

Certified by the American Association of Poison Control Centers

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, MD 20852

Reference: FDA #2010-P-0526, #2010-P-0540 and #2011-P-0473
Supplemental Information Submission Attached

28 March 2013

Dear Sir or Madam,

The following is a submission of supplemental information and comments to the Citizen Petitions #FDA-2010P-0526, #FDA-2010-P-0540 and #FDA-2011-P-0473.

I certify that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the action requested herein first became known to me on or about 01 March 2012.

If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: **I do not expect to receive any payments for filing this information.** I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Sincerely,

Richard C. Dart, MD, PhD
Executive Director, RADARS System, Denver Health and Hospital Authority
Professor, University of Colorado Health Sciences Center

Celebrating 50 Years of Serving the Community

Poison Center • Drug Consultation Center • DH NurseLine • Research & Consulting • Medical Toxicology

Mailing Address: 777 Bannock Street, Mail Code 0180 • Denver, CO 80204-4507
Location: 990 Bannock Street • Denver, CO 80204-4028
T: 303-389-1100 • **F:** 303-389-1119
www.rmpdc.org



RADARS® System
777 Bannock Street, MC0180
Denver, Colorado 80204
(303) 389-1240
www.radars.org

28 March 2013

Re: Supplemental Information for FDA Docket #FDA-2010-P-0526, #FDA-2010-P-0540,
#FDA-2011-P-0473

Abuse Deterrent Formulations of Prescription Opioid Analgesics: Changes in Abuse Indicators Following Introduction of Abuse Deterrent Formulations

Document Summary

Abuse deterrent formulations (ADF) of prescription opioids have been proposed to deter the diversion and abuse of these products. We examined rates of diversion and abuse before and after introduction of reformulated versions of OxyContin and Opana ER compared to other opioids using the Researched Abuse, Diversion and Addiction Related Surveillance (RADARS® System), a national surveillance system for diversion and abuse of prescription opioids and stimulants.

- Diversion of prescription analgesics. The average rates of diversion of OxyContin and Opana ER decreased 30% to 60% in the Drug Diversion Program after the introduction of the reformulated products and continue to decrease through the fourth quarter of 2012. In contrast, the diversion rate for other opioids continued at the same rate after introduction of the reformulated products.
- Street price of illicitly-traded opioid analgesics. The value of abuse deterrent formulations on the street is 27% to 38% lower than that of the original formulation for OxyContin and Opana ER. This observation suggests that the new formulations are less desirable for diversion.
- Acute health events. The average rate of cases involving abuse of OxyContin and Opana ER in the Poison Center Program has decreased 30% to 68% since the introduction of ADF versions.
- Opioid dependent patients. The average rate of endorsement by patients entering treatment of substance abuse decreased 20% for OxyContin per population. This trend was not observed for Opana ER. The retrospective nature of the survey (past month abuse) and experience with other drugs suggests that there may be a lag in the expected reduction in Opana ER abuse by two quarters following reformulation.

- Young initiates. The College Survey Program did not demonstrate a change after the introduction of reformulated OxyContin or Opana ER. Abuse of prescription opioids by routes requiring tampering is very low in the cohort studied.

Results from multiple RADARS System programs as well as other sources indicate that the original formulations of opioid analgesics are less safe than the abuse deterrent versions.

Abuse Deterrent Formulations of Prescription Opioid Analgesics: Changes in Abuse Indicators Following Introduction of Abuse Deterrent Formulations

The Debate Regarding Abuse Deterrent Formulations of Prescription Opioids

Abuse deterrent formulations (ADF) are designed to potentially deter snorting, smoking, or injecting a drug - reducing behaviors that potentially place users at risk for contracting HIV and viral hepatitis, as well as death from respiratory depression. The role of ADFs as an important tool in controlling prescription drug abuse is supported by a variety of groups such as the Attorneys General of the United States, the Center for Lawful Access and Abuse Deterrence (CLAAD) and the FDA. (1,2,3) In addition, federal legislation allowing for requirement of ADFs has been introduced.

Anecdotal support of the potential value of abuse deterrent formulations is illustrated in recent reports on the worldwide web after crushable formulations of extended release oxycodone and oxymorphone were introduced as generic formulations of OxyContin in Canada and Opana ER in the United States: step-by-step examples of intravenous injection of the original formulations were promptly posted to inform other potential abusers about the desirability of these new, non-abuse deterrent products (4,5). In contrast to the enthusiastic posts regarding crushable formulations, the response from the internet drug abuse community regarding abuse deterrent formulations has been negative. Blog reports suggest that overcoming the ADF features is laborious, time-consuming and generally unrewarding (6).

However, anecdotal reports cannot establish the effectiveness of an ADF. Extensive debate has developed about whether abuse deterrent features are effective. To help inform this debate, we provide data about the abuse and diversion of two opioid analgesics before and after they were reformulated with abuse deterrent features:

- The reformulated version of OxyContin® (oxycodone HCl controlled-release) began distribution on August 2010, and
- Reformulated Opana® ER (oxymorphone HCl extended-release) began distribution in February 2012.

The reformulated versions of OxyContin and Opana ER use technology that makes the product difficult to crush or mill to a particle size that is suitable for nasal insufflation (snorting) or IV injection. When wet, both also form viscous gels that interfere with nasal or intravenous abuse.(7) Other products have been produced with abuse deterrent properties. We focus on OxyContin and Opana ER because these products allow a within-product comparison of rates before and after reformulation.

The Challenge of Surveillance for Abuse of Prescription Medications

Similar to abuse of illicit drugs like heroin, abuse of prescription drugs is a complex social phenomenon that is difficult to measure because the abuser conceals their activities. The occult nature of prescription drug abuse requires information from a variety of sources to “triangulate”

on different aspects of the problem to obtain a complete view. Drug diversion and abuse can be revealed when certain events occur, like an arrest for drug possession, acute health events that lead to an emergency department visit or call to a poison center, or admission for treatment of substance abuse. The use of multiple datasets to create a “mosaic” picture of abuse allows evaluation of a drug from several complementary perspectives. (8)

The RADARS System operates six different programs specifically designed to perform surveillance of prescription opioid and stimulant abuse in the United States (www.RADARS.org). The system is comprised of programs that capture incidents of diversion and abuse of prescription drugs from several different sources: law enforcement encounters, acute health events, and substance abuse treatment. Programs have also been developed to study abuse in newer initiates such as college students. Other programs have been developed to determine the street price paid for illicitly-purchased prescription opioid medications; a drop in street price suggests either decreased desirability or oversupply of a specific drug product. Each program collects product-specific data, which allows the differentiation of individual pharmaceutical products. To date, RADARS System contains 27 months of data since the reformulation of OxyContin and 9 months of data since the reformulation of Opana ER.

The RADARS System is supported by subscriptions from multiple generic and branded manufacturers of prescription opioids and stimulants. By contractual agreement, subscribers do not have access to data and cannot influence analysis of the data or affect publication of the results. No manufacturer was involved in the conception, analysis or reporting of this analysis of abuse deterrent formulations.

Evaluating a Natural Experiment in Abuse Deterrent Formulations

In the case of both OxyContin and Opana ER, an easily-abused product without tamper-resistant characteristics was replaced by another product with the same brand name, but with abuse-deterrent properties. In both cases, shipment of the original product from the manufacturer was switched entirely to the reformulated version. It still takes months for the reformulated version to fill the distribution network, but complete replacement with the reformulated version offers an opportunity for monitoring the response to the reformulated version. Initial evidence had suggested that reformulation of these products had impacted their abuse liability, but further evidence is needed (9,10).

Event ratios (termed rates) were calculated based on population (events per 100,000 persons). Population-based rates estimate the overall public health burden associated with abuse or diversion of each opioid. Population denominators are calculated based on the number of persons residing in each 3-digit Zip code area covered by each RADARS System program in that year-quarter, using US Census data.

In order to account for differences in drug availability and prescribing practices, we also calculated rates based on the number of patients filling a prescription for each opioid of interest

(events per 1,000 Unique Recipients of a Dispensed Drug, URDD). One URDD is a single patient filling a prescription for a specific product in a 3-digit Zip code area in a year-quarter. Sales data used to calculate URDD were purchased from IMS Health Solutions (Parsippany, NJ).

The RADARS System monitors all forms of 10 opioid medications sold in the US: oxycodone, hydrocodone, oxymorphone, hydromorphone, morphine, fentanyl, methadone, buprenorphine, tapentadol and tramadol every 3 months. Each RADARS System identifies the specific pharmaceutical product involved in an event. To examine the potential effect of secular trends, we also compared results for the specific drugs involved in this study to Other Opioids. In this report, the term Other Opioids means all forms of other opioids monitored by RADARS System excluding extended release oxycodone, extended release oxymorphone, and unidentified oxycodone and oxymorphone products.

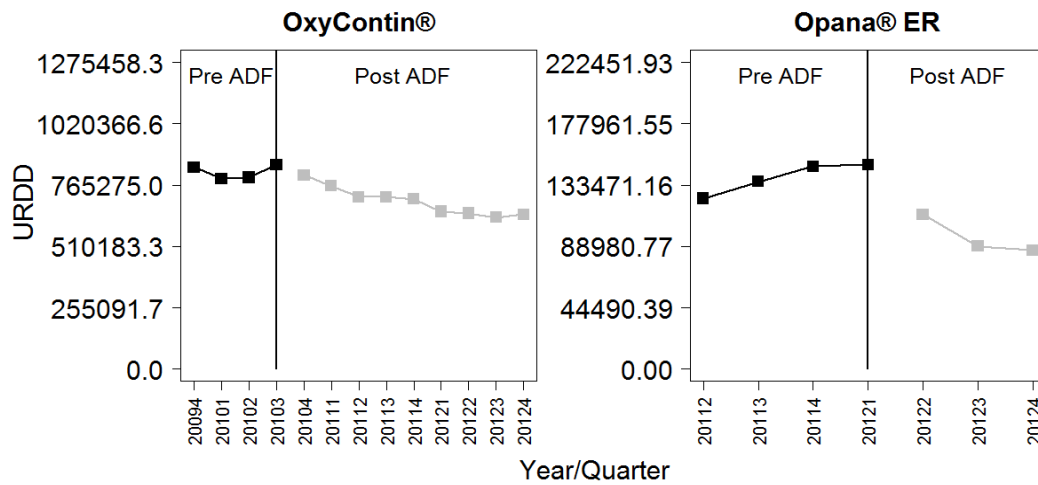
Prior to their introduction, we hypothesized three changes would be observed after the introduction of abuse deterrent formulations:

1. Due to decreased interest in obtaining prescriptions to divert for abuse, fewer individual would actually fill prescriptions. Therefore, the number of people filling prescriptions for OxyContin and Opana ER (termed Unique Recipients of Dispensed Drug, URDD) would be lower in the quarters following reformulation relative to the year prior to reformulation.
2. Rates of abuse and diversion of OxyContin and Opana ER would be lower following introduction of the reformulations reflecting lower levels of abuse. This decline would be different than changes in other prescription opioids and would be independent of changes in drug availability.
3. Use of these drugs through non-oral routes of abuse would decline relative to oral abuse because the new products were intended to deter crushing and solubilization of the drugs.

Results

Figure 1. URDD for OxyContin and Opana ER.

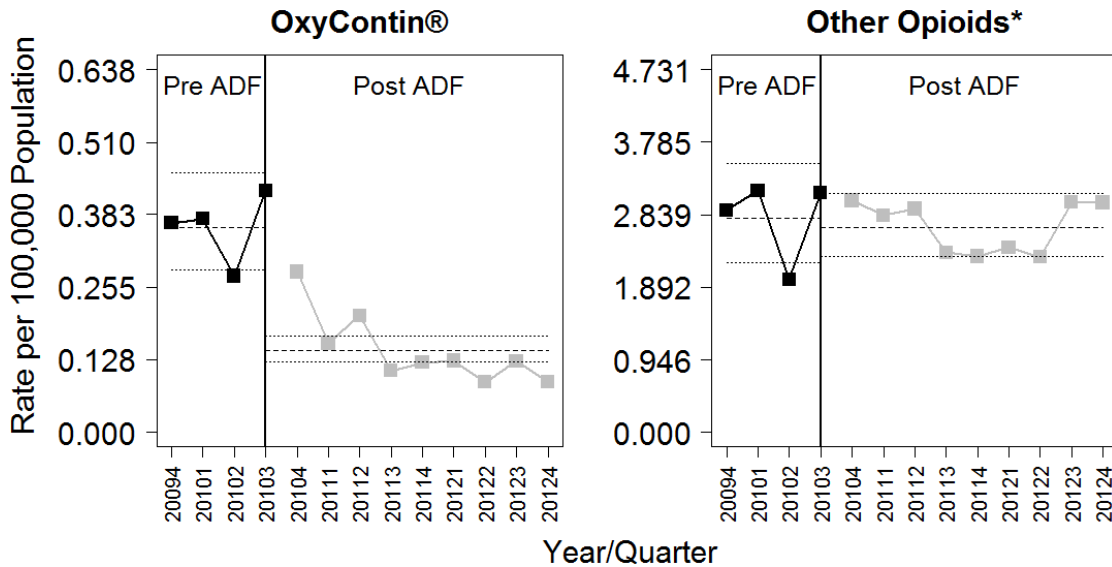
Key Findings: Average mean OxyContin URDD decreased 15% following introduction of the ADF. Opana ER URDD decreased 31% following introduction of the ADF.



URDD = Unique Recipients of Dispensed Drug

Figure 2. OxyContin Drug Diversion Program rates per 100,000 population

Key Findings: OxyContin average diversion rates decreased 60% following introduction of the ADF. This decline was greater than the change observed for other opioids, indicating that there was not a secular trend that explains the decrease.



Drug group	Average rate (95% CI) Pre ADF	Average rate (95% CI) Post ADF	Average percent change (95% CI)	p-value	Interaction p-value [†]
OxyContin®	0.361 (0.285 to 0.456)	0.145 (0.123 to 0.170)	-59.9 (-69.8 to -46.7)	<.001	<.001
Other Opioids*	2.791 (2.218 to 3.512)	2.676 (2.296 to 3.119)	-4.1 (-27.3 to 26.4)	0.766	.

CI = confidence intervals

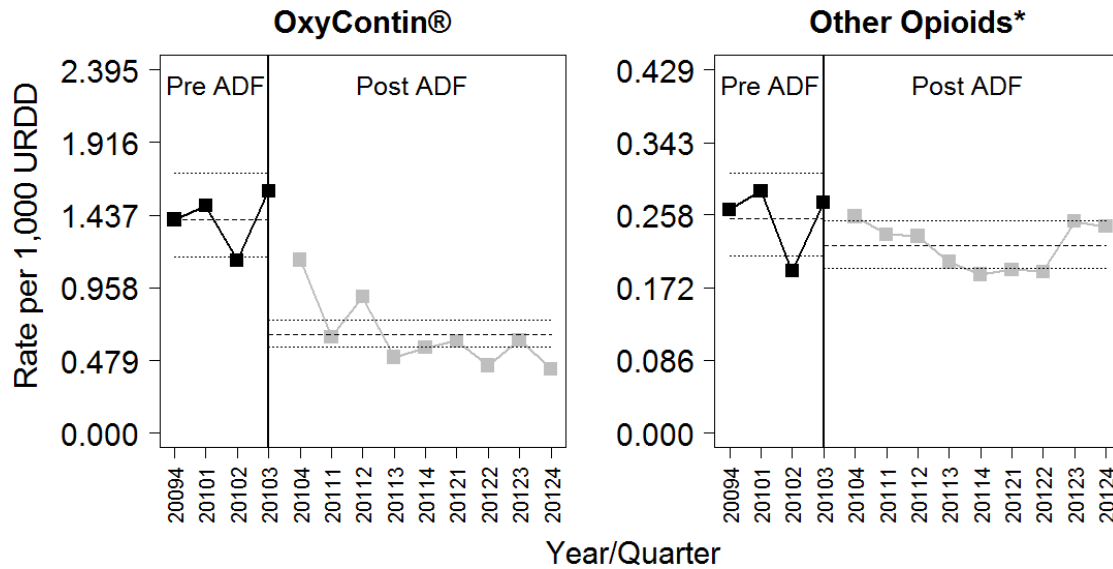
URDD = Unique Recipients of Dispensed Drug

* Other Opioids = total opioids excluding extended release oxycodone, extended release oxymorphone, and unidentified oxycodone and oxymorphone products

[†] The interaction p-value indicates the probability that the change in rates for the two drug groups is different.

Figure 3. OxyContin Drug Diversion Program rates per 1,000 URDD

Key Findings: OxyContin average diversion rates decreased 54% following introduction of the ADF. This decline was greater than the change observed for other opioids, indicating that there was not a secular trend that explains the decrease.



Drug group	Average rate (95% CI) Pre ADF	Average rate (95% CI) Post ADF	Average percent change (95% CI)	p-value	Interaction p-value [†]
OxyContin®	1.409 (1.158 to 1.715)	0.648 (0.565 to 0.744)	-54.0 (-63.8 to -41.5)	<.001	<.001
Other Opioids*	0.253 (0.209 to 0.307)	0.221 (0.195 to 0.251)	-12.7% (-30.7 to 9.9)	0.246	.

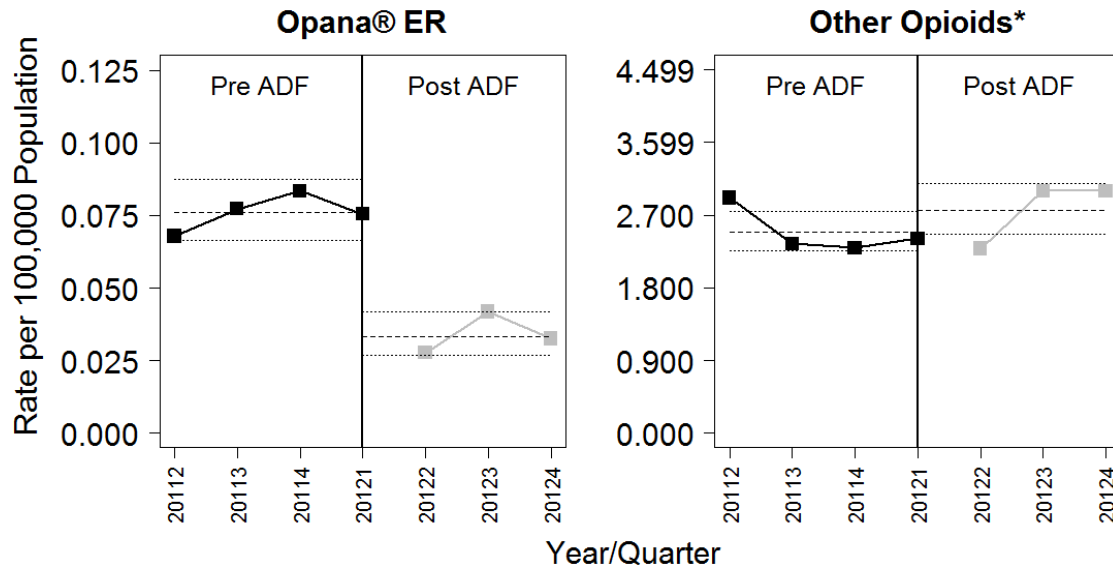
CI = confidence intervals.

* Other Opioids = total opioids excluding extended release oxycodone, extended release oxymorphone, and unidentified oxycodone and oxymorphone products

[†] The interaction p-value indicates the probability that the change in rates for the two drug groups is different.

Figure 4. Opana ER Drug Diversion Program rates per 100,000 population

Key Findings: Opana ER average diversion rates decreased 56% following introduction of the ADF. This decline was greater than the change observed for other opioids, indicating that there was not a secular trend that explains the decrease.



Drug group	Average rate (95% CI) Pre ADF	Average rate (95% CI) Post ADF	Average percent change (95% CI)	p-value	Interaction p-value [†]
Opana® ER	0.076 (0.066 to 0.087)	0.033 (0.027 to 0.042)	-56.1 (-66.3% to -42.9%)	<.001	<.001
Other Opioids*	2.489 (2.259 to 2.743)	2.757 (2.464 to 3.086)	10.8% (-4.5 to 28.5)	0.178	.

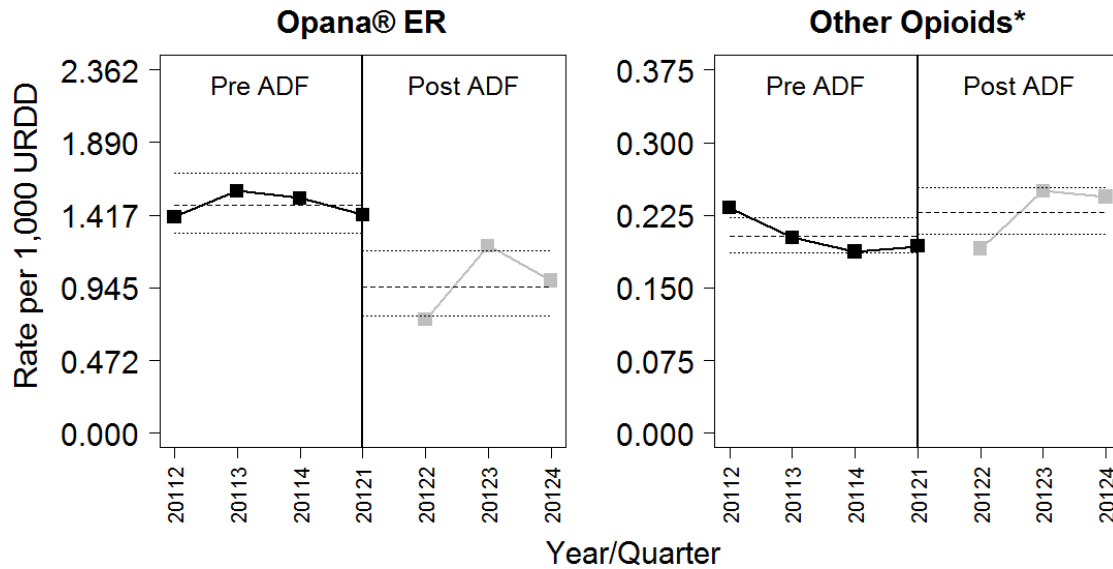
CI = confidence intervals

* Other Opioids = total opioids excluding extended release oxycodone, extended release oxymorphone, and unidentified oxycodone and oxymorphone products

[†] The interaction p-value indicates the probability that the change in rates for the two drug groups is different.

Figure 5. Opana ER Drug Diversion Program rates per 1,000 URDD

Key Findings: Opana ER average diversion rates decreased 36% following introduction of the ADF. This decline was greater than the change observed for other opioids, indicating that there was not a secular trend that explains the decrease.



Drug group	Average rate (95% CI) Pre ADF	Average rate (95% CI) Post ADF	Average percent change (95% CI)	p-value	Interaction p-value [†]
Opana [®] ER	1.483 (1.299 to 1.693)	0.952 (0.763 to 1.188)	-35.8 (-50.4 to -16.9)	<.001	<.001
Other Opioids*	0.204 (0.186 to 0.223)	0.228 (0.205 to 0.253)	12.0% (-2.5 to 28.6)	0.110	.

CI = confidence intervals

URDD = Unique Recipients of Dispensed Drug

* Other Opioids = total opioids excluding extended release oxycodone, extended release oxymorphone, and unidentified oxycodone and oxymorphone products

[†] The interaction p-value indicates the probability that the change in rates for the two drug groups is different.

RADARS System StreetRx Program

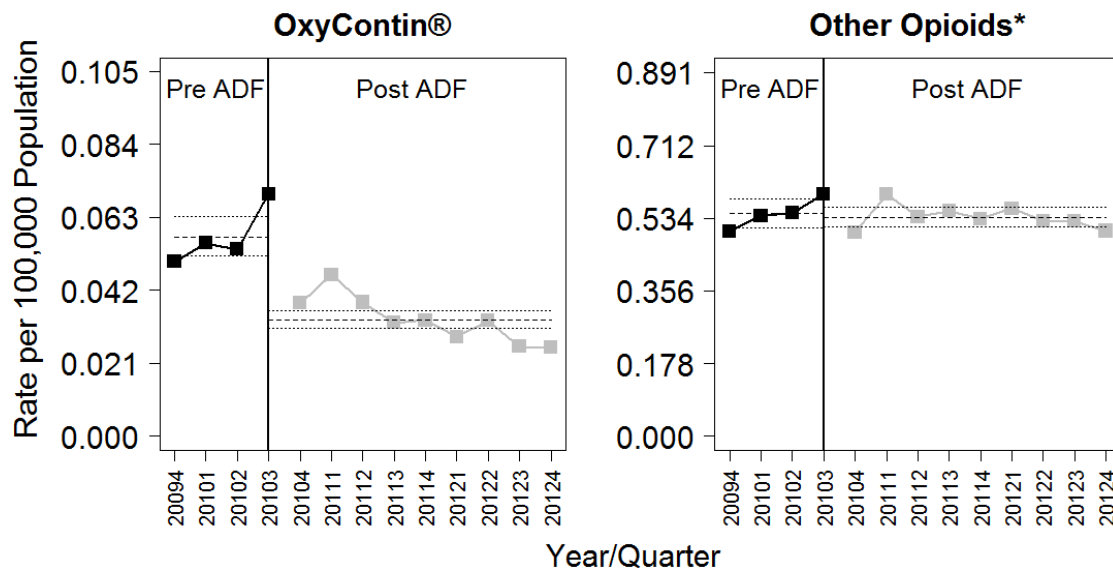
Table 1. Median street price for OxyContin and Opana ER by formulation.

Key Findings: The street price of both OxyContin and Opana ER decreased after reformulation.

Product	Median (IQR)	P-Value
OxyContin® (new OP, hard to crush)	\$0.63 (\$0.50,\$1.00)	
OxyContin® (old OC, crushable)	\$1.00 (\$0.63,\$1.25)	0.0003
Opana® ER (new, hard to crush)	\$1.00 (\$0.40,\$1.00)	
Opana® ER (old crushable)	\$1.38 (\$1.00,\$2.67)	0.0580

Figure 6. OxyContin Poison Center Program intentional abuse exposure endorsement rates per 100,000 population

Key Findings: OxyContin average intentional abuse exposure endorsement rates decreased 42% following introduction of the ADF. This decline was greater than the change observed for other opioids, indicating that there was not a secular trend that explains the decrease.



Drug group	Average rate (95% CI) Pre ADF	Average rate (95% CI) Post ADF	Average percent change (95% CI)	p-value	Interaction p-value [†]
OxyContin®	0.057 (0.052 to 0.063)	0.034 (0.031 to 0.036)	-41.6 (-48.6 to -33.7)	<.001	<.001
Other Opioids*	0.546 (0.511 to 0.583)	0.537 (0.514 to 0.560)	-1.7% (-9.1 to 6.4)	0.675	.

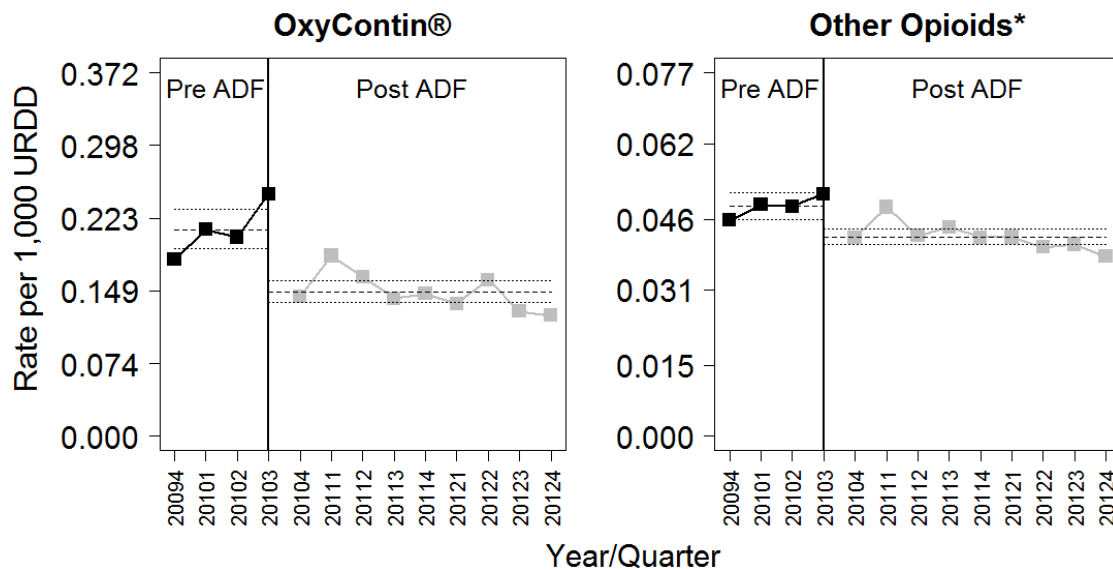
CI = confidence intervals

* Other Opioids = total opioids excluding extended release oxycodone, extended release oxymorphone, and unidentified oxycodone and oxymorphone products

[†] The interaction p-value indicates the probability that the change in rates for the two drug groups is different.

Figure 7. OxyContin Poison Center Program intentional abuse exposure endorsement rates per 1,000 URDD

Key Findings: OxyContin average intentional abuse exposure endorsement rates decreased 30 % following introduction of the ADF. This decline was greater than the change observed for other opioids, indicating that there was not a secular trend that explains the decrease.



Drug group	Average rate (95% CI) Pre ADF	Average rate (95% CI) Post ADF	Average percent change (95% CI)	p-value	Interaction p-value [†]
OxyContin®	0.211 (0.192 to 0.232)	0.148 (0.137 to 0.160)	-30.1 (-38.2 to -20.9)	<.001	0.003
Other Opioids*	0.049 (0.046 to 0.052)	0.042 (0.041 to 0.044)	-13.3 (-19.2 to -6.9)	<.001	.

CI = confidence intervals

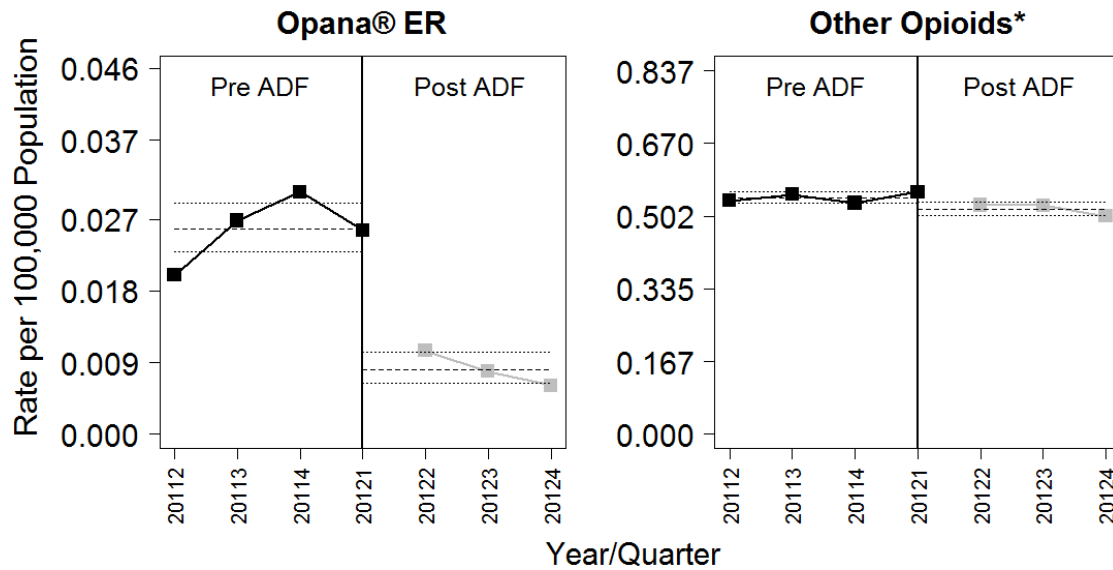
URDD = Unique Recipients of Dispensed Drugs

* Other Opioids = total opioids excluding extended release oxycodone, extended release oxymorphone, and unidentified oxycodone and oxymorphone products

[†] The interaction p-value indicates the probability that the change in rates for the two drug groups is different.

Figure 8. Opana ER Poison Center Program intentional abuse exposure endorsement rates per 100,000 population

Key Findings: Opana ER average intentional abuse exposure endorsement rates decreased 68% following introduction of the ADF. This decline was greater than the change observed for other opioids, indicating that there was not a secular trend that explains the decrease.



Drug group	Average rate (95% CI) Pre ADF	Average rate (95% CI) Post ADF	Average percent change (95% CI)	p-value	Interaction p-value [†]
Opana® ER	0.026 (0.023 to 0.029)	0.008 (0.006 to 0.010)	-68.4 (-75.8 to -58.8)	<.001	<.001
Other Opioids*	0.545 (0.532 to 0.559)	0.519 (0.504 to 0.535)	-4.8 (-8.5 to -1.0)	0.013	.

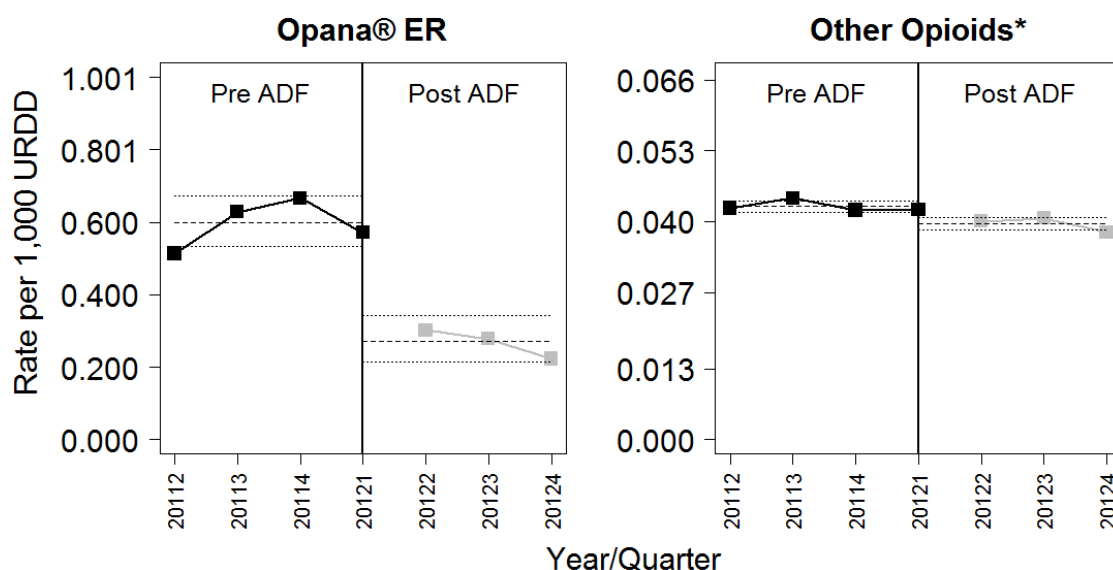
CI = confidence intervals

* Other Opioids = total opioids excluding extended release oxycodone, extended release oxymorphone, and unidentified oxycodone and oxymorphone products

[†] The interaction p-value indicates the probability that the change in rates for the two drug groups is different.

Figure 9. Opana ER Poison Center Program intentional abuse exposure endorsement rates per 1,000 URDD

Key Findings: Opana ER average intentional abuse exposure endorsement rates decreased 55% following introduction of the ADF. This decline was greater than the change observed for other opioids, indicating that there was not a secular trend that explains the decrease.



Drug group	Average rate (95% CI) Pre ADF	Average rate (95% CI) Post ADF	Average percent change (95% CI)	p-value	Interaction p-value [†]
Opana® ER	0.599 (0.533 to 0.673)	0.271 (0.213 to 0.343)	-54.8 (-65.3 to -41.1)	<.001	<.001
Other Opioids*	0.043 (0.042 to 0.044)	0.040 (0.038 to 0.041)	-7.4 (-11.0 to -3.7)	<.001	.

CI = confidence intervals

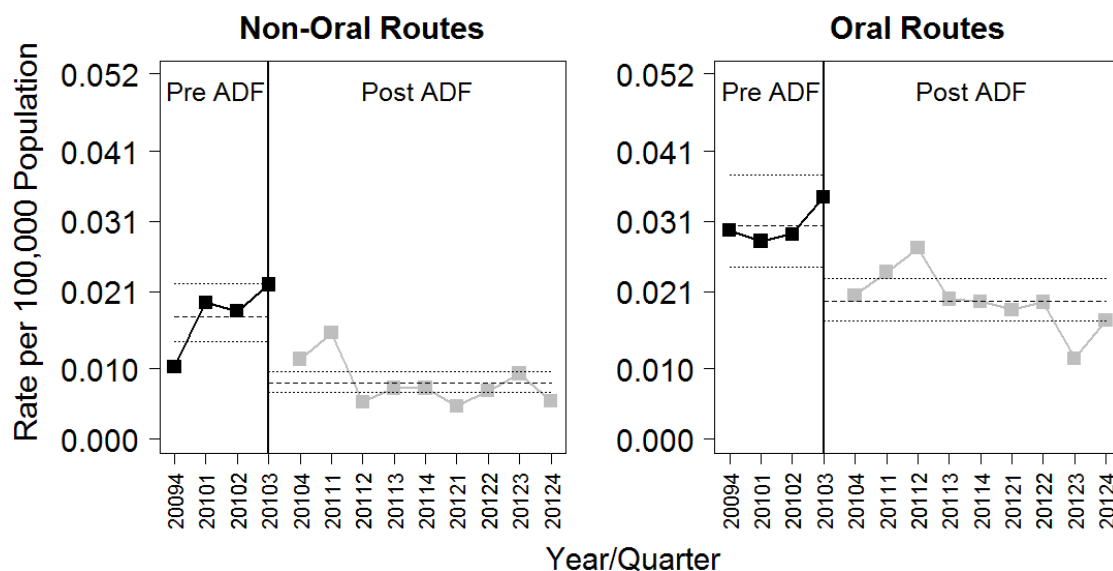
URDD = Unique Recipients of Dispensed Drugs

* Other Opioids = total opioids excluding extended release oxycodone, extended release oxymorphone, and unidentified oxycodone and oxymorphone products

[†] The interaction p-value indicates the probability that the change in rates for the two drug groups is different.

Figure 10. OxyContin Poison Center Program intentional abuse exposure endorsement rates per 100,000 population

Key Findings: OxyContin average intentional abuse exposure endorsement rates for non-oral routes decreased 54% following introduction of the ADF. This decline approached, but did not reach, statistical significance.



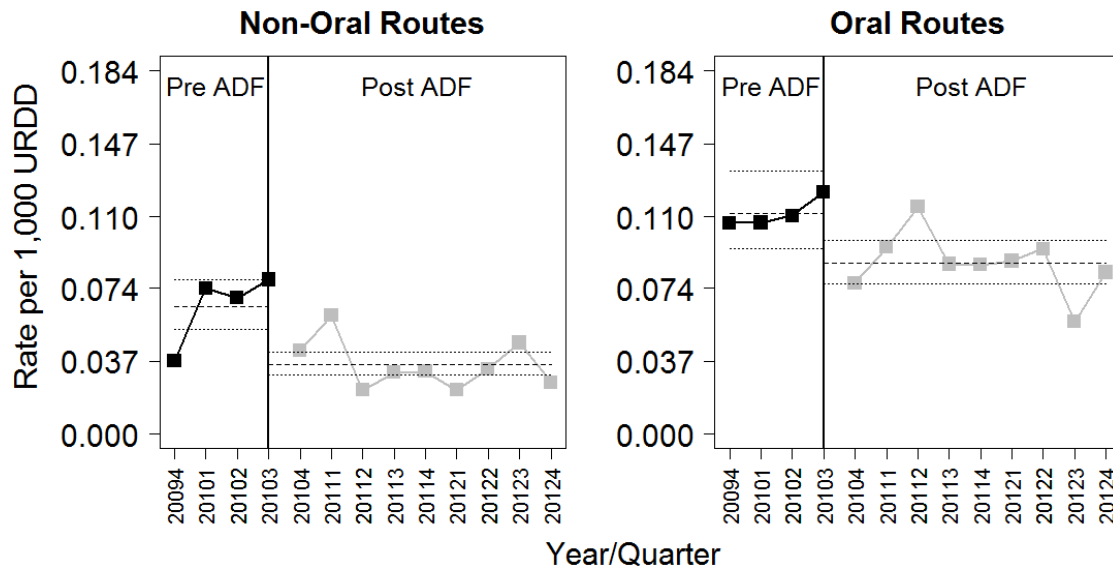
Route	Average rate (95% CI) Pre ADF	Average rate (95% CI) Post ADF	Average percent change (95% CI)	p-value	Interaction p-value [†]
OxyContin Non-Oral	0.017 (0.014 to 0.022)	0.008 (0.007 to 0.010)	-54.0 (-0.7 to -38.0)	<.001	0.093
OxyContin Oral	0.030 (0.025 to 0.038)	0.020 (0.017 to 0.023)	-35.3 (-0.5 to -15.8)	0.001	.

CI = confidence intervals

[†] The interaction p-value indicates the probability that the change in rates for Non-Oral and Oral groups is different.

Figure 11. OxyContin Poison Center Program intentional abuse exposure endorsement rates per 1,000 URDD

Key Findings: OxyContin average intentional abuse exposure endorsement rates for non-oral routes decreased 45% following introduction of the ADF. The effect for Non-Oral Route was statistically greater than for Oral route.



Route	Average rate (95% CI) Pre ADF	Average rate (95% CI) Post ADF	Average percent change (95% CI)	p-value	Interaction p-value [†]
OxyContin Non-Oral	0.064 (0.053 to 0.078)	0.035 (0.030 to 0.042)	-45.2 (-57.6 to -29.0)	<.001	0.044
OxyContin Oral	0.112 (0.094 to 0.133)	0.087 (0.076 to 0.098)	-22.6 (-37.5 to -4.0)	0.019	.

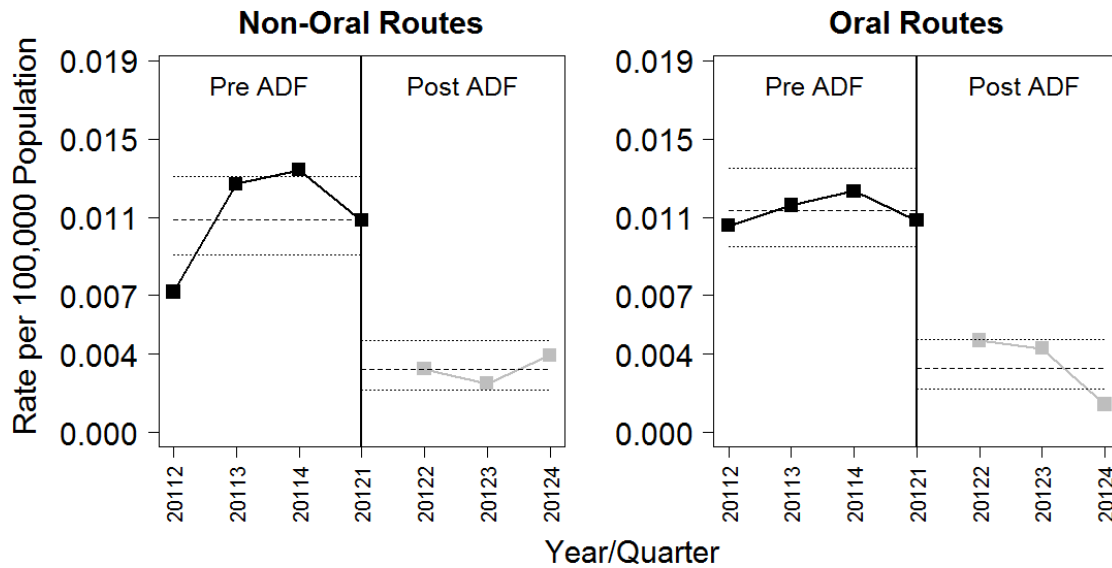
CI = confidence intervals

URDD = Unique Recipients of Dispensed Drugs

[†] The interaction p-value indicates the probability that the change in rates for Non-Oral and Oral groups is different.

Figure 12. Opana ER Poison Center Program intentional abuse exposure endorsement rates per 100,000 population

Key Findings: Opana ER average intentional abuse exposure endorsement rates for non-oral routes decreased 71% following introduction of the ADF. This decline was not greater than the change observed for oral routes.



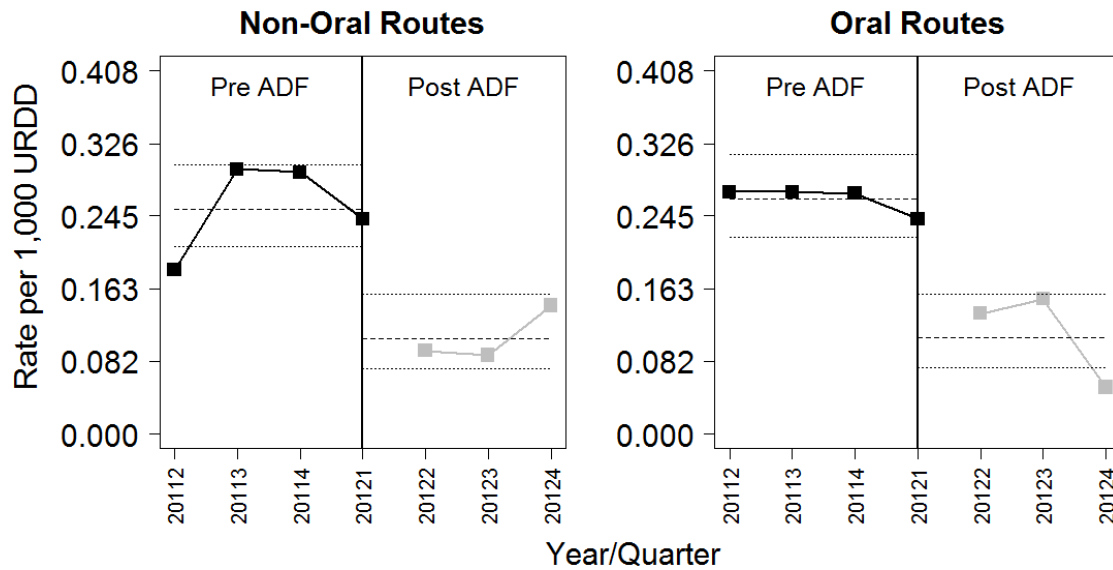
Route	Average rate (95% CI) Pre ADF	Average rate (95% CI) Post ADF	Average percent change (95% CI)	p-value	Interaction p-value [†]
Opana ER Non-Oral	0.011 (0.009 to 0.013)	0.003 (0.002 to 0.005)	-70.5 (-80.6 to -55.1)	<.001	0.951
Opana ER Oral	0.011 (0.009 to 0.014)	0.003 (0.002 to 0.005)	-71.1 (-80.9 to -56.2)	<.001	.

CI = confidence intervals

[†] The interaction p-value indicates the probability that the change in rates for Non-Oral and Oral groups is different.

Figure 13. Opana ER Poison Center Program intentional abuse exposure endorsement rates per 1,000 URDD

Key Findings: Opana ER average intentional abuse exposure endorsement rates for non-oral routes decreased 57% following introduction of the ADF. This decline was not greater than the change observed for oral routes.



Route	Average rate (95% CI) Pre ADF	Average rate (95% CI) Post ADF	Average percent change (95% CI)	p-value	Interaction p-value [†]
Opana ER Non-Oral	0.252 (0.211 to 0.302)	0.107 (0.074 to 0.157)	-57.4 (-72.0 to -35.3)	<.001	0.898
Opana Oral	0.264 (0.221 to 0.314)	0.108 (0.074 to 0.157)	-59.0 (-72.9 to -37.9)	<.001	.

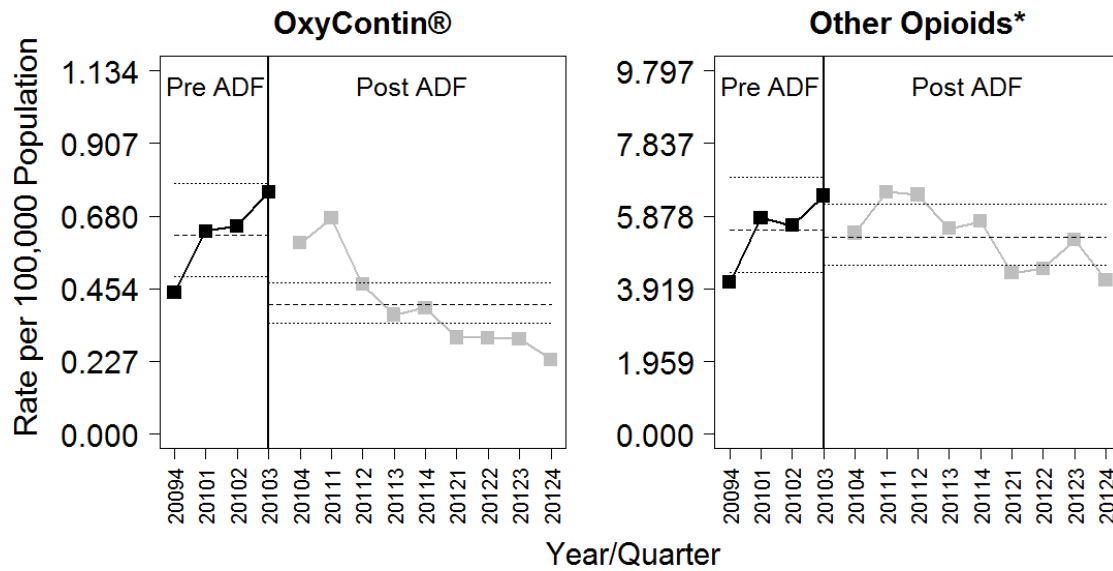
CI = confidence intervals

URDD = Unique Recipients of Dispensed Drugs

[†] The interaction p-value indicates the probability that the change in rates for Non-Oral and Oral groups is different.

Figure 14. OxyContin Treatment Center Programs past 30-day abuse endorsement rates per 100,000 population

Key Findings: OxyContin average past 30-day abuse endorsement rates decreased 35% following introduction of the ADF. This decline was greater than the change observed for other opioids, indicating that there was not a secular trend that explains the decrease.



Drug group	Average rate (95% CI) Pre ADF	Average rate (95% CI) Post ADF	Average percent change (95% CI)	p-value	Interaction p-value [†]
OxyContin®	0.620 (0.491 to 0.782)	0.404 (0.345 to 0.472)	-34.9 (-50.8 to -13.9)	0.003	0.048
Other Opioids*	5.493 (4.364 to 6.914)	5.320 (4.563 to 6.202)	-3.1 (-26.5 to 27.7)	0.821	.

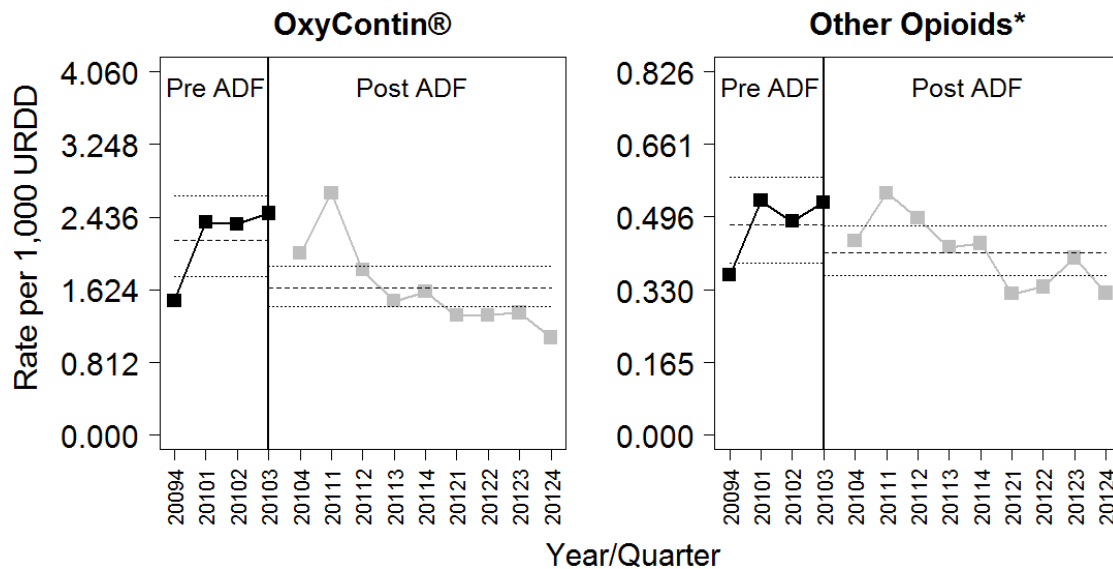
CI = confidence intervals

* Other Opioids = total opioids excluding extended release oxycodone, extended release oxymorphone, and unidentified oxycodone and oxymorphone products

[†] The interaction p-value indicates the probability that the change in rates for the two drug groups is different.

Figure 15. OxyContin Treatment Center Programs past 30-day abuse endorsement rates per 1,000 URDD

Key Findings: OxyContin average past 30-day abuse endorsement rates decreased 24% following introduction of the ADF. This decline was not greater than the change observed for other opioids.



Drug group	Average rate (95% CI) Pre ADF	Average rate (95% CI) Post ADF	Average percent change (95% CI)	p-value	Interaction p-value [†]
OxyContin®	2.178 (1.773 to 2.676)	1.648 (1.436 to 1.892)	-24.3 (-40.9 to -3.0)	0.028	0.443
Other Opioids*	0.478 (0.390 to 0.586)	0.415 (0.362 to 0.475)	-13.3 (-32.1 to 10.7)	0.253	.

CI = confidence intervals

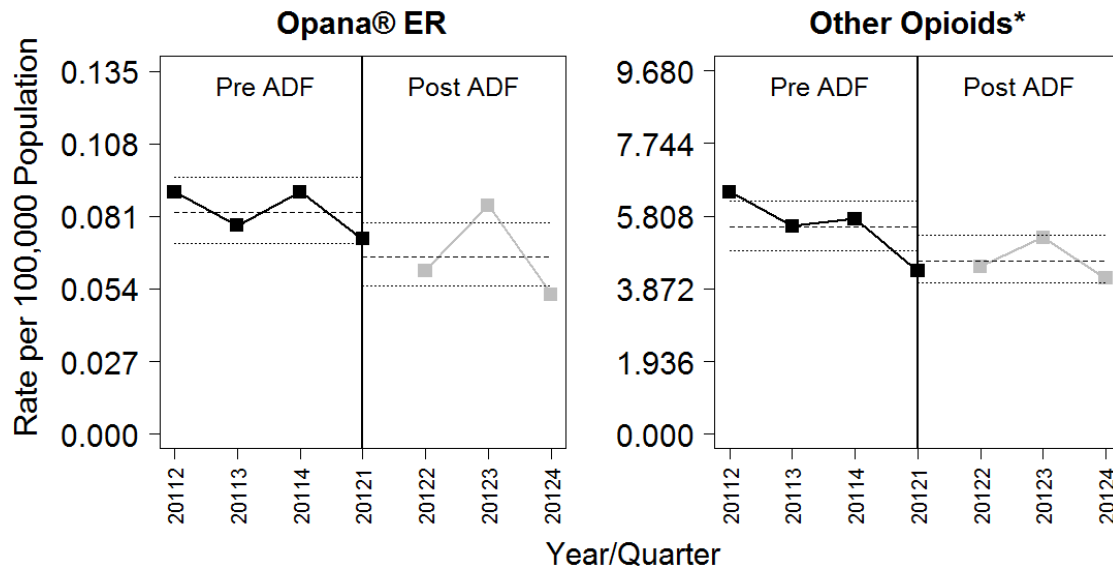
URDD = Unique Recipients of Dispensed Drugs

* Other Opioids = total opioids excluding extended release oxycodone, extended release oxymorphone, and unidentified oxycodone and oxymorphone products

[†] The interaction p-value indicates the probability that the change in rates for the two drug groups is different.

Figure 16. Opana ER Treatment Center Programs past 30-day abuse endorsement rates per 100,000 population

Key Findings: Opana ER average past 30-day abuse endorsement rates decreased 20%, but were marginally statistically significant following introduction of the ADF. This decline was not greater than the change observed for other opioids.



Drug group	Average rate (95% CI) Pre ADF	Average rate (95% CI) Post ADF	Average percent change (95% CI)	p-value	Interaction p-value [†]
Opana® ER	0.082 (0.071 to 0.096)	0.066 (0.055 to 0.079)	-20.2 (-36.8 to 0.8)	0.058	0.754
Other Opioids*	5.518 (4.894 to 6.221)	4.617 (4.020 to 5.304)	-16.3 (-30.3 to 0.5)	0.057	.

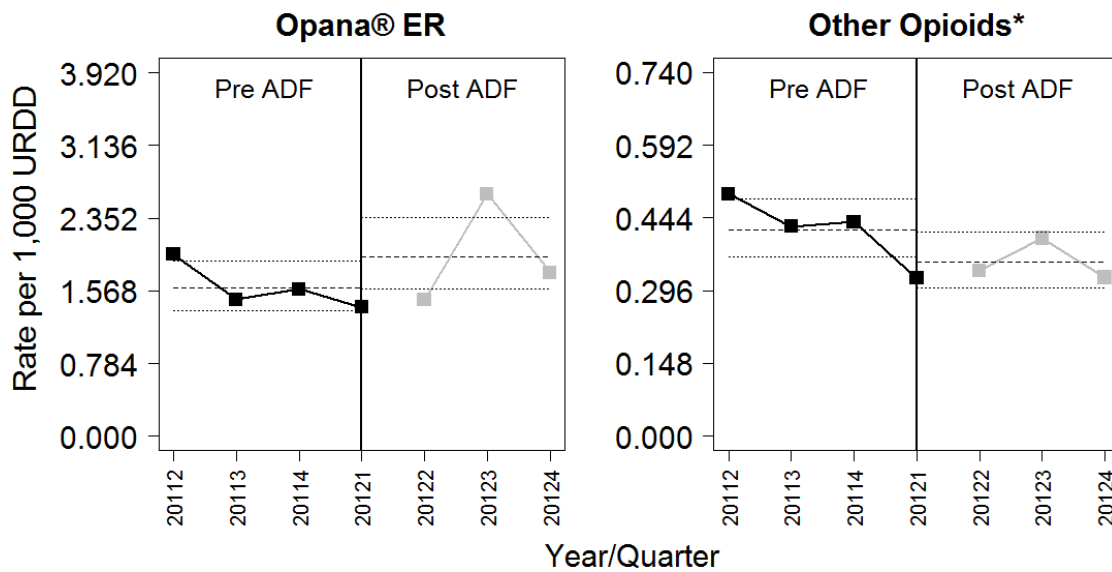
CI = confidence intervals

* Other Opioids=total opioids excluding extended release oxycodone, extended release oxymorphone, and unidentified oxycodone and oxymorphone products

[†] The interaction p-value indicates the probability that the change in rates for the two drug groups is different.

Figure 17. Opana ER Treatment Center Programs past 30-day abuse endorsement rates per 1,000 URDD

Key Findings: Opana ER average past 30-day abuse endorsement rates are unchanged following introduction of the ADF. The group of Other Opioids decreased during the same period. The interaction was statistically significant.



Drug group	Average rate (95% CI) Pre ADF	Average rate (95% CI) Post ADF	Average percent change (95% CI)	p-value	Interaction p-value [†]
Opana® ER	1.597 (1.353 to 1.884)	1.935 (1.589 to 2.355)	21.2 (-6.3 to 56.7)	0.143	0.034
Other Opioids*	0.419 (0.365 to 0.482)	0.354 (0.302 to 0.416)	-15.0% (-31.7 to 4.4)	0.119	.

CI = confidence intervals

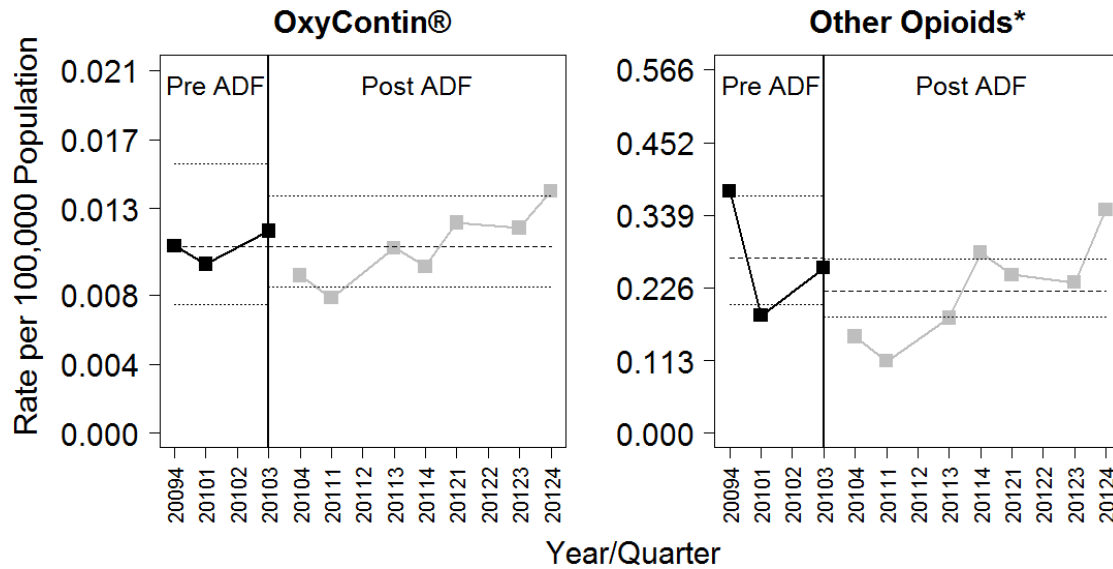
URDD = Unique Recipients of Dispensed Drugs

* Other Opioids = total opioids excluding extended release oxycodone, extended release oxymorphone, and unidentified oxycodone and oxymorphone products

[†] The interaction p-value indicates the probability that the change in rates for the two drug groups is different.

Figure 18. OxyContin College Survey Program past 3-month endorsement rates per 100,000 population

Key Findings: OxyContin average past 30-day abuse endorsement rates are unchanged following introduction of the ADF. This change was not different than the change observed for other opioids.



Drug group	Average rate (95% CI) Pre ADF	Average rate (95% CI) Post ADF	Average percent change (95% CI)	p-value	Interaction p-value [†]
OxyContin®	0.011 (0.007 to 0.016)	0.011 (0.008 to 0.014)	-0.0 (-35.6 to 55.3)	1.000	0.480
Other Opioids*	0.272 (0.201 to 0.369)	0.222 (0.181 to 0.271)	-18.6 (-43.4 to 17.1)	0.268	.

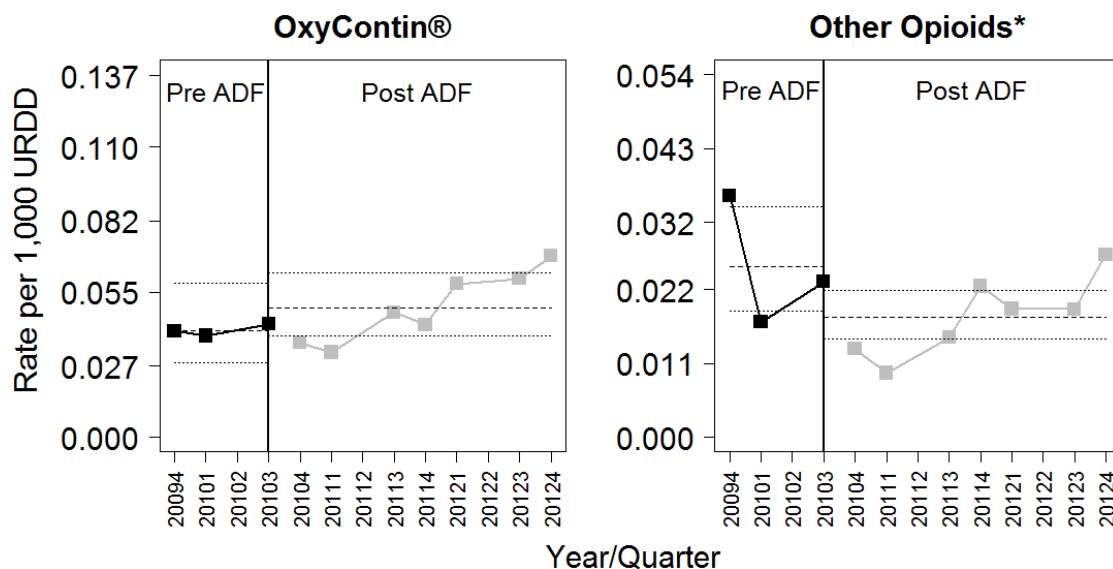
CI = confidence intervals

* Other Opioids = total opioids excluding extended release oxycodone, extended release oxymorphone, and unidentified oxycodone and oxymorphone products

[†] The interaction p-value indicates the probability that the change in rates for the two drug groups is different.

Figure 19. OxyContin College Survey Program past 3-month endorsement rates per 1,000 URDD

Key Findings: OxyContin average past 3-month endorsement rates was unchanged following introduction of the ADF. This increase was not different than the change observed for other opioids.



Drug group	Average rate (95% CI) Pre ADF	Average rate (95% CI) Post ADF	Average percent change (95% CI)	p-value	Interaction p-value [†]
OxyContin®	0.041 (0.028 to 0.059)	0.049 (0.039 to 0.062)	20.6 (-22.1 to 86.6)	0.401	0.063
Other Opioids*	0.025 (0.019 to 0.034)	0.018 (0.015 to 0.022)	-29.5 (-50.8 to 1.0)	0.057	.

CI = confidence intervals

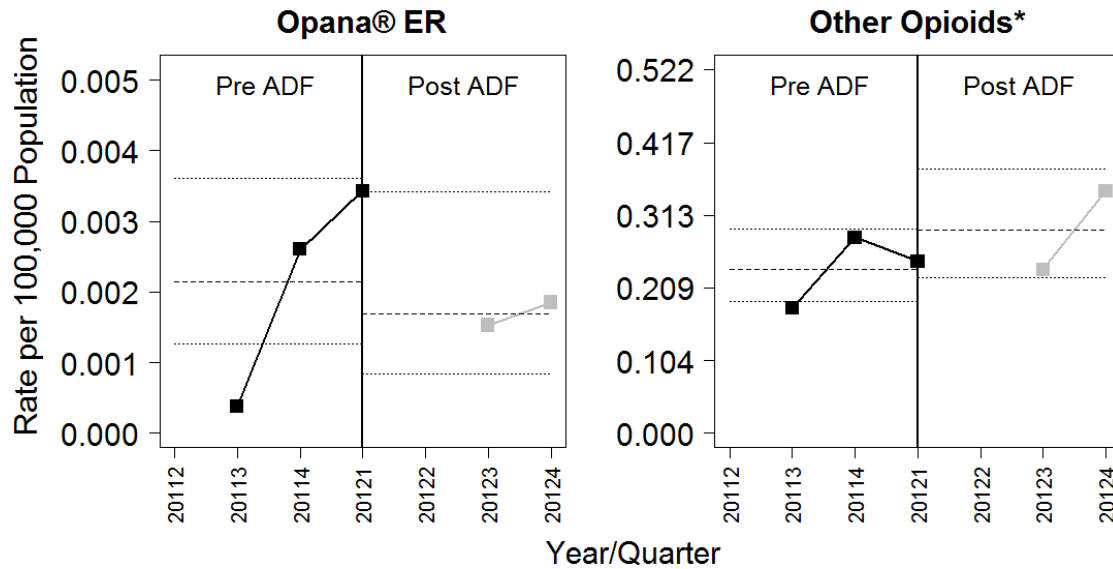
URDD = Unique Recipients of Dispensed Drugs

* Other Opioids = total opioids excluding extended release oxycodone, extended release oxymorphone, and unidentified oxycodone and oxymorphone products

[†] The interaction p-value indicates the probability that the change in rates for the two drug groups is different.

Figure 20. Opana ER College Survey Program past 3-month endorsement rates per 100,000 population

Key Findings: Opana ER average past 3-month endorsement rates was unchanged following introduction of the ADF. This decline was not different than the change observed for other opioids.



Drug group	Average rate (95% CI) Pre ADF	Average rate (95% CI) Post ADF	Average percent change (95% CI)	p-value	Interaction p-value [†]
Opana® ER	0.002 (0.001 to 0.004)	0.002 (0.001 to 0.003)	-21.0 (-67.1 to 89.4)	0.597	0.349
Other Opioids*	0.235 (0.190 to 0.292)	0.291 (0.224 to 0.379)	23.7 (-12.1 to 74.1)	0.223	.

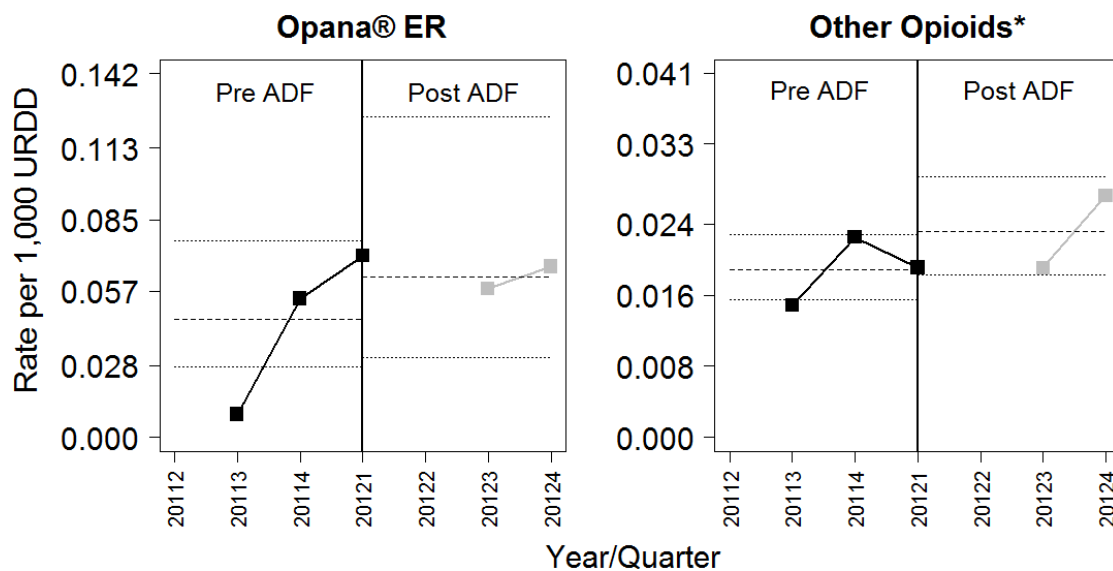
CI = confidence intervals

* Other Opioids = total opioids excluding extended release oxycodone, extended release oxymorphone, and unidentified oxycodone and oxymorphone products

[†] The interaction p-value indicates the probability that the change in rates for the two drug groups is different.

Figure 21. Opana ER College Survey Program past 3-month endorsement rates per 1,000 URDD

Key Findings: Opana ER average past 3-month endorsement rates was unchanged following introduction of the ADF. This increase was not different than the change observed for other opioids.



Drug group	Average rate (95% CI) Pre ADF	Average rate (95% CI) Post ADF	Average percent change (95% CI)	p-value	Interaction p-value [†]
Opana® ER	0.046 (0.028 to 0.077)	0.062 (0.031 to 0.125)	35.7 (-42.7 to 221.4)	0.487	0.833
Other Opioids*	0.019 (0.015 to 0.023)	0.023 (0.018 to 0.029)	23.0 (-9.6 to 67.2)	0.188	.

CI = confidence intervals

URDD = Unique Recipients of Dispensed Drugs

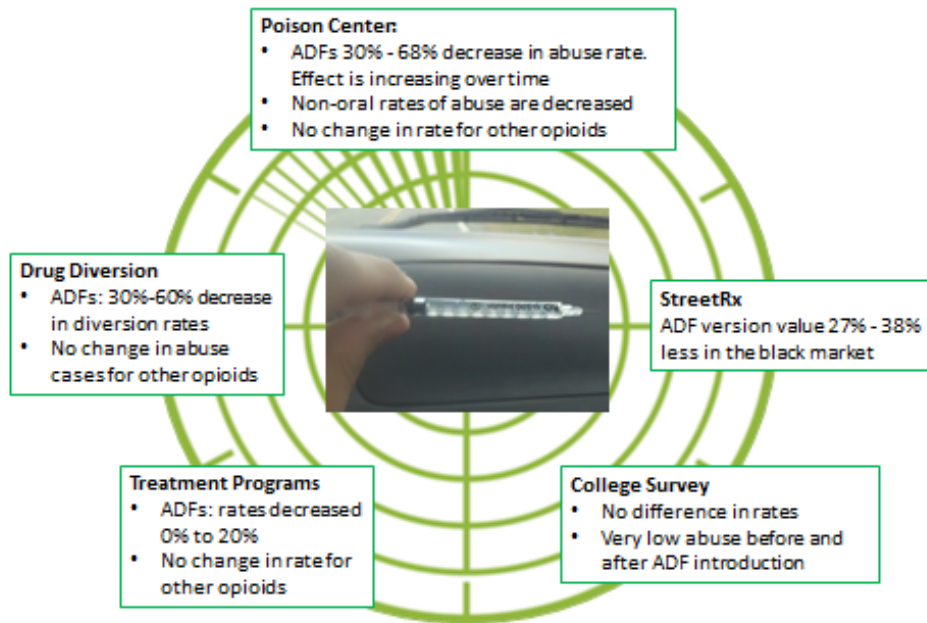
* Other Opioids = total opioids excluding extended release oxycodone, extended release oxymorphone, and unidentified oxycodone and oxymorphone products

[†] The interaction p-value indicates the probability that the change in rates for the two drug groups is different.

Assessment

Mosaic assessment: Data from RADARS System programs indicate that diversion and abuse of OxyContin and Opana ER have fallen substantially since the introduction of their reformulated versions:

Summary of Surveillance of Abuse Deterrent Formulations by RADARS® System



Of note, recalculation of the rates adjusting for drug availability as represented by URDD does not eliminate the observed relationship. Therefore, the data indicate that both reduction in people filling prescriptions of the ADF drug and reduction of abuse by individuals who do fill a prescription contribute to the effect. The effect was not explained by secular trends in overall abuse of prescription opioid analgesics.

Illegal street activity: The rates of diversion in the Drug Diversion Program decreased dramatically after the introduction of reformulated OxyContin and Opana ER. The rate of diversion cases for both products has continued to decrease through the fourth quarter of 2012. We examined the effect of decreased sales of the drugs by using URDD. After adjusting for the falling number of people filling a prescription, the observed decrease remained, indicating less illegal activity on the street for both OxyContin and Opana ER. Rates of diversion for other opioids continued at the same rate after introduction of the reformulated products.

Rates of diversion for OxyContin in the Drug Diversion Program have continued to decrease for the subsequent two years. This observation may be caused by the unexpected and prolonged availability of the original OxyContin formulation through illicit channels. The proportion of drug identified by drug diversion investigators that were the original OxyContin formulation

decreased to 29% in 2012. This observation suggests that a large reservoir of original formulation OxyContin was present at the time it was discontinued or that drug is entering the United States from other countries. Thus, the preferred original formulation has remained available for a prolonged period despite the fact that the original version has not been sold to pharmaceutical distributors in the US since August 9, 2010. The gradual decline in the availability of the original OxyContin may explain the progressive decrease in diversion.

Street Price: Consistent with the data from the Drug Diversion Program, the price of the reformulated versions is lower than that of the original formulation for both OxyContin and Opana ER. This observation suggests that the new formulations are less desirable.

Acute health events: People call a poison center when they believe that they are sick or are concerned about a drug they have taken. In the Poison Center Program, the abuse rate for OxyContin and Opana ER has decreased greatly since the introduction of ADF. In the case of OxyContin, the downward trend has continued and intensified through the 2.5 years since the introduction of the reformulated OxyContin. As described in Drug Diversion Program summary above, this phenomenon may be due to slow clearance of the original formulation from the black market. Rates of abuse for other opioids continued at the same rate after introduction of the reformulated products.

Patients that are dependent on prescription opioids: The rate of endorsement by patients entering treatment for substance abuse decreased for OxyContin per population. This trend was not observed for Opana ER. The follow-up period for Opana ER may be too short because it was introduced more recently. Also, the retrospective nature of the survey (past month abuse) suggests that there may be a lag in the observed reduction in Opana ER abuse. Results from OxyContin suggest that the decline in abuse in the treatment programs appeared approximately two quarters following reformulation.

Young initiates: The College Survey Program did not demonstrate a change after the introduction of reformulated OxyContin or Opana ER. This observation could be due to the fact that endorsement of nonmedical use was already very low for OxyContin and Opana ER (roughly 10% of rate for other opioids). Therefore, it may not be reasonable to expect a decrease. The low non-medical use rate may be due to the fact that non-oral routes of abuse comprise a small proportion of respondents in the College Survey Program. Finally, the low case counts suggest the power to detect a difference is very low. In short, the College Survey Program may be less effective than other programs in detecting the impact of formulation change in the target population, individuals who tamper with these products prior to abusing them.

Analysis of Causality

Observational data like those from the RADARS System cannot prove that the introduction of ADF was the cause of the observed reductions. Correlation does not prove causation. However,

the relationship of ADF introduction for OxyContin and Opana fulfills several of the Hill criteria for causation.

- **Strength of association** is notable for both products. A large relative decrease in mean diversion or abuse rates was observed in all programs except College Survey. Furthermore, the observed rates decreased as diminishing amounts of original formulation OxyContin are present on the street.
- **Consistency.** The decrease in reported events after introduction of the reformulated products is evident in nearly all groups studied, including diversion on the street (Drug Diversion Program), acute health events (Poison Center Program), individuals entering treatment for substance abuse (Treatment Programs) as well as the street price of the drugs. The one exception is College Survey Program.
- **Specificity.** The effect is specific to the formulations studied. In most cases, the decrease in rates for the reformulated products was not evident for Other Opioids combined.
- **Temporal relationship** is strong for both drugs. After increasing oxycodone abuse in all programs for many years, the introduction of reformulated OxyContin was followed not only by reversal of the upward trend, but by a substantial decrease. Oxymorphone has not been followed for as long, but shows the same trends.
- **Biological gradient.** It is difficult to create a dose-response concept for abuse of medications. However, the progressive deepening of effect as the reformulated OxyContin replaced the original formulation supports this concept.
- **Plausibility** is present because a well-defined intervention was introduced that is focused on a specific group (abuse that requires crushing like snorting or injection). The Poison Center Program records route of administration. The reduction in OxyContin abuse was largest in the group that abuses non-orally.
- **Coherence** is shown by the concordance of comments posted by abusers and RADARS System surveillance. Comments regarding abuse of the original formulations of OxyContin and Opana ER have strongly endorsed the abusability of these products. In contrast, blog comments condemn the difficulty in abusing the reformulated products. These external everyday comments correspond well to the results of postmarketing surveillance.
- **Experiment (reversibility)** cannot yet be demonstrated. However, other natural experiments have developed that will provide useful information. For example, Canada has recently approved generic version of the original OxyContin formulation.
- **Analogy (alternate explanations).** There are several potential alternate explanations for the observed effect. However, they are much less likely than the explanation that ADFs are effective in deterring abuse.
 - The most commonly proposed explanation is that some other intervention is confounding the measurement. For example, could state-based prescription drug monitoring plans (PDMPs) explain the decrease? This source seems unlikely because PDMPs would be expected to reduce the abuse of all opioid

analgesics and the data indicate that the decrease was specific to the reformulated products.

- Increased attention by law enforcement or other programs may explain the decreasing rates of abuse for OxyContin and Opana ER. The problem with these explanations is that interdiction efforts are generally aimed at all illegal diversion of opioid analgesics, not just the two products studied. In fact, we found that in general, the rates for diversion and abuse of Other Opioid analgesics continued unabated.
- Another drug effect has led to decreased abuse. While not yet completely understood, a blood dyscrasia may be associated with the intravenous use of Opana ER.(11) The effect and timing of this discovery relative to the introduction of the reformulated version is unclear. However, this issue would influence only Opana ER and not OxyContin.
- It is possible that some of the observed effect was due to decreased prescriptions for the drug. This is an expected outcome because decreased attractiveness for abuse should decrease the number of people attempting to inappropriately procure prescriptions (or forge prescriptions), thereby reducing the number of people filing a prescription for the drug. This effect was found and indicates a beneficial effect. We also found that the reduction in event ratio was still statistically significant after adjustment for URDD in all programs except College Survey.

Conclusions

Hypothesis 1: the number of people filling prescriptions for OxyContin and Opana ER (URDD) would be lower in the quarters following reformulation relative to the year prior to reformulation.

The average URDD per quarter declined 15% for OxyContin and 31% for Opana ER following reformulation.

Hypothesis 2: Rates of abuse and diversion of OxyContin and Opana ER would be lower following introduction of the reformulations reflecting lower levels of abuse. This decline would be different than changes in other prescription opioids and would be independent of changes in drug availability. In contrast, rates of abuse for other opioid analgesics did not decrease.

For both OxyContin and Opana ER, rates of diversion were markedly decreased. Intentional abuse rates in the Poison Center Program were lower following introduction of their reformulated versions. The effect still observed after adjustment for availability of the drug (URDD) and was significantly different than trends observed for other opioids. The street price for the reformulation of OxyContin was significantly less than the street price for the original formulation in the time period after reformulation. The street price for the reformulation of Opana ER was lower but not significantly different than the original formulation. Rates of OxyContin abuse declined in treatment programs

per population. No other differences were observed in the Treatment Programs or in the College Survey Program.

Hypothesis 3: Use of these drugs through non-oral routes of abuse would decline relative to oral abuse because the new products were intended to deter crushing and solubilization of the drugs. For OxyContin, declines in use through non-oral routes tended to be greater than declines in use through oral routes. This was not observed for Opana ER. For both Opana ER and OxyContin, significant declines were observed in abuse through both oral and non-oral rates.

It appears likely that the introduction of ADF reformulations of prescription opioids results in the reduction of abuse for those products. Therefore, the original formulations are less safe than the reformulated versions. In light of this national data from several perspectives, it would be poor policy to approve new formulations of prescription opioid analgesics that can be easily crushed and solubilized for abuse when safer products are available.

References

1. http://www.coloradoattorneygeneral.gov/sites/default/files/press_releases/2013/03/11/031113_fda_letter.pdf, accessed March 14, 2013
2. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm334785.htm>, accessed March 14, 2013
3. <http://www.claad.org/>, accessed March 14, 2012
4. [http://forum.opiophile.org/showthread.php?43129-Global-Pharma-s-Generic-15mg-\(g76\)-Review](http://forum.opiophile.org/showthread.php?43129-Global-Pharma-s-Generic-15mg-(g76)-Review)
5. <http://www.drugs-forum.com/forum/showthread.php?t=185912>
6. http://blogs.seattleweekly.com/dailyweekly/2011/01/top_three_weirdest_ways_to_abu.php
7. http://www.grunenthal.com/grt-intac/GRT-INTAC_en_Home/INTAC_/Q&A_/212100129.jsp;jsessionid=C2FA05F78DAC6D4E79D5729E7BB8E6EC.drp1, accessed March 14, 2013.
8. Dart RC. Monitoring risk: Post marketing surveillance and signal detection. Drug Alcohol Depend 2009;105, Supplement 1, S26-S32.
9. Butler SF, Cassidy TA, Chilcoat, H, et al. Abuse rates and routes of administration of reformulated extended-release oxycodone: initial findings from a sentinel surveillance sample of individuals assessed for substance abuse treatment. J Pain 2012 doi: pii: S1526-5900(12)00803-6. 10.1016/j.jpain.2012.08.008.
10. Severtson, S.G., Bucher Bartelson, B., Davis, J.M., Muñoz, A., Schneider, M.F., Chilcoat, H., Coplan, P.M., Surratt, H., Dart, R.C. Reduced abuse, therapeutic errors, and diversion following reformulation of extended-release oxycodone in 2010. Manuscript submitted for publication.
11. <http://www.cdc.gov/mmwr/pdf/wk/mm6201.pdf>, accessed March 14, 2013