CDC Outbreak Investigations Involving OPANA® ER

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CDC Outbreak Investigations Involving OPANA® ER

Tennessee 2012

– Thrombotic Thrombocytopenic Purpura-like Illness

Indiana 2015

– HIV Outbreak

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
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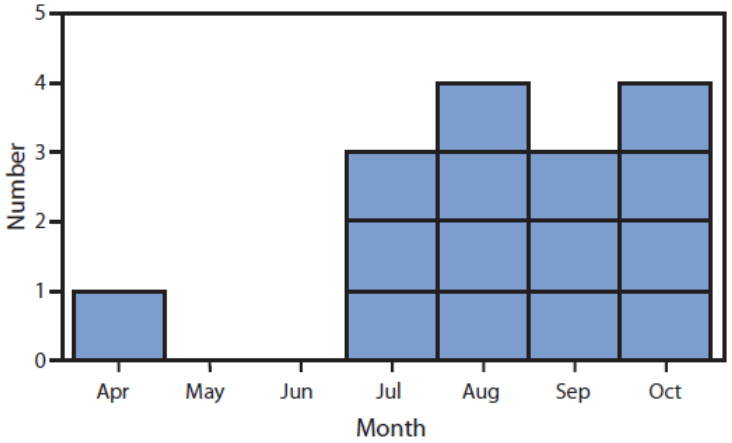
Thrombotic Thrombocytopenic Purpura (TTP)–Like Illness Associated with Intravenous Opana ER Abuse — Tennessee, 2012

FIGURE. Number of cases (N = 15) of thrombotic thrombocytopenic purpura (TTP)–like illness, by month of first presentation — Tennessee, 2012



- Northeastern Tennessee
- 15 cases TTP-like illness, no deaths
  - 7 also treated for sepsis
    - No STEC bacteria
    - No exposures to quinine
- Conducted case-control study
  - 15 cases, 28 controls

Centers for Disease Control and Prevention (CDC) Thrombotic thrombocytopenic purpura (TTP)-like illness associated with intravenous Opana ER abuse--Tennessee, 2012. MMWR Morb Mortal Wkly Rep. 2013 Jan 11;62(1):1-4.

TTP–Like Illness Associated with Intravenous Opana ER Abuse

Key Findings

- In case-control study limited to persons without sepsis, odds ratio for the association of OPANA® ER injection and for TTP-like illness was 17.5 (95% confidence interval 1.8-166)
  - 7 of 8 case patients compared with 8 of 28 controls injected OPANA® ER
- Exposures to other drugs not associated with TTP-like illness
  - Cases (n=5): hydromorphone, oxycodone, cocaine
  - Controls (n=22): oxycodone, morphine
- FDA and CDC issued warning
- Etiology at the time the outbreak unknown
- TTP-like illness not observed in 2015 Indiana HIV Outbreak

Centers for Disease Control and Prevention (CDC) Thrombotic thrombocytopenic purpura (TTP)-like illness associated with intravenous Opana ER abuse--Tennessee, 2012. MMWR Morb Mortal Wkly Rep. 2013 Jan 11;62(1):1-4.

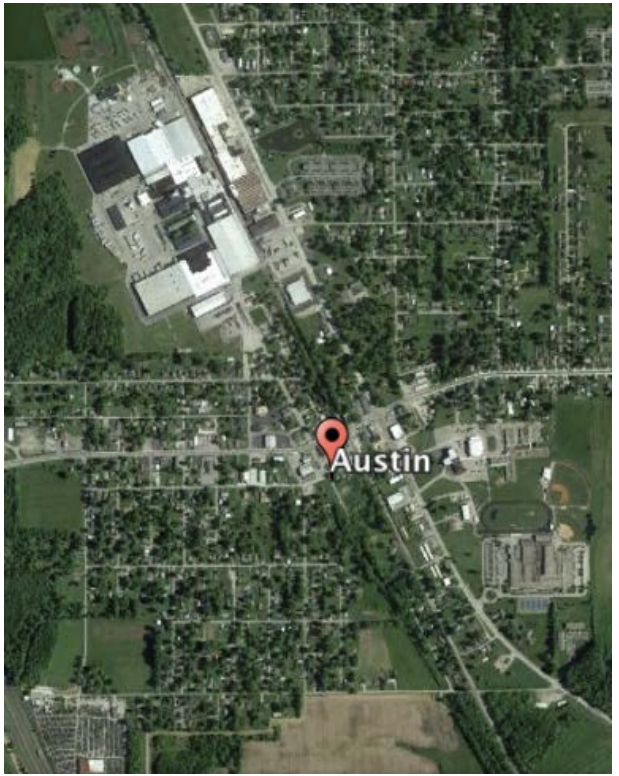
Indiana 2015 HIV Outbreak
Qualitative Study of Drug Use Practices

Specific Aims

- Qualitative study to understand the challenges and behaviors of people who inject drugs (PWID) in Scott County, Indiana, that contributed to the rapid spread of HIV/HCV infection

Methods

- Indiana University and CDC IRB approval
- Eligibility criteria
  - 18 years of age or older
  - Resident of Scott County
  - Able to complete interview in English
  - Injected drugs in the past 12 months
  - Able to provide informed consent



Methods

- Sampling
  - Targeted sampling strategy
  - Syringe service program (SSP), street recruitment, and peer-to-peer
- Interview setting
  - Local church and SSP
  - Ensure privacy

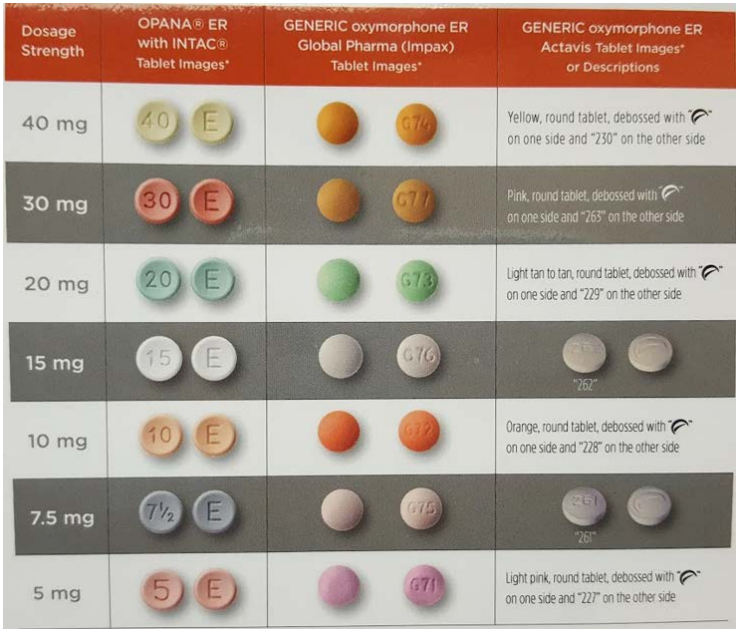
Methods

- Data Collection: June-September, 2015
  - 4 focus groups (31 individuals)
  - 25 private interviews (25 individuals)
  - Audio-recorded and interview notes
  - No identifying information collected

Methods

- If interviewee could not accurately describe formulation used, presented photo cards of tablets to aid accurate recall.

Example for extended release (ER) formulations:



Dosage Strength	OPANA® ER with INTAC® Tablet Images*	GENERIC oxymorphone ER Global Pharma (Impax) Tablet Images*	GENERIC oxymorphone ER Actavis Tablet Images* or Descriptions
40 mg	40 E	G74	Yellow, round tablet, debossed with "" on one side and "230" on the other side
30 mg	30 E	G77	Pink, round tablet, debossed with "" on one side and "263" on the other side
20 mg	20 E	G73	Light tan to tan, round tablet, debossed with "" on one side and "229" on the other side
15 mg	15 E	G76	"262"
10 mg	10 E	G72	Orange, round tablet, debossed with "" on one side and "228" on the other side
7.5 mg	7½ E	G75	"261"
5 mg	5 E	G71	Light pink, round tablet, debossed with "" on one side and "227" on the other side

Methods

- Data Analysis
  - Interviews transcribed
  - Cross-checked and prepared for descriptive content analyses*
  - Two researchers independently reviewed transcripts and compared notes for inter-coder agreement.
  - Thematic review of OPANA® ER preparation and injection drug practices.

* NVivo 10 software, QSR International

Characteristics of Interviewees

	Focus Groups (n=31 persons* in 4 groups)	Private Interviews (n=25 persons)
Age, years	30-39 (59%)	median 33 (range 19-57)
White, non-Hispanic	29 (100%)	25 (100%)
Female	16 (52%)	11 (44%)
Enrolled in SEP	27 (90%)	19 (76%)
HIV-positive**	17 (57%)	10 (40%)
HCV-positive**	28 (90%)	21 (84%)
Drug use	Drugs injected	Primary drug injected
	• Any drug, past week 31 (100%)	• OPANA® ER 22 (88%)
	• OPANA® ER, past year 30 (97%)	• OPANA® IR 1 (4%)
		• Methamphetamine 2 (8%)

* Percentage calculated from among respondents (e.g., 3 non-responders regarding race/ethnicity)

** By self report

Pill and Drug Recall

- Participants were knowledgeable about OPANA® ER and could describe accurately the 40 mg biconvex tablet without prompting
  - Few participants needed to be shown card to aid recall
  - One participant recognized OPANA® IR (his drug of choice) was absent
- In another survey of 148 early participants in the SSP, PWID reported the following as the drug they were injecting at enrollment
  - 131 (89%) OPANA® ER
  - 25 (17%) heroin
  - 4 (3%) other, NOS

Patel *et al.* unpublished data

Key Finding #1:
Frequent Injection Episodes with Multiple Injections

- Most participants who injected OPANA® ER reported injecting often
  - 3-7 injection events times per day
  - 2-4 injections per injection events
  - Typically shared a quarter of a pill with 2-4 injection partners
- Practice reported to be common among PWID in the community

Key Finding #2:
Users “Browned” OPANA® ER for Injection

- INTAC®, a proprietary high-molecular-weight polyethylene oxide, added to OPANA®ER during reformulation in 2012:
  - Deterrent to prevent crushing and insufflation
  - Forms viscous gel in aqueous environment that slowly releases drug through diffusion and erosion during gastrointestinal transit
- Users in Scott County applied moderate heat to “brown” OPANA® ER tablets to facilitate dissolution in water and reduction in gelling

Key Finding #3
Several Themes Related to Reformulated OPANA® ER Associated with Injecting the Drug and Injecting Often

1. Opioid potency and duration of action
2. Deterrent to prevent crushing and insufflation
3. Gelling capability to extend gastrointestinal release
4. Rinse shots
5. Economics of supply and demand

Opioid Potency: Analgesic Equivalency

Drug*	Route of Administration		Duration of action
	Oral, mg	Parenteral, mg	
Morphine	30	10	3-4 hours
Hydromorphone	7.5	1.5	3-4 hours
Oxymorphone	10	1.0	3-4 hours

* parenteral equivalency for oxycodone and hydrocodone not available, oral equivalency for fentanyl not available

Adapted from Gordon DB, Stevenson KK, Griffie J, et al. Opioid equianalgesic calculations. J Palliat Med. 1999;2(2):29-218.

Potency of Opioid

Increased potency of drug increased intensity of withdrawal symptoms

- *"Then after they took OxyContins off the market, then they came out with the OPANAs. Which was 10 times worse than that OxyContin. With like the intensity of the withdrawals."* (JZ08)
- *"I could not find any of the OxyContins and someone came to me with an Opana, and that's how I ended up doing Opana but I had a lot of people tell me 'Don't do Opana because a lot of people say you do it one time and you're hooked'. You'll be sick the next day so you'll have to get another one. And that's exactly what happened. I did one that night and the next morning I woke up and I just felt, I felt terrible. And so I had to get another one. You get hooked on 'em really fast, the Opanas. Very fast."* (DB08)

Potency of Opioid

Short duration of action increased need to inject frequently

- *But, the Opana don't last near as long as the other stuff…The feeling of Opana will last 30 minutes... [It takes 4 or 5 hours with the Opana before you are sick] and then you got to do it again, or you feel really bad again. If you don't do enough Opana, then in a couple hours, you feel really bad again and… [have to inject]. Inject 6,7,8 times but only like small amounts.”* (DB01)

* Text in brackets are added by the researchers based on the full narrative to make the individual quotes free-standing and understood without reading the entire interview.

Deterrent to Prevent Crushing and Insufflation

Inability to crush OPANA® ER cited as a reason to move to injection

- *" [I was] probably 24....I snorted the Opanas. It was when the government put the formula in where you had to cook them…. It pretty much forced me to have to inject really... If there was a possible way I could snort them, I'd rather snort than shoot."* (JZ04)
- *"I couldn't find Opanas or any other type of pain medicine to snort. It became almost non-existent. So I was turned on to shooting up. So that's pretty much how that went down. [That was a couple years ago. I hadn't injected before a couple years ago after I couldn't find anything to snort]. I couldn't handle the withdrawals… Opana [was the first drug I injected]... I was doing the OxyContin before, snorting OxyContin….when I was 18. I don't know, it was probably 23, 24 [when I first started snorting Opana] because they had a snortable kind before. "* (JD01)
- *"These [Opana ER] you can't. They're like, plastic. Real hard. Well, I shot too, but I, mostly I would snort it. But, and then, when you couldn't snort it at all. I started shooting it."* (JD02)

Gelling Compound to Extend Gastrointestinal Release

Presence of gelling capability increased the amount of solvent needed to adequately dilute diverted OPANA® ER tablets for injection

- *"You take a lighter and you melt it, because it gels up if you put water on it. It kills the gel in it, that way you can draw it up. It takes so much water, if you wanted to work the whole thing up, it would get so thick and be hard to draw up."* (DB03)
- *You can't get it all in one shot... you've got to put more [water] in there than what you can draw... You can get by with 120 units, but its real thick... It's real hard to draw up. You still have 50 left, and then even after that, you put more water on it and mix it some more because there's stuff left over.* (JZ05)

Rinse Shots

Users rinsed the cooker after the first injection (“rinse shot”) to create at least one more injection to ensure all drug was used.

- *“And then even after that [2 shots from a quarter of ER oxymorphone], you put more water on it and mix it some more because there's stuff left over. So, that's 3 shots right there. Just off a quarter piece. Some people rinse it more than once. They'll rinse it again. So, they're doing 4 shots.”*(FG3)

Rinse Shots

Rinse shots not common with other injected drugs

- *"If you've got decent dope [methamphetamine], you do a shot and you're good, you know. . . Heroin, I've seen people try to take, get three or four shots off of it, but you can't, you know, because heroin it's one shot and you're done."* (DB05)

Economics of Supply and Demand

Increasing price of diverted drug created pressure to inject together

- *"Well, if you buy, these pills, a whole pill is like 200 dollars if you buy it. And, we'd always, sometimes we'd have just enough [money] to get high for a quarter of a one. Sometimes 2 or 3 of us would do a quarter of a pill."* (DB05)
- *"There are sometimes, another person [I inject with]…And it's usually to help us because we can't make enough money to get that quarter, and it's usually like the first quarter of the day because I'm sick, I've only made maybe $20, I'm short $15. There might be another person that's short the other $20, so we'll all get together, throw our money in together, and then we'll go do the quarter three ways."* (JD01)

Summary of Drug Characteristics and Infection Risk

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Summary of Drug Characteristics and Infection Risk

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Opioids:	Addiction potential	
	Effect duration hours →	More injection events per day
Oxymorphone:	Greater potency →	More intense withdrawal
OPANA® ER:	Crush resistance →	Users move to injecting drug
	Greater solvent need	More injections per event
	Rinse shots	
	Higher cost →	Increased equipment sharing

Hepatitis C Virus (HCV) Outbreak, New York State, 2011 Association Drugs Injected and Risk for HCV Infection

Drug injected	Hepatitis C Status		p-value
	Reactive (n=34)	Nonreactive (n=66)	
Prescription opioids	26 (77%)	27 (41%)	<0.001
Heroin	9 (26%)	24 (36%)	0.32
Cocaine	9 (26%)	11 (17%)	0.25
Bath salts	7 (21%)	3 (5%)	0.01
Crack	2 (6%)	2 (3%)	0.49
Methamphetamine	2 (6%)	1 (2%)	0.23
Other	0 (0%)	8 (11%)	0.08

Zibbell *et al.* 2014, Am J Pub Health 104(11): 2226-2232

Hepatitis C Virus (HCV) Outbreak, New York State, 2011
Types of Prescription Opiates Injected

Prescription opioids	Number of persons reporting use
OPANA® (oxymorphone)	58 (61%)
OxyContin® (oxycodone)	21 (22%)
Dilaudid® (hydromorphone)	7 (7%)
Roxycontin® (oxycodone)	3 (3%)
Morphine	4 (4%)
Vicodin® (hydrocodone)	1 (1%)
Percocet® (oxycodone)	1 (1%)

Zibbell *et al.* 2014, Am J Pub Health 104(11): 2226-2232

Conclusions Regarding OPANA® ER and Risk for Injury

- In 2012, injection of OPANA® ER associated with TTP; however, mechanism for this action not fully understood at the time and TTP not observed in the 2015 Indiana HIV outbreak.
- In the 2015 Indiana HIV outbreak, certain factors, including some factors associated with latest formulation of OPANA® ER, unintentionally increased risk of transmitting bloodborne infections when tablets diverted for injection.
- In at least one outbreak prior to the Indiana event, injection of prescription opioids tablets was associated with increased risk having acquired a bloodborne infection (HCV) compared with injection of heroine or cocaine.

Pubic Health Research Questions

- What is the biological mechanism by which polyethylene oxide compounds may cause TTP-like illness?
- How does “browning” OPANA® ER alter crush deterrent and gelling properties of INTAC®?
- Are there alternative means of achieving crush deterrence and extended release so that if tablets were diverted and prepared for injection, the risks of TTP-like illness and of bloodborne pathogen transmission are minimized?
- Why might prescription opioids be associated with greater risk of transmitting bloodborne infections?

Acknowledgments

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