to biased effect estimates if misclassification is unchanged over time. The use of ICD-9 diagnosis codes from claims data may introduce outcome misclassification. Our sensitivity analysis excluding opioid overdoses potentially attributable to surgical anesthesia did not alter the results. We are not aware of systematic changes to coding during the course of the study time frame, and it is unlikely that the interventions studied would have affected the coding of overdose events. The cohort was limited to commercially insured persons aged 18 to 64 years, and our results may not be generalizable outside this population. Our findings might be more pronounced in populations with higher overdose risk, such as Veterans Affairs and Medicaid.<sup>36,43</sup>

Our results have significant implications for policymakers and health care professionals grappling with the epidemic of opioid abuse and overdose. Changes imposed through regulatory mandates or voluntary company actions may be a viable approach to stemming prescription abuse. However, identifying interventions that reduce opioid supply without affecting access to individuals who benefit from opioid therapy remains a challenge. Opioid formulations with high abuse potential or narrow therapeutic window, such as OxyContin and propoxyphene, may represent model targets. A new long-acting formulation of hydrocodone without abuse-deterrent properties has raised concerns, leading to efforts to restrict its use from the outset.<sup>44</sup> Finally, although restricted opioid supplies might decrease new-onset addiction in the future, it will not cure existing addiction. Regardless of the mediating mechanism, a transition from prescription opioid to heroin abuse has been well documented.<sup>45-48</sup> and further efforts are needed to improve identification and treatment of these individuals.

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## Conclusions

In a large, national, commercially insured population, introduction of abuse-deterrent OxyContin and withdrawal of propoxyphene were associated with substantial decreases in both prescription opioid dispensing and overdose. Pharmaceutical market interventions may be a viable option toward reducing prescription opioid abuse. Complementary strategies that improve recognition and treatment of opioid abuse and addiction, including overdose prevention, are urgently needed.

## ARTICLE INFORMATION

**Accepted for Publication:** December 23, 2014.

**Published Online:** April 20, 2015.  
doi:10.1001/jamainternmed.2015.0914.

**Author Contributions:** Dr Larochelle had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.  
*Study concept and design:* Larochelle, Ross-Degnan, Wharam.

*Acquisition, analysis, or interpretation of data:* All authors.

*Drafting of the manuscript:* Larochelle, Wharam.  
*Critical revision of the manuscript for important intellectual content:* All authors.

*Statistical analysis:* Larochelle, Zhang.

*Obtained funding:* Wharam.

*Administrative, technical, or material support:* Larochelle, Wharam.

*Study supervision:* Larochelle, Ross-Degnan, Wharam.

**Conflict of Interest Disclosures:** None reported.

**Funding/Support:** Dr Larochelle was supported by Health Resources and Services Administration (T32 HP10251, T32 HP12706), the Ryoichi Sasakawa Fellowship Fund, and the Harvard Pilgrim Health Care Institute.

**Role of the Funder/Sponsor:** The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Previous Presentation:** Results of this study were presented at the 37th Annual Meeting of the Society of General Internal Medicine; April 25, 2014; San Diego, California.

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