A Framework for Opioid REMS Assessment



Gregory M. Bogdan, PhD Administrative Director Rocky Poison & Drug Center – Denver Health

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Background

- FDAAA authorizes FDA to require Risk Evaluation and Mitigation Strategy (REMS)
- A single class-wide REMS is proposed for certain products
 - Extended Release formulations of morphine, oxycodone, oxymorphone

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- Methadone, transdermal fentanyl
- Not included
 - All other formulations (IR, IV, transbuccal)

Non-REMS Opioids 58,079,471

REMS Opioids 3,836,899



URDD = Unique Recipients of Dispensed Drug; equivalent to "projected patients"

How Can Surveillance Data Help?

- Goals of Opioid REMS
 - Ensure that the benefits of a opioid product achieves appropriate balance with the risks through:
 - Proper patient selection
 - Minimizing the risk of overdose, both accidental and intentional
 - Minimizing the risk of abuse
 - Ensure that prescribers, dispensers, and patients are aware and understand the risks and appropriate use of these products

Hertz S: http://www.fda.gov/cder/meeting/opioid/3Hertzsponsormeeting3-3-09.pdf

REMS Questions

- Evaluation of the REMS concept
 - Will the creation of a class-wide REMS affect misuse, abuse and diversion of drugs?
- Evaluation of the effect of REMS on specific medications
 - Will the creation of a class wide REMS affect misuse, abuse and diversion of MY drug?
- Will all drugs in the class respond similarly to class-wide REMS?

Framework Background

- Opioid REMS assessment must follow basic principles of surveillance and public health
- Evaluation framework should be designed to monitor both the <u>intended</u> consequences (reduction in the unintended consequences of outpatient opioid use) and potential <u>unintended</u> consequences of the proposed opioid REMS

Framework for Opioid REMS: Basic Surveillance and Public Health Principles

- Evaluation should include effects on misuse, abuse, addiction, diversion and overdose
- All types of opioid products must be included in evaluation: branded and generic as well as extended-release and immediate-release.
- The risks unique to specific formulations of prescription opioids must be measured separately (e.g. patch, tamper resistant, etc)
- The evaluation should be comprehensive, including both the benefits and risks

Framework for Opioid REMS: Basic Surveillance and Public Health Principles

- Multiple perspectives on the natural history of substance use disorders are needed to assess opioid REMS, measured separately but in parallel
- The impact on opioid treatment programs must be evaluated
- Assessments must be conducted on prescheduled basis (required by Section 505-1).

Framework for Opioid REMS: Basic Surveillance and Public Health Principles

- Outcomes in specific populations must be monitored (e.g. young children, adolescents, etc). The effects of opioid REMS on patients and non-patients (e.g. abuse) must be included.
- Evaluation must assess whether existing disparities in access to opioid pain medications by vulnerable minorities is not exacerbated

Opioid REMS Assessment Objectives



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Analysis Objectives

- Effect of class-wide REMS on overall rates abuse, misuse and diversion
- Administration route
- Medical consequences
- Ages of individuals involved in abuse and misuse
- Source of drug abused
- Street price
- Evaluation of natural experiments

*for REMS and non-REMS opioids

Mosaic of Prescription Drug Abuse



Mosaic of Prescription Drug Abuse





MMIT



RADARS® System

Researched Abuse, Diversion and Addiction-Related Surveillance System

- Prescription drug abuse, misuse and diversion surveillance system that collects timely product-and geographicallyspecific data.
- Measures rates of abuse, misuse and diversion throughout the US, contributing to the understanding of trends and aiding the development of effective interventions.
- Data assist pharmaceutical companies in fulfillment of their regulatory obligations such as REMS.





RADARS System Reporting 3-Digit ZIP Codes, 2009



Class-Wide REMS - Opioids

REMS

- Methadone products
- ER morphine products
- ER oxycodone products
- ER oxymorphone products
- ER hydromorphone
- Transdermal fentanyl products

Non-REMS

- Buprenorphine products
- Hydrocodone products
- Tramadol products
- Hydromorphone
 products
- IR morphine products
- IR oxycodone products
- IR oxymorphone
 products
- Fentanyl products, transbuccal or IV

Objective #1:

Effect of class-wide REMS on abuse, misuse and diversion rates

- If a class-wide REMS is effective:
- 1. Abuse, misuse, diversion of REMS opioids will decrease
- 2. Abuse of an individual product will decrease

RADARS System **Poison Center** Program Intentional Exposure Rate per 100,000 Population 2006-2009



Intentional Exposure Mentions: Suspected Suicidal, Intentional Misuse, Abuse, Unknown, Withdrawal

RADARS System **Poison Center** Program Intentional Exposure Rate per 1,000 URDD 2009



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Intentional Exposure Mentions: Suspected Suicidal, Intentional Misuse, Abuse, Unknown, Withdrawal

RADARS System Drug Diversion Program Rate per 100,000 Population 2006-2009



RADARS System Drug Diversion Program Rate per 1,000 URDD 2009



REMS Opioids



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RADARS System Drug Diversion Program Rate per 1,000 URDD 2009



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RADARS System Drug Diversion Program Rate per 1,000 URDD 2005-2009



YearQuarter

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-0.5

Implications

- The massive use of IR formulations causes a much greater number of events.
- But when examining a single use of a drug, the risk is greater for REMS drugs.
- We need both population and URDD views to understand what transpires.
- Will increased intervention on REMS drugs without corresponding effort on IR result in 'squeezing the balloon'?

Pain Patients vs. Non-Patients

- Poison Center Program
 - Intentional exposures are defined: suspected suicide, misuse, abuse, unknown, withdrawal
 - Pain Patients: intentional misuse exposure
 - Non-Patients: intentional exposure excluding misuse
- Opioid Treatment Program
 - Pain Patients: enrolling in substance use disorder treatment to treat bodily pain
 - Non-Patients: pursuing treatment for other reasons

RADARS System **Poison Center** Program Pain Patients vs. Non-Patients 2009



RADARS System **Poison Center** Program Pain Patients vs. Non-Patients 2009



Pain Patients



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Objective #2:

Route of Abuse

If a class-wide REMS is effective:

- 1. Higher risk routes of abuse of REMS opioids will decrease
- 2. Higher risk routes of abuse for an individual product will decrease

RADARS System College Survey Route of Abuse 2009



Objective #3:

Medical Consequences

- If a class-wide REMS is effective:
- 1. Major events and deaths will decrease for REMS opioids
- 2. Major events and deaths for an individual product will decrease

RADARS System **Poison Center** Program Associated Medical Outcome 2009



Intentional Exposures: Suspected Suicidal, Intentional Misuse, Intentional Abuse

Minor, Self-Resolving Conditions: no effect, minor effect, not followed – nontoxic, not unrelated effect, confirmed non-exposure

PD,S3S

clinical effects,

RADARS System **College Survey** DAST-10 Score Categories 2009



Objective #4:

Age of individuals reporting abuse and misuse

- If a class-wide REMS is effective:
- 1. Frequency will decrease for all age groups in REMS drugs without an increase in non-REMS drugs
- 2. Frequency will decrease for individual drug

RADARS System **Poison Center** Program Age Category (years) 2009



Intentional Exposures: Suspected Suicidal, Intentional Misuse, Intentional Abuse, Intentional Unknown, Withdrawal

RADARS System **Poison Center** Program Age Category (years) 2009 **REMS Opioids Only** 8000 Non-REMS Opioids Only Number of Intentional Exposure Cases REMS and Non-REMS Opioids 6000 Mortality Data 4000 2000 0-56-12 13-19 20 - 2930-39 40 - 4950-59 Unk 60 +Age Category (years) DRUG SAFETY SUMMIT

Intentional Exposures: Suspected Suicidal, Intentional Misuse, Intentional Abuse, Intentional Unknown,

Objective #5:

Opioid Source

If a class-wide REMS is effective:

- 1. Frequency of diversion will decrease for REMS drugs without an increase in non-REMS drugs
- 2. Frequency will decrease for individual drug

RADARS System College Survey Source of Prescription Opioids 2009



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Future Directions

- Street price data will be obtained from Drug Diversion Program
 - A difference in street price between REMS and non-REMS opioids may indicate the demand for one drug category over another
- Natural experiments will be identified for additional analyses after the launch of classwide REMS



Closing Comments

- Class-wide opioid REMS discussions continue
- Data will be needed to evaluate both intended and potential unintended consequences on opioid use
- RADARS System data can evaluate some of the anticipated and unanticipated effects of REMS
- The evaluation will not be simple depending on the outcome measures chosen



RADARS System Contacts

Greg Bogdan, PhD Administrator Director Rocky Mountain Poison & Drug Center (303) 389-1239 Greg.Bogdan@rmpdc.org

