

# Setting the Stage: Are Abuse-Deterrent Opioids Formulations Ready for Prime Time?

Lewis S. Nelson, MD

New York University School of Medicine

New York City Poison Control Center



## EPIDEMIC: RESPONDING TO AMERICA'S PRESCRIPTION DRUG ABUSE CRISIS

### Research and Development:

- Expedite research, through grants, partnerships with academic institutions, and priority New Drug Application review by FDA, on the development of treatments for pain with no abuse potential as well as on the development of abuse-deterrent formulations (ADF) of opioid medications and other drugs with abuse potential. **(NIDA/FDA)**

2011



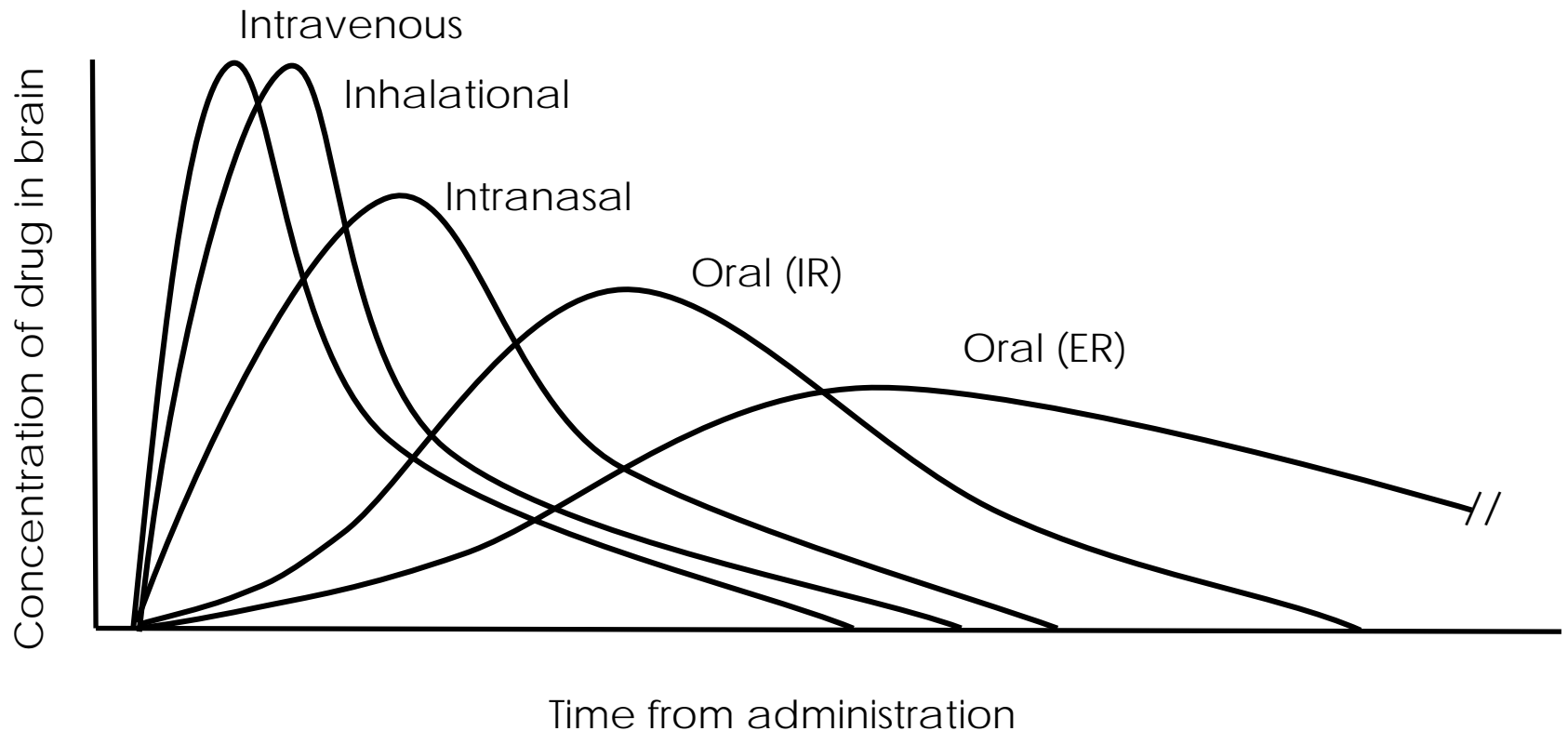
# Opioid Abuse Liability

: the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect.

FDA Guidance 2015

- Reinforcing
- Rapid onset
- High intensity
- Rapid offset
- Low cost
- Low effort

# Abuse pharmacokinetics



## **WARNING:**

**OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.**

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.


**OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.**

**OxyContin Tablets are NOT intended for use as a prn analgesic.**

**OxyContin 60 mg, 80 mg, and 160 mg Tablets, or a single dose greater than 40 mg, ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. A single dose greater than 40 mg, or total daily doses greater than 80 mg, may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory depressant effects of opioids.**

**OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.**

# What does Abuse Deterrent Mean?

- 
- Reinforcing
  - Rapid onset
  - High intensity

**Improve the Risk:Benefit Relationship**

- Low cost
- Low effort

**Individual Patients & Public Health**

# What does Abuse Deterrent Mean to FDA?

- 2008: has to be shown to deter abuse in appropriately designed (epidemiologic) studies
- 2012: likely to reduce abuse based on preclinical testing

excludes the definition of abuse.<sup>3</sup> This guidance uses the term *abuse-deterrent* rather than *tamper-resistant* because the latter term refers to, or is used in connection with, packaging requirements applicable to certain classes of drugs, devices, and cosmetics.<sup>4</sup>

Guidance for Industry, April 2015

- Does not mean that the formulation deters abuse *per se*
  - Deter misuse by specific routes
  - Included in labeling information

# Concepts in ADF

- Physico-chemical barriers to tampering
- Combination with antagonist that is released during inappropriate use
- Inclusion of noxious ingredients

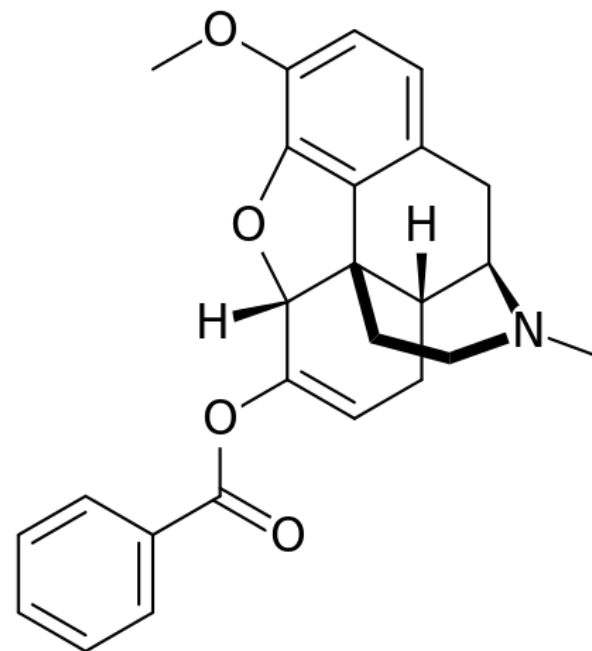
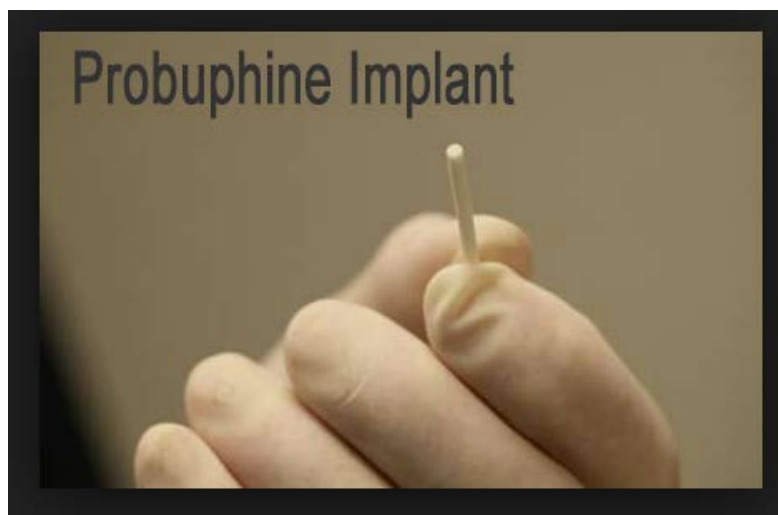
The medication still needs to work as intended



# Examples of ADFs

- OxyContin (oxycodone, crush/extraction resistant): April, 2013
- Targeniq (oxycodone hydrochloride and naloxone, aversive): July, 2014
- Embeda (morphine/naltrexone, aversive): October, 2014
- Hysingla (hydrocodone, crush/extraction resistant): November, 2014
- MorphaBond (morphine, crush/extraction resistant): October, 2015

# Potential Abuse Deterrent Formulations



benzoate-hydrocodone

# FDA Guidance

- The FDA outlines the abuse deterrence of solid oral opioid drug products
- Requires post-marketing study to assess the impact of the new formulation

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## Abuse-Deterrent Opioids — Evaluation and Labeling

Guidance for Industry

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)

Clinical Medical  
April 2015

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# Tiered Approach For Assessment of Formulations with Potential Abuse Deterrent Features

## Premarketing

1. Laboratory based in vitro manipulation and extraction studies
  - ▣ Ability to compromise preparation of drug product for administration by other routes
2. Pharmacokinetic/Pharmacodynamic (PK/PD) studies
  - ▣ Compared to original formulation
  - ▣ Assessments may depend on route of administration
3. Human abuse liability studies
  - ▣ Real world potential

## Postmarketing

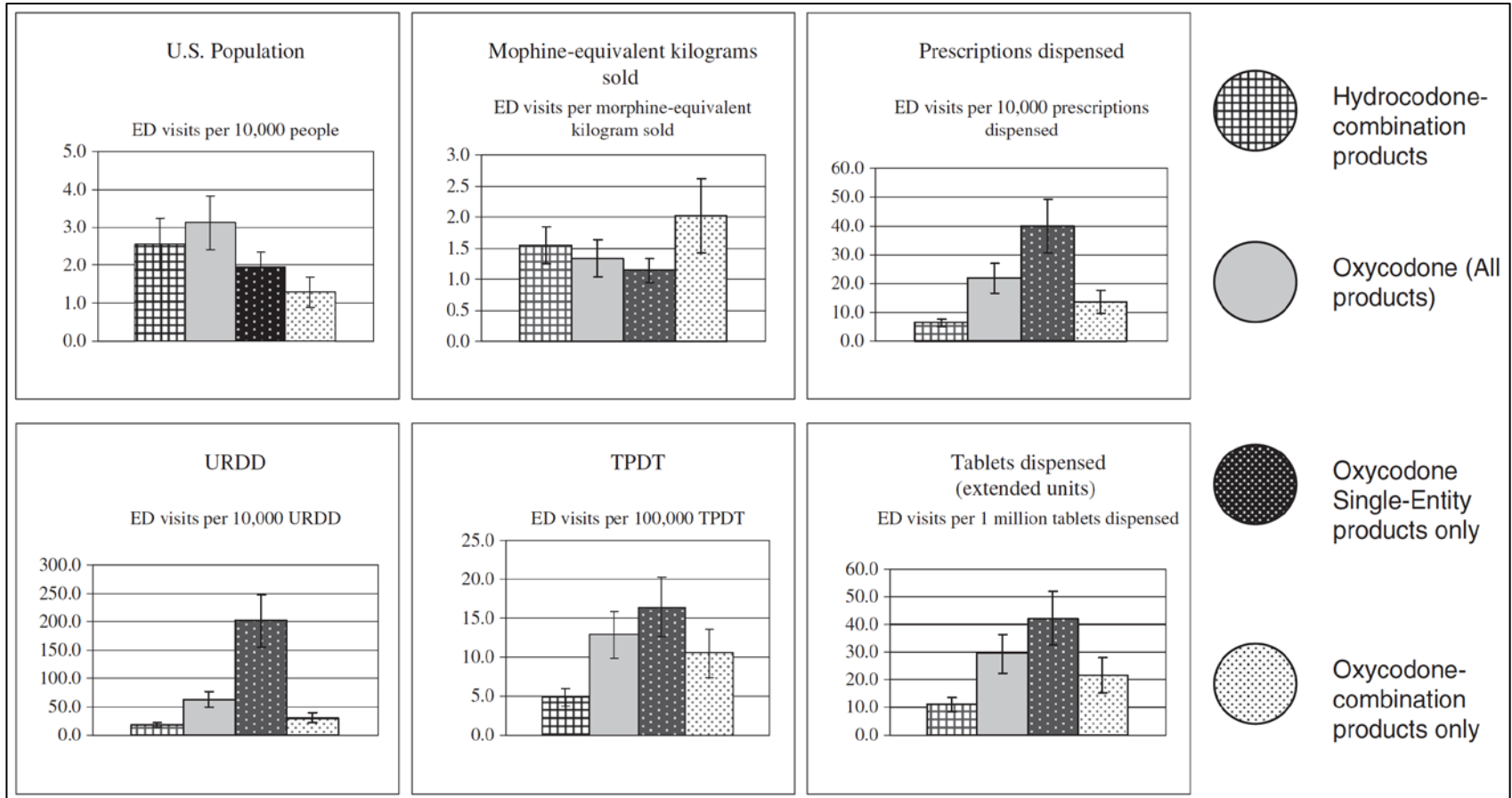
4. Assess the impact of an abuse-deterrent formulation on actual abuse

FDA: "Adaptive, flexible approach"

# Acquiring Category 4 Data

- The sources of post-marketing data have critical limitations
  - Unable to identify individual products
  - Cannot reliably differentiate routes of abuse or methods of tampering
  - Under-reporting and miscoding
  - Denominator issues

# Denominator issues



Secora AM, et al. Pharmacoepidemiol Drug Safety, 2014; 23: 1227-1237

# The Perfect ADF

- Lets just say it existed...would it help.



The Holy Grail

# OxyContin users entering treatment

- Survey pre-reformulation
- 27,816 patients
  - 157 treatment programs
- 1425 had used OC

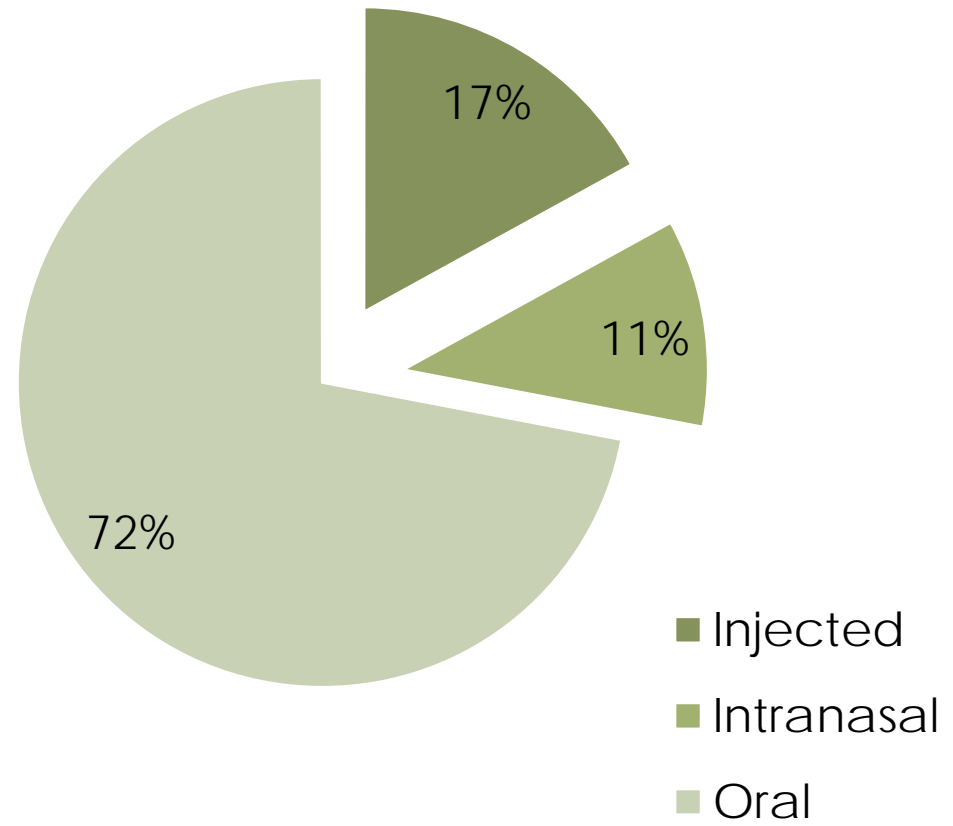
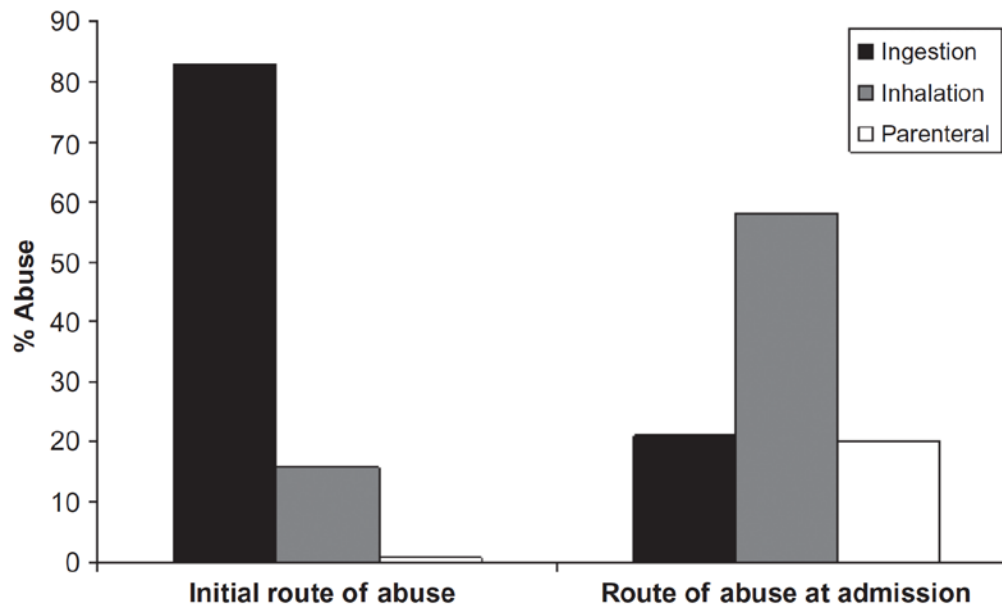




TABLE 1. Routes of administration for prescription opioids used nonmedically, by population: summary of various studies.

Study reference	Population	Route of abuse		
		Ingestion (%)	Inhalation (%)	Injection (%)
McCabe et al. (7)	College students who admit being lifetime nonmedical users of POs	97	13	.5
Davis and Johnson (8)	Drug users in New York City	66	15	4
TEDS (37)	Persons admitted to substance abuse treatment in 2006	71	15	12
TEDS (DASIS report 2004) (9)	Persons admitted to substance abuse treatment in 2002	77	8	11
NIDA-CEWG 2007 (38)	Persons admitted to substance abuse treatment in San Diego	79	8	10
NIDA-CEWG 2007 (39)	Persons admitted to substance abuse treatment in Baltimore area (2002, 2003, 2004, 2005, 2006)	79–86	6–14	ND
NIDA-CEWG 2007 (volume 2) (38)	Persons admitted to substance abuse treatment and primarily addicted to “other opiates” <sup>1</sup> in various US states in 2006	ND	ND	3–14 <sup>2</sup>
RADARS College Survey 2009 <sup>3</sup>	College students	79% swallow whole, 64% chew and swallow	52	28



## Poison Center Data

<sup>1</sup>Source Data for Figure 5

Route of misuse, abuse, or withdrawal	No effect	Minor effect	Moderate effect	Major effect	Death	Total	%	% of route leading to major/death
Ingestion	1030	2320	1982	432	67	5831	91.8	8.6
Inhalation	55	121	112	31	2	321	5.1	10.2
Parenteral	23	62	82	32	1	200	3.1	16.5
Total	1108	2503	2176	495	70	6352	100	
%	17.4	39.4	34.3	7.8	1.1	100		

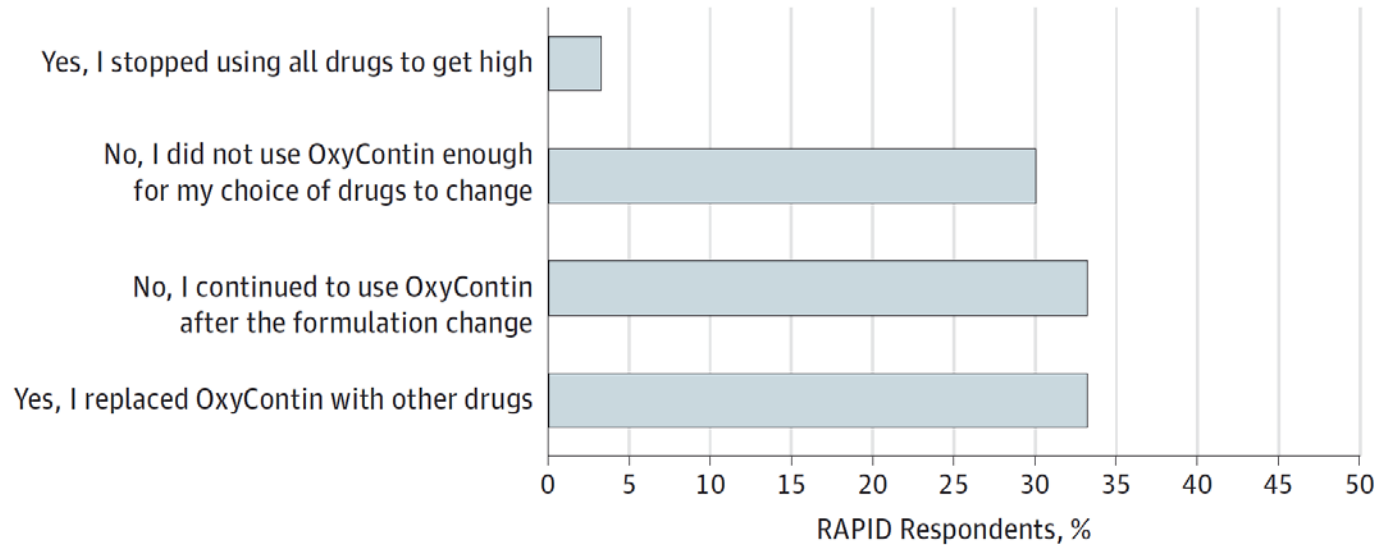
# Abuse-Deterrent Formulations and the Prescription Opioid Abuse Epidemic in the United States

## Lessons Learned From OxyContin

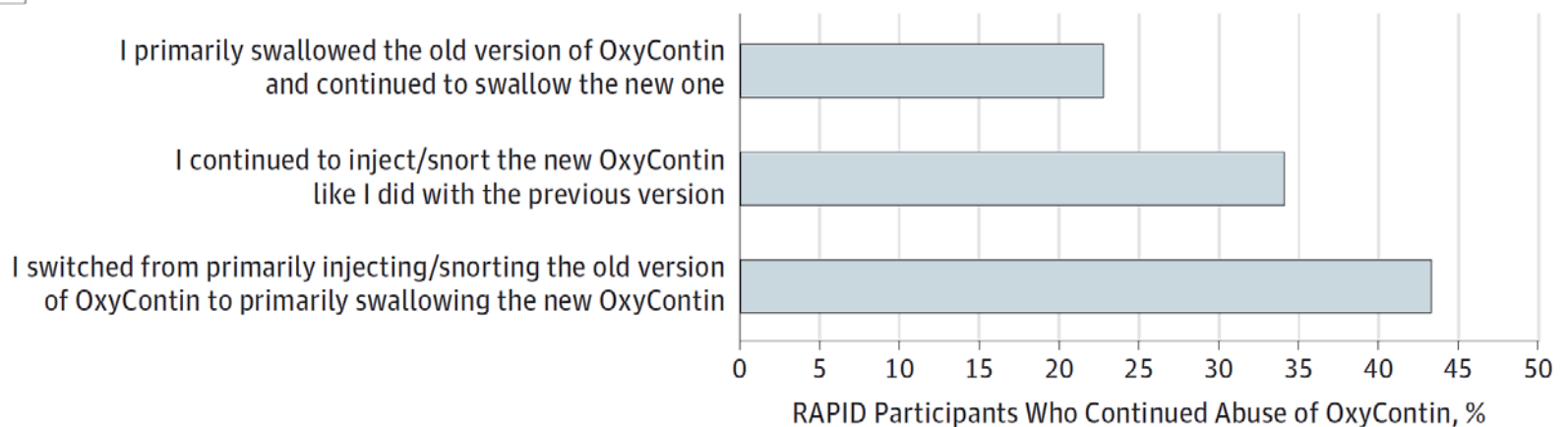
Theodore J. Cicero, PhD; Matthew S. Ellis, MPE

- Mixed methods analysis using SKIP program, entering treatment programs
  - 11,782 surveyed
  - 244 interviewed
  
- Evaluating OxyContin to get high in previous 30 days
  - Pre-reformulation (pre-2010)
    - 45%
  - Following reformulation (2012)
    - 26%

**A** Did the formulation change of OxyContin have any impact on the drugs you chose to get high with?



**B** Which of the following ways apply to your use of both new and old formulations of OxyContin to get high/alter your mood?

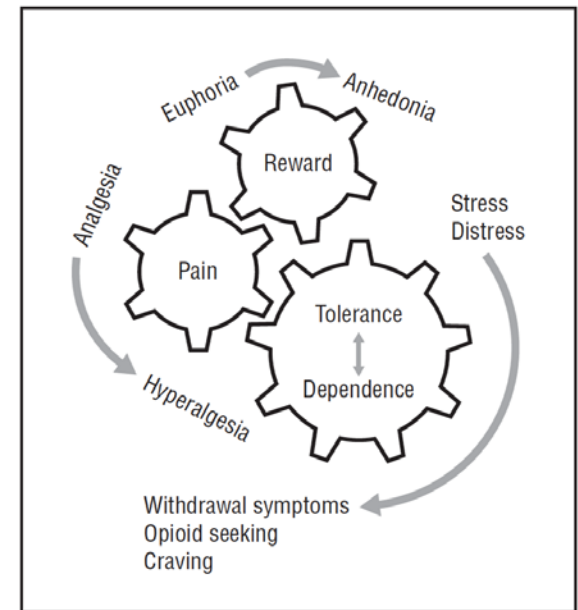


# Addiction vs Abuse

- Clearly related phenomena
  - National Institutes of Health: about 5% of patients taking opioids as directed for a year develop addiction
  - Meta-analysis (Vowles) found addiction rate (high quality studies) was between 0.7% and 23%
- The majority of addicted patients did NOT abuse

# Addiction vs Abuse

- ❑ DSM-5 excludes tolerance and withdrawal from the diagnosis of opioid use disorder
- ❑ Arises during medical drug therapy
- ❑ Only aberrant behaviors count
- ❑ May not reflect prescription drug users' behaviors



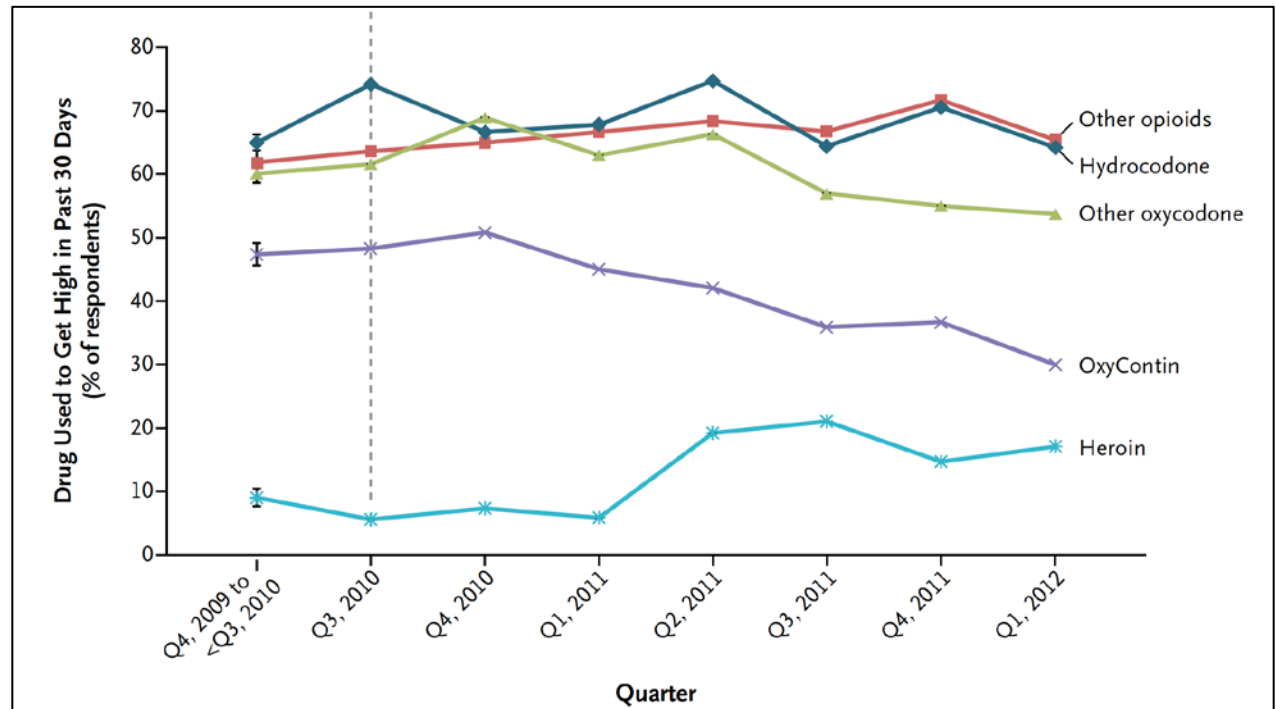
# Unintended consequences

103 Surveyed

Entering treatment program for PO addiction

24% overcame tamper resistance

66% said they switched to another opioid, primarily heroin

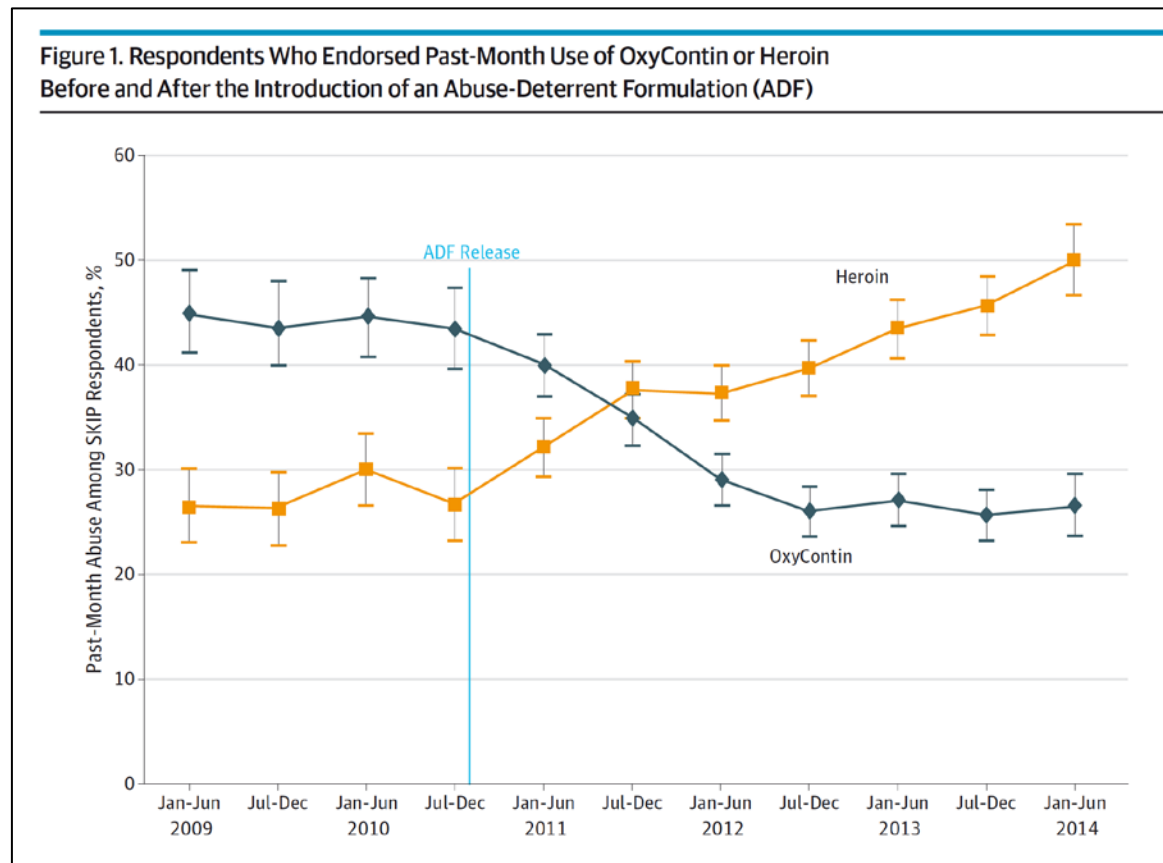


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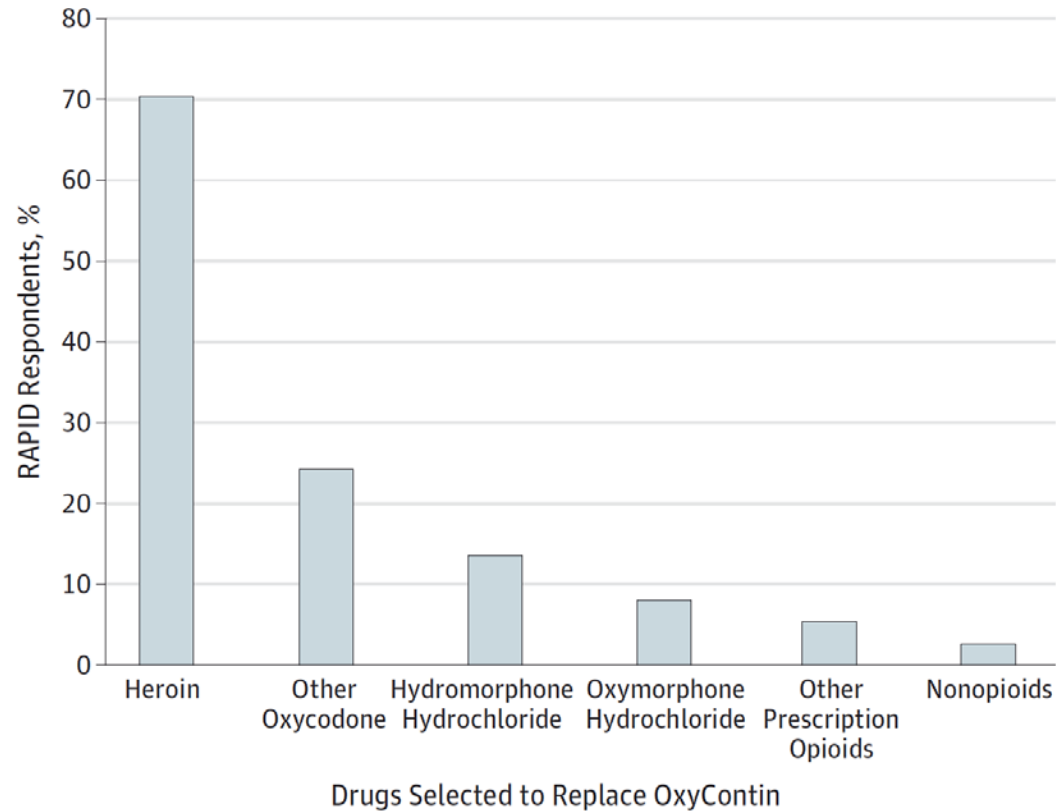
Theodore J. Cicero, PhD; Matthew S. Ellis, MPE

SKIP data





**Figure 3. Drugs Used to Replace OxyContin After the Introduction of the Abuse-Deterrent Formulation (ADF)**

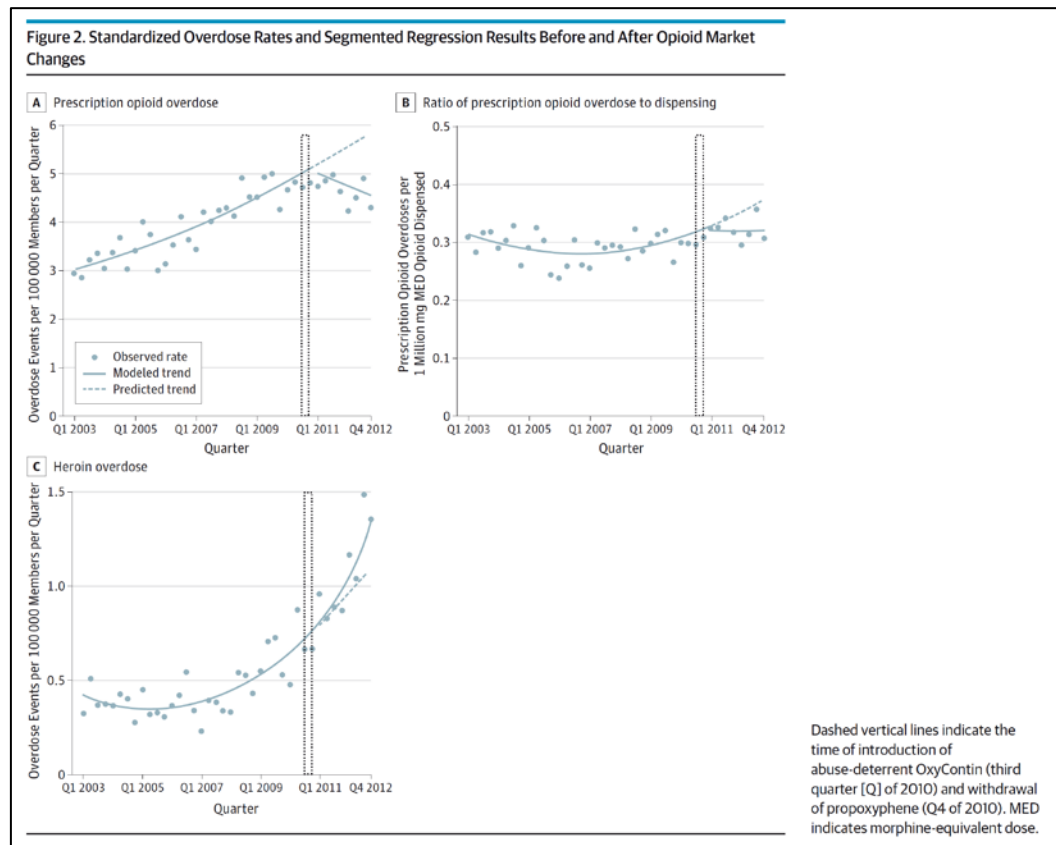


Data show the drugs used by the 51 participants in the Researchers and Participants Interacting Directly (RAPID) study sample in response to the question, "What drugs did you replace OxyContin with?" Because multiple drugs were used, percentages total more than 100. OxyContin is a proprietary formulation of oxycodone hydrochloride.

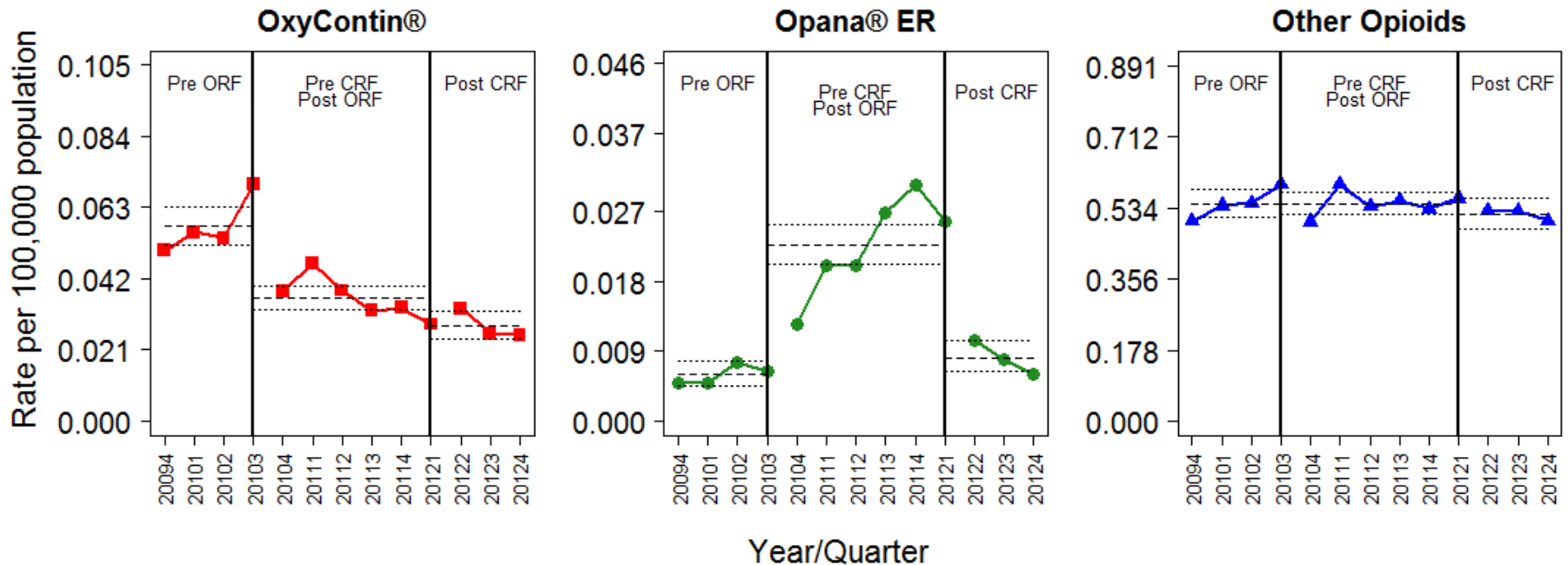
# Rates of Opioid Dispensing and Overdose After Introduction of Abuse-Deterrent Extended-Release Oxycodone and Withdrawal of Propoxyphene

Large claims database

Timed around  
introduction of  
OxyContin OP and  
withdrawal of  
propoxyphene



# Unintended consequences





ORF = OxyContin ADF (Q3, 2010)  
 CRF = Opana ER ADF (Q1, 2012)

# Opana (oxymorphone)

- Rural county in Southeastern Indiana
- Epidemic (>160 cases/normal 5) of:
  - TTP
  - Hepatitis C
  - HIV

Outbreak of Recent HIV and HCV Infections among Persons Who Inject Drugs



 **HAN**  
HEALTH ALERT NETWORK

This is an official  
**CDC HEALTH ADVISORY**

This information is for historic and reference purposes only. Content has not been updated since the last updated date at the bottom of this page.

Distributed via the CDC Health Alert Network  
April 24, 2015, 11:00 ET (11:00 AM ET)  
CDCHAN-00377

**Summary**

The Indiana State Department of Health (ISDH) and the Centers for Disease Control and Prevention (CDC) are investigating a large outbreak of recent human immunodeficiency virus (HIV) infections among persons who inject drugs (PWID). Many of the HIV-infected individuals in this outbreak are co-infected with hepatitis C virus (HCV). The purpose of this HAN Advisory is to alert public health departments and healthcare providers of the possibility of HIV outbreaks among PWID and to provide guidance to assist in the identification and prevention of such outbreaks.

**Background**

From November 2014 to January 2015, ISDH identified 11 new HIV infections in a rural southeastern county where fewer than 5 infections have been identified annually in the past. As of April 21, 2015, an on-going investigation by ISDH with assistance from CDC has identified 135 persons with newly diagnosed HIV infections in a community of 4,200 people; 84% were also HCV infected. Among 112 persons interviewed thus far, 108 (96%) injected drugs; all reported dissolving and injecting tablets of the prescription-type opioid oxymorphone (OPANA® ER) using shared drug preparation and injection equipment.<sup>1</sup>

<http://emergency.cdc.gov/han/han00377.asp>



## FDA Statement: Original Opana ER Relisting Determination

5/20/2013

FDA conclusions include:

- While there is an increased ability of the reformulated version of Opana ER to resist crushing relative to the original formulation, study data show that the reformulated version's extended-release features can be compromised when subjected to other forms of manipulation, such as cutting, grinding, or chewing, followed by swallowing.
- Reformulated Opana ER can be readily prepared for injection, despite Endo's claim that these tablets have "resistance to aqueous extraction (i.e., poor syringeability)." It also appears that reformulated Opana ER can be prepared for snorting using commonly available tools and methods.
- The postmarketing investigations are inconclusive, and even if one were to treat available data as a reliable indicator of abuse rates, one of these investigations also suggests the troubling possibility that a higher percentage of reformulated Opana ER abuse is via injection than was the case with the original formulation.

# Where there's a will, there's a way

25-09-2010 20:13

Method for IV'ing OP OxyContin Tablets:

TOOLS REQUIRED for Injecting/Banging/IV:

Tool 1.) Standard Kit for Injecting OxyContin pills -- including filters  
-- I recommend Qtip, it seems to work better on OP's than cigarette filters do  
Tool 2.) Use a 1 CC syringe. A 0.5 CC WILL work, BUT, you can't do very much.  
-- So a 1 CC syringe IS very recommended, as it can hold more water and more pills  
Tool 3.) Alcohol and sterile water

Step 1.) FOR Injecting/Banging/IV: Follow the instructions above ALL THE WAY TO below:

Step 2.) Prepare a spoon with water & TWO (2) filters - preferably QTip filters,

Step 3.) Now, like before, scrape the Oxy, and try to chop it up into small pieces, but don't want too.  
-- Chopping the Oxy a little makes it a bit easier to mix up.

Step 4.) After you have water in the spoon, add an extra 30 whole units of water to

Step 6.) Now VERY carefully mix it up, and VERY EXTRA CAREFULLY cook the mixture, tries to boil over

Step 7.) Now add only 10 (TEN) units of water from the syringe into the mix, and cook VERY CAREFULLY again

25-09-2010 20:13

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-- I recommend Qtip, it seems to work better on OP's than cigarette filters do

**I DO NOT ADVISE OR RECOMMEND INJECTING, SNORTING OR ABUSING DRUGS SUCH AS OXYCONTIN. I AM MAKING THIS GUIDE FOR PEOPLE WHO HAVE TROUBLE DIGESTING THE NEW OP PILLS\*\* OR PEOPLE WHO WANT BREAKTHROUGH OR IMMEDIATE PAIN RELIEF EVEN WITH THE NEW OP PILLS. - I AM NOT RESPONSIBLE FOR ANY DAMAGES CAUSED BY THIS METHOD OR ABUSING OXYCONTIN!!-**

Step 13.) After it's cooked again, drop in the 2nd filter right next to the first filter and QUICKLY draw the rest  
-- IT should be A LOT easier and a smidgin quicker to draw into the syringe after the second cooking.

Step 14.) Now, IF, and ONLY IF, there is any room  
Step 15.) BEFORE you get the air bubbles out\*, shake  
--\* If there are no air bubbles, add an ok sized air bubble

Step 16.) Prep your arm with an alcohol swab and clean  
-- I always wipe the needle with the alcohol swab as

NOTE: Even though it doesn't seem like it, there is a danger,  
BUT IT IS STILL DANGEROUS to inject even a SMIDG  
I have tested this FIVE (5) times already, and EVER

NOTE2: NOW, because there is a SMIDGE of gel, IT  
BUT, YOU WILL GET THE SAME RUSH AS THE OC'S, ALL AT ONCE.  
It just takes a minute as it moves slower through your body.

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\*\* The new OP pills give some people moderate stomach pain and very moderate to severe head-aches.

GOOD LUCK EVERYONE!!!  
I really hope it works well for you..

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[www.bluelight.org/vb/threads/526460-Method-for-snorting-IV-OP-OxyContin](http://www.bluelight.org/vb/threads/526460-Method-for-snorting-IV-OP-OxyContin)

# Primary Care Physicians' Knowledge And Attitudes Regarding Prescription Opioid Abuse and Diversion

National survey of 1000 primary care physicians  
May 2104  
58% response rate

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	Strongly or Somewhat Agree (%)
Abuse-deterrent formulations (ADFs)	
An ADF of a drug will have a lower addictive potential than a non-ADF of the same drug	46
ADFs of prescription opioids will result in large or moderate reductions of morbidity and mortality	27
I have a lot or some experience prescribing ADFs	12

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False sense of security

We need better education, training, and marketing

The New York Times

## *Panel: Painkiller Training Should Be Required for Physicians*

By THE ASSOCIATED PRESS MAY 4, 2016, 5:47 P.M. E.D.T.



WASHINGTON — Doctors who prescribe painkillers should be required to undergo training aimed at reducing misuse and abuse of the medications, according to federal health experts, though they acknowledge the challenge of putting such a mandate in place.

The group of advisers to the Food and Drug Administration voted unanimously Wednesday that the agency should change its risk-management programs for opioid painkillers, highly addictive medications at the center of a national epidemic of addiction and abuse.



# Necessary but not sufficient

“We recognize that abuse-deterrent technology is still evolving and is only one piece of a much broader strategy to combat the problem of opioid abuse. But strongly encouraging innovation to increase access to generic forms of abuse-deterrent opioid medications is an important element in that strategy.”

FDA Commissioner Robert Califf

# Final thoughts

- The many moving parts make it difficult to discern causality of interventional effectiveness
- Epidemiologic proof of abuse or addiction reduction should be obtained to allow advanced labeling claims
  - Needed to justify the increased expense of ADF, especially branded
- We must continue to educate patients *and* prescribers about ADFs and opioids in general
  - Rationalize expectations
  - Harm reduction efforts
- Need to focus on primary prevention
  - ADF have a role, but we cannot rely on engineering controls to fix the epidemic of opioid abuse and addiction

Thank you!