National Academy of Medicine Session 4

Opioid Analgesics with Abuse-Deterrent Properties: Current Data and Future Opportunities

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Opioids with Abuse Deterrent Properties: Current Data and Future Opportunities

- Oxycodone ER fulfills the Hill criteria for causation
 - Plausibility
 Consistency
 - Temporality
 Specificity
 - Effect Size Alternative explanations
- Questions and Issues

- National Academy of Science
- US Food and Drug Administration

Hill Criteria: Plausibility

 A plausible mechanism between cause and effect is helpful (but understanding of the mechanism is limited by current knowledge)

Scientific Basis of Abuse-Deterrent Opioids

- Prescription drug abuse is like other drug abuse, except with an additional "route" of abuse:
 - Oral = intact + chewed or crushed
 - Intranasal
 - Intravenous
- Importance of manipulating drug
 - Crucial transition
 - Changes perception of heroin use¹
 - Risk of acute (overdose, death) and chronic events (addiction, infections, death) higher after intranasal or IV abuse than oral abuse

1. Vosburg. J Child Adol Subst Abuse 2016.

Biological Plausibility



Intervening in Prescription Drug Abuse



Hill Criteria: Temporality

- Effect has to occur after the cause (including a delay, if expected)
- Minimal delay expected for oxycodone ER
 - All drug shipped after August 9, 2010 was reformulated version
 - Pharmacy turnover of opioids is rapid
- Only oxycodone ER has adequate data to evaluate effectiveness

Oxycodone ER Prescriptions Dispensed Decreased Promptly After Reformulation



Other Opioids = Oral dosage forms of opioid analgesics: hydrocodone, hydromorphone, morphine, oxymorphone, tramadol, tapentadol, and IR oxycodone

RADARS® System Surveillance of Prescription Drug Abuse

- Independent postmarketing surveillance program focusing solely on prescription drug abuse
- Most manufacturers of prescription opioids are subscribers
 - Limited to use for regulatory and risk-management use



Why Adjust for Population?

Population-adjusted		# Events in Geographic Area
Rate	=	Population in same Geographic Area

- Accounts for obtaining drug (reduction in doctor shopping)
- Abuse after prescription is dispensed
- What if we had a perfect ADF?
 - \downarrow doctor shopping, \downarrow pill mill activity
 - ↓ high risk abuse after Rx

Temporality: 3 Phases of Oxycodone ER Abuse and Diversion, Adjusted for Population, 2010 – 2016Q2





Hill Criteria: Effect Size

A small association does not mean that there is not a causal effect, though the larger the association, the more likely that it is causal.

Effect Size: Oxycodone ER Abuse and Diversion, Adjusted for Population, 2010-2016





Hill Criteria: Consistency

 Consistent findings observed by different persons in different places with different samples strengthens the likelihood of an effect

Consistency: Oxycodone ER Associated with Lower Rates Across Many Data Sources

Outcome	Source	Pre vs. Post % Change [95% Cl] Since Reformulation		
Misuse	RADARS (Poison Centers)	⊢ +	ER Oxycodone	
	RADARS (Poison Centers)	⊢● ₁ ⊢−● −−	Other Opioids	
Abuse	NPDS (Poison Centers)	⊢● -1 ●-		
	NAVIPPRO (Treatment Centers)	H O H K)	
	RADARS SKIP (Treatment Centers)	•	•	
	RADARS OTP (Treatment Centers)	•		
Opioid Use Disorder	Database of Opioid Users (Marketscan)	H	⊢-● 1	
Overdose	Database of Opioid Users (Marketscan)	F	 !	
Diversion	RADARS (Drug Diversion)	⊢ ∎-1 ⊢—-	▶	
Doctor Shopping	IMS Prescription Data	•	·•	
Data adjusted for prescription volume -100% -50% 0% 50% 10				
onlan et al. <i>Clin Pharmacol</i>	Ther 2016	Decrease		

Coplan et al. Clin Pharmacol Ther. 2016.

National Survey of Drug Use and Health, OxyContin Nonmedical Use



Poison Center Cases: Response to Reformulation of Oxycodone ER and Oxymorphone ER



Hill Criteria: Specificity

- The more specific an association between a factor and an effect is, the bigger the probability of a causal relationship¹
- Results specific to oxycodone ER compared to other analgesic opioids
 - FDA Concerns²

"For data streams that collect information on a variety of events (e.g., abuse, adverse reactions), changes should be limited to abuse-related categories"



Relative Change in Population Rate

"For evaluation of ADFs, changes should be seen only in the routes of abuse expected to be affected"



All routes of abuse should be low with an effective ADF

Alternate Explanations Fail the Temporality and Specificity Criteria



↑ PDMP Initiation

Other Issues

- Effect of ADFs on opioid related harm in the community
- FDA policies and procedures of review, approval, and monitoring
- Gaps in Research
- Immediate Release vs. Extended Release
 Formulations

Effect of Abuse Deterrent Opioids on Opioid-Related Harm in the Community

- Extended release products have a small part of opioid market
- ER products account for small portion of total abuse
- Oxycodone ER can reduce its own abuse, not entire market

FDA Policies and Procedures Gaps in Research

- Guidance was excellent beginning
- Definitions
 - Meaningful reduction
 - Addiction, Overdose
 - Totality of the evidence no framework to address
- Comparator drugs
- IR/ER abuse usually starts on IR, but no special risk management

Conclusions and Implications

- Specificity, consistency and effect size indicate that abuse deterrent opioids are likely to be effective in reducing abuse and its outcomes
- Similar effects for crush-resistant oxymorphone ER
- Widespread use would reduce prices and reduce the crucial transition from intact swallowing to crushing
- Education, training, and other interventions needed as well

Backup Slides

Temporality: Oxycodone ER Abuse and Diversion, Dosage Units Dispensed, 2010-2016







Effect Size: Oxycodone ER Abuse and Diversion, Adjusted Dosing Units Dispensed, 2009-2016





Specificity of Reduction in Abuse of Oxycodone ER



Relative change in dosing units dispensed rate

Specificity of Reduction in Abuse of Oxycodone ER by Route



Relative change in dosing units dispensed rate

ADFs Will Increase Opioid Use: ER Opioid Prescriptions Have Been Decreasing Over Last 5 Years



IMS National Prescription Audit (2011-2015)

IV and Intranasal Opioid Abuse Associated With Higher Risk of Death or Major Effects



RADARS System Poison Center Program, 2015 Data on File

Reformulated Oxycodone ER Replaced Original Formulation Quickly



Did Introduction of Oxycodone ER Cause an Increase in Heroin Abuse?

E National Survey on Drug Use and Health



Approaches to Abuse Deterrence

- Physical / chemical barriers
 - Hydrocodone (Hysingla®, Vantrela®)
 - Morphine (Arymo®, Morphabond®)
 - Oxycodone (OxyContin®, Xtampza®)
- Agonist / antagonist
 - Morphine (Embeda®)
 - Oxycodone (Troxyca® ER)
- Aversion
- Delivery System (incl. depot forms and implants)
- New molecular entities and prodrugs
- Combination Two or more methods combined
- Novel approaches

Abuse-Deterrent ER Oxycodone Reduces IV Abuse in Australia



Street Price of Reformulated Oxycodone ER 45% Lower Than Original Version



Adjustment for Population or Dosing Units Provides Different Perspectives

Population

Events in Geographic Area

Population in same Geographic Area

Accounts for obtaining drug (reduction in doctor shopping)

- Abuse after prescription is dispensed
- What if we had a perfect ADF?
 - \downarrow doctor shopping, \downarrow pill mill activity
 - \downarrow high risk abuse after Rx

Dosage Units Dispensed

Events in Geographic Area

Dosage Units Dispensed in same Geographic Area

- Evaluates abuse <u>after</u> user has obtained the drug
- Does <u>not</u> include reduction in doctor shopping or prescribing behavior