

Research Design Considerations for Clinical Studies of Abuse Deterrent Opioid Analgesics

Poison Center Data to Assess the Relative Abuse Rates of Prescription Opioids

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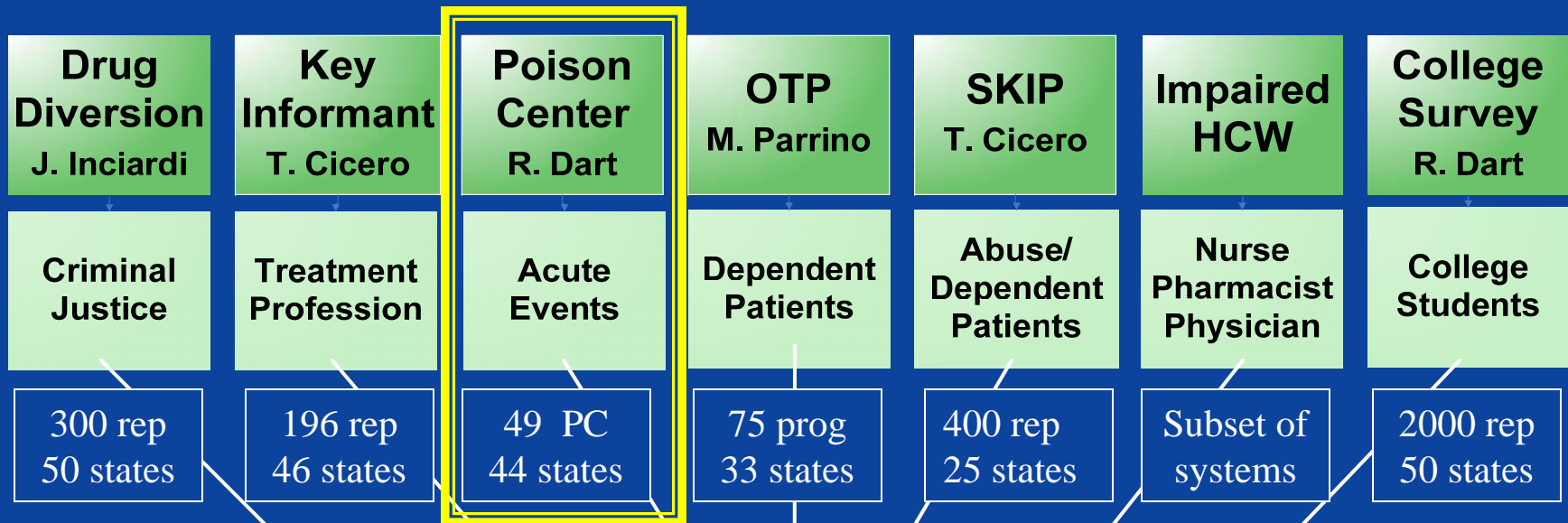
A New "Abuse Resistant" Product

- Goal: Minimize abuse and diversion (MAD) while providing pain control for patients.
- A claim of decreased abuse is difficult to study
 - Behaviors to be measured are illegal, heavily stigmatized, and concealed.
- Use systems to measure when the subject is “forced” to expose themselves (the “mosaic” approach).
- Conclusions may vary depending on measure

Relative Abuse Rates of Prescription Opioids

- Is the new drug abused?
- How does the abuse compare to other drugs?
 - Importance of denominators
- *Who* abuses the product?
- *How* is the new product being abused?
 - Ingestion, Inhalation (snorting), Injection, other
- Are there unintended victims?
- How will the information be applied?
 - To assess abuse resistance/deterrence?

RADARS® System Mosaic



Prescription Medication Issues

- Hidden events & motives
- Indications
- Formulations

POISON CENTERS

1-800-222-1222 Nationwide



- Poison Center.
- ◆ Poison Center that serves other States.
- ⊗ State that does not have a Poison Center and is served by another State.

Refer to the information below for detailed coverage information.

POISON
Help.

1-800-222-1222

POISON CENTERS

1-800-222-1222 Nationwide



- 85% Home
- 15% Health care

- All States
- Public Health Depts
- Chemical Mfrs
- Consumer Product Mfrs
- Pharmaceutical Mfrs
- Petroleum Industry
- Retail Industry

Nationally Standardized Data Collection System
2.5 million exposures 2007

Medical Advice



Incoming Call

Initial Triage

Care Advice

Disposition

Reporting & QA/QC

- Triage and care advice
 - 800-222-1222, 24 x 7 x 365
- National standards
 - Certified staff
 - Accredited centers
- Prehospital guidelines
- Board certified physician backup

Data Collection

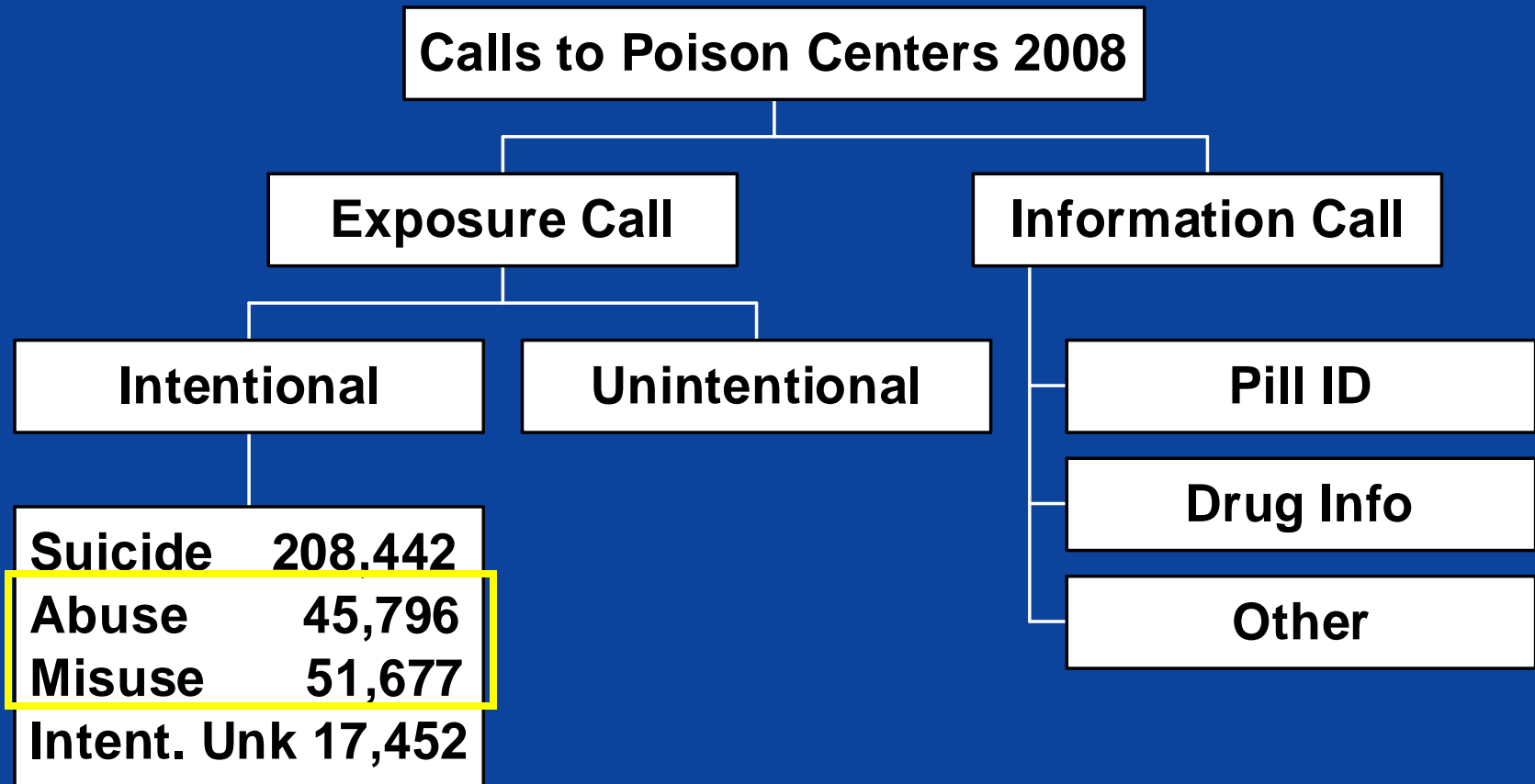
- All centers report data to National Poison Data System (NPDS) every 14 minutes
- Standardized data fields
 - Explicit definitions
 - Demographics
 - Substance information
 - Exposure information
 - Clinical effects
 - Therapy
 - Outcomes

NPDS FIELD NAMES

NUMBER OF CHOICES

Age	
Call Type & Call Type Subcategory	
Information Calls	120
Caller Site	9
Chronicity	4
Clinical Effects .	131
Duration of Effect	9
Exposure Duration	6
Exposure Site	9
Final HCF	12
Gender	4
Initial HCF	12
Level of HCF Care	6
Location	
Management Site	5
Medical Outcome	10
Override	
Pregnancy Duration	
Reason	19
Route	12
Scenario Category, Scenario ID	54
Species	2
Start Date	
State	60
Substance, Certainty	3
Substance, Formulation	7
Substance, Generic	
Substance, Product Specific Code	
Substance, Quantity	
Substance, Quantity Unit	17
Therapy	68
Weight	
Year	

NPDS Classification System



Smith MY, et al. Clinician validation of Poison Center (PCC) intentional exposure cases involving prescription opioids. *Am J Drug Alcohol Abuse* 2006;32:465-78.

Strengths of Data Collection

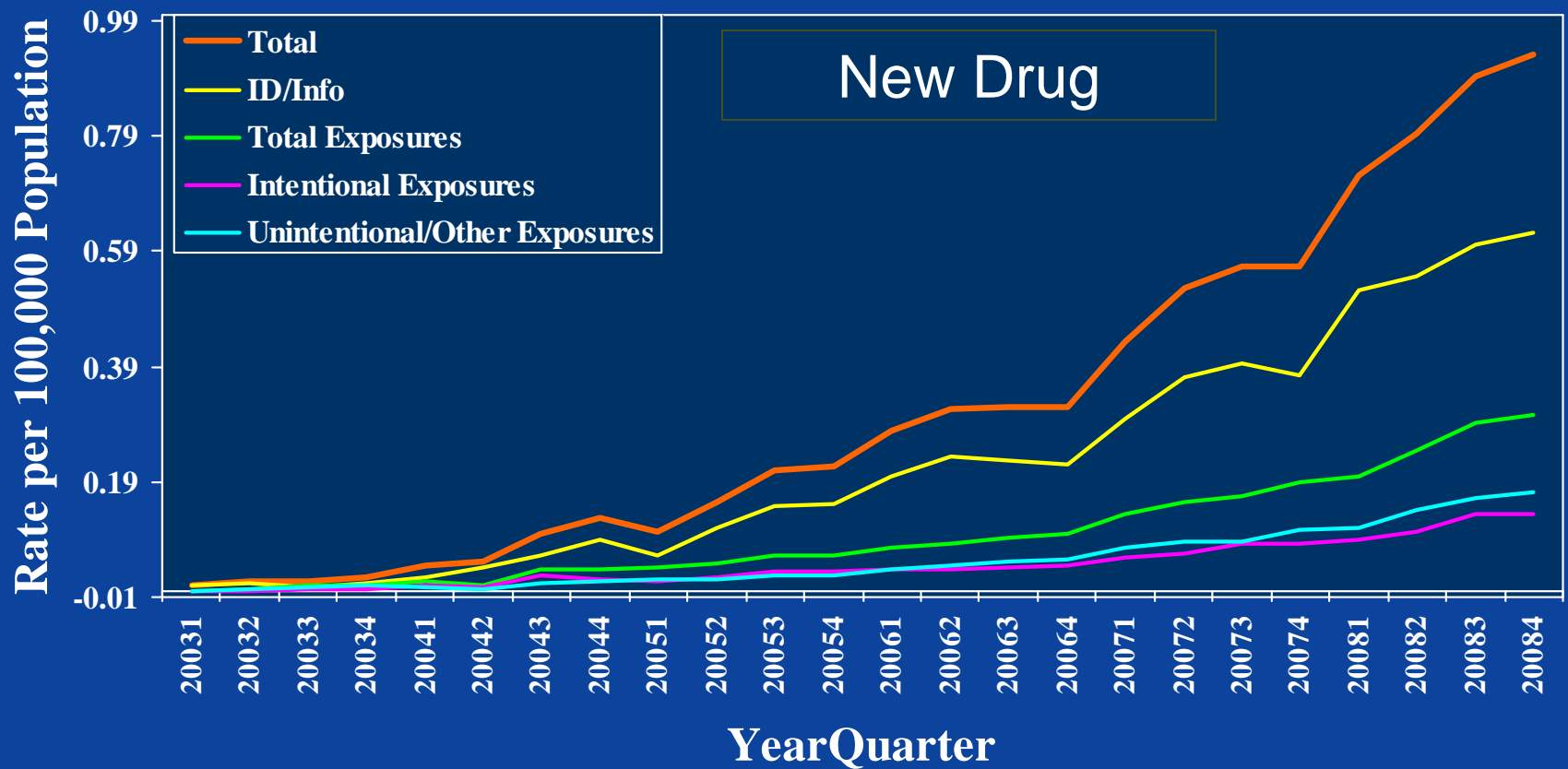
- Standardized data collection
- Health care professionals (RN, PharmD)
 - National certification exam
- Entire US population has access
 - Marketing to promote use
 - Toll free number - 24/7/365
 - Real time data collection
- Product specificity
- Geographic specificity (3DZ)
- Quality assurance
 - Fields have rules

Weaknesses of Data Collection

- Spontaneous reporting
 - PCs required to maintain call volume from all 3 DZ in their area
- Quality assurance
- Omissions
- Clinical judgments are recorded
- Case notes are not available

Can Poison Centers Detect Introduction of New Drug?

Rate per 100,000 Population



Can Poison Center Data Detect Changes?



Unlawful Narcotics Investigations,
Treatment and Education

www.operationunite.org

UNITE Background

- First activities early 2004 - 29 counties in Eastern Kentucky



- Methods
 - Undercover narcotics investigations
 - Treatment for substance abusers 1-866-90-UNITE
 - Provides support to families and friends of abusers
 - Educates the public about the dangers of using drugs

One Tool Used by UNITE

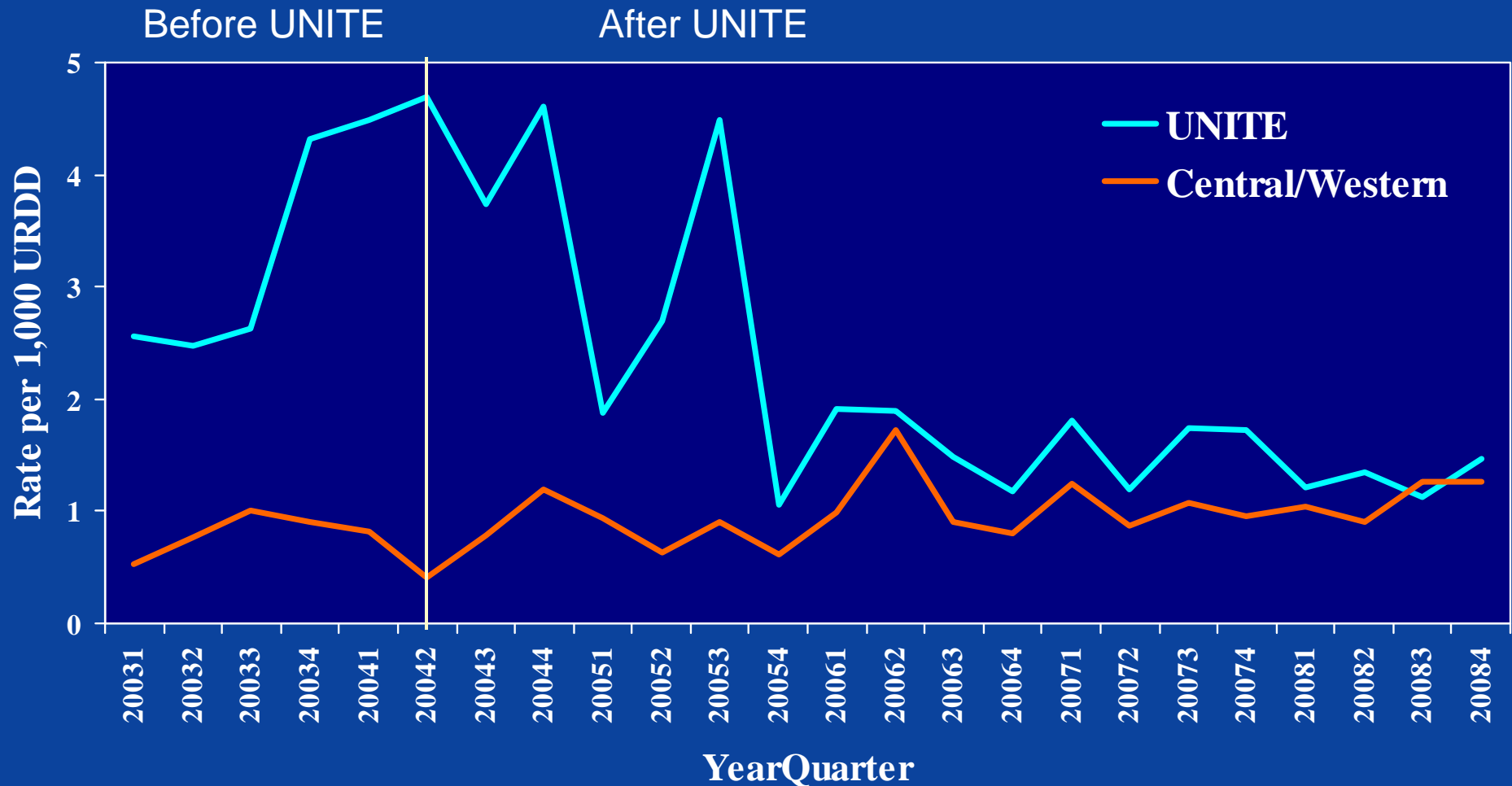
Drug Roundups

On April 6, 2004, Operation UNITE conducted a roundup of 210 suspected drug dealers in the eight-county Kentucky River area – the largest such operation in Kentucky's history. The sweep involved numerous city, county and state law enforcement agencies.

Through December 30, 2008, there have been 120 roundups, with at least one in each of the 29 counties in the Fifth Congressional District.

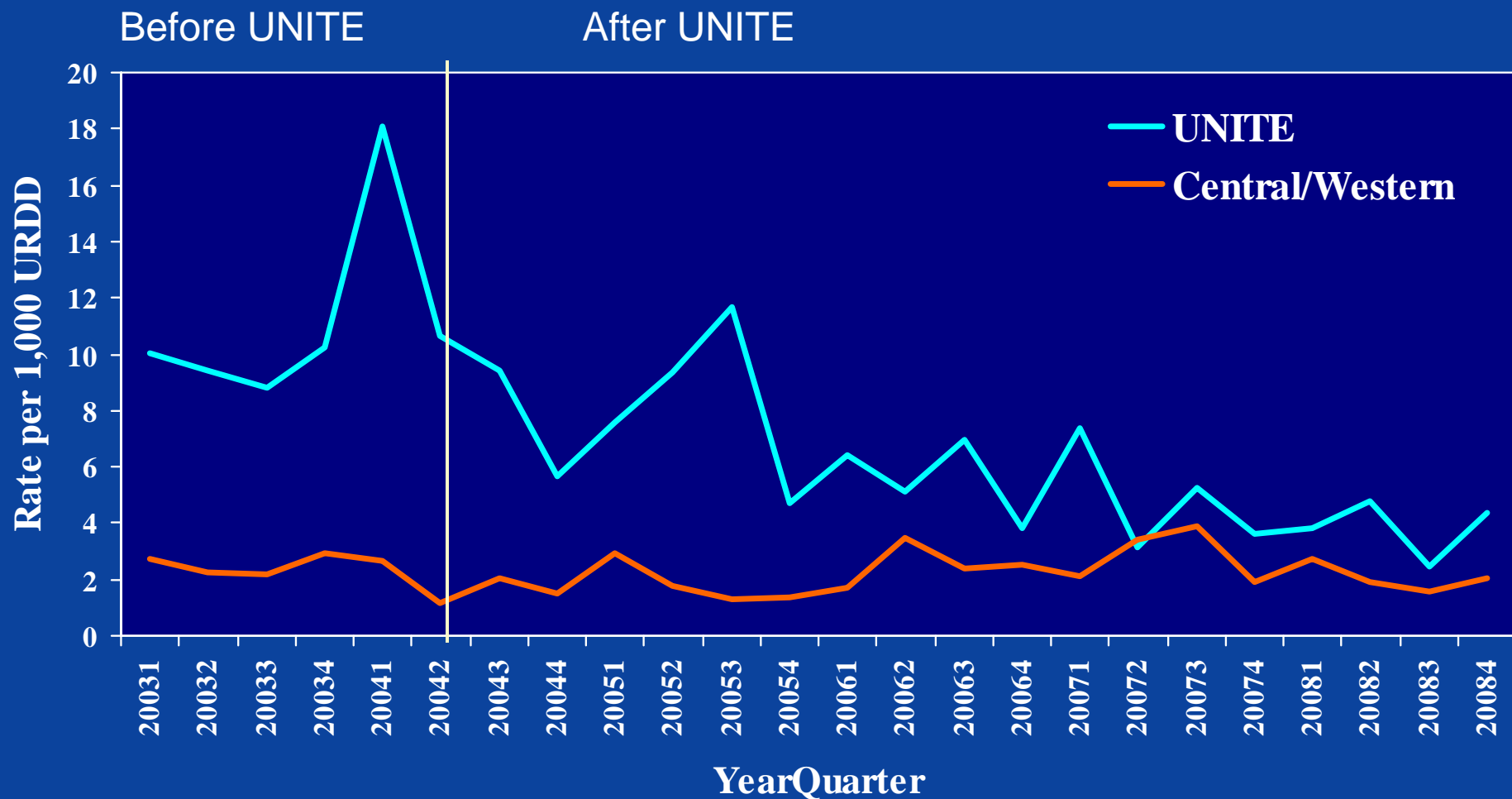
UNITE Region v. Central/Western KY

Poison Center Intentional Exposures



UNITE v. Central/Western KY

Methadone Average URDD Rates



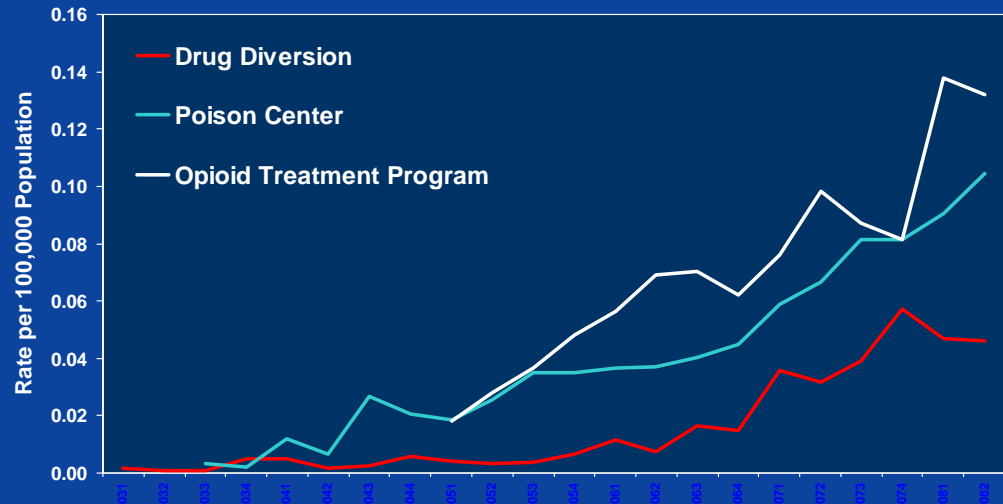
Applying PC Data to a Abuse Resistant Product

Is The New Product Abused?

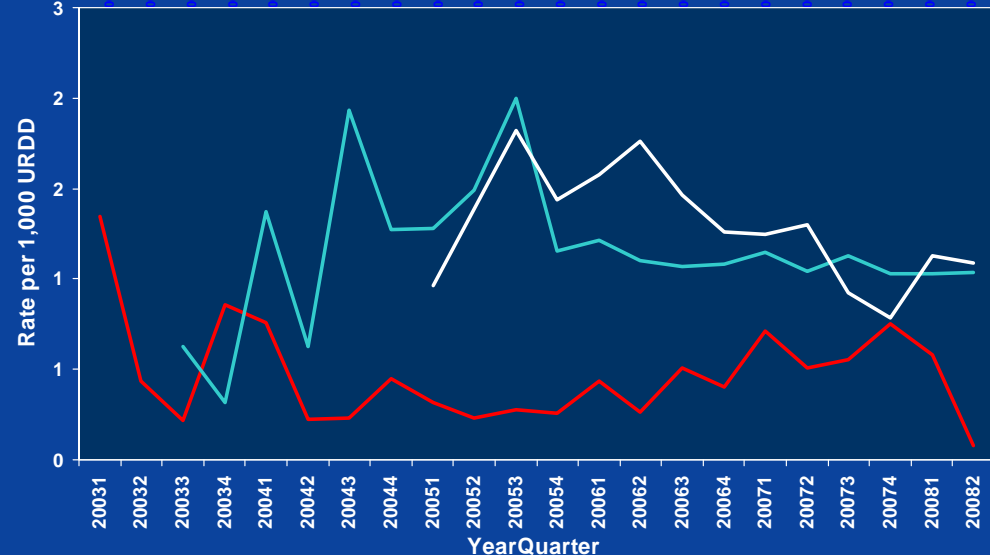
RADARS® System Poison Centers, Rates for all centers

Yes, new product is abused

Rate
per 100,000 population



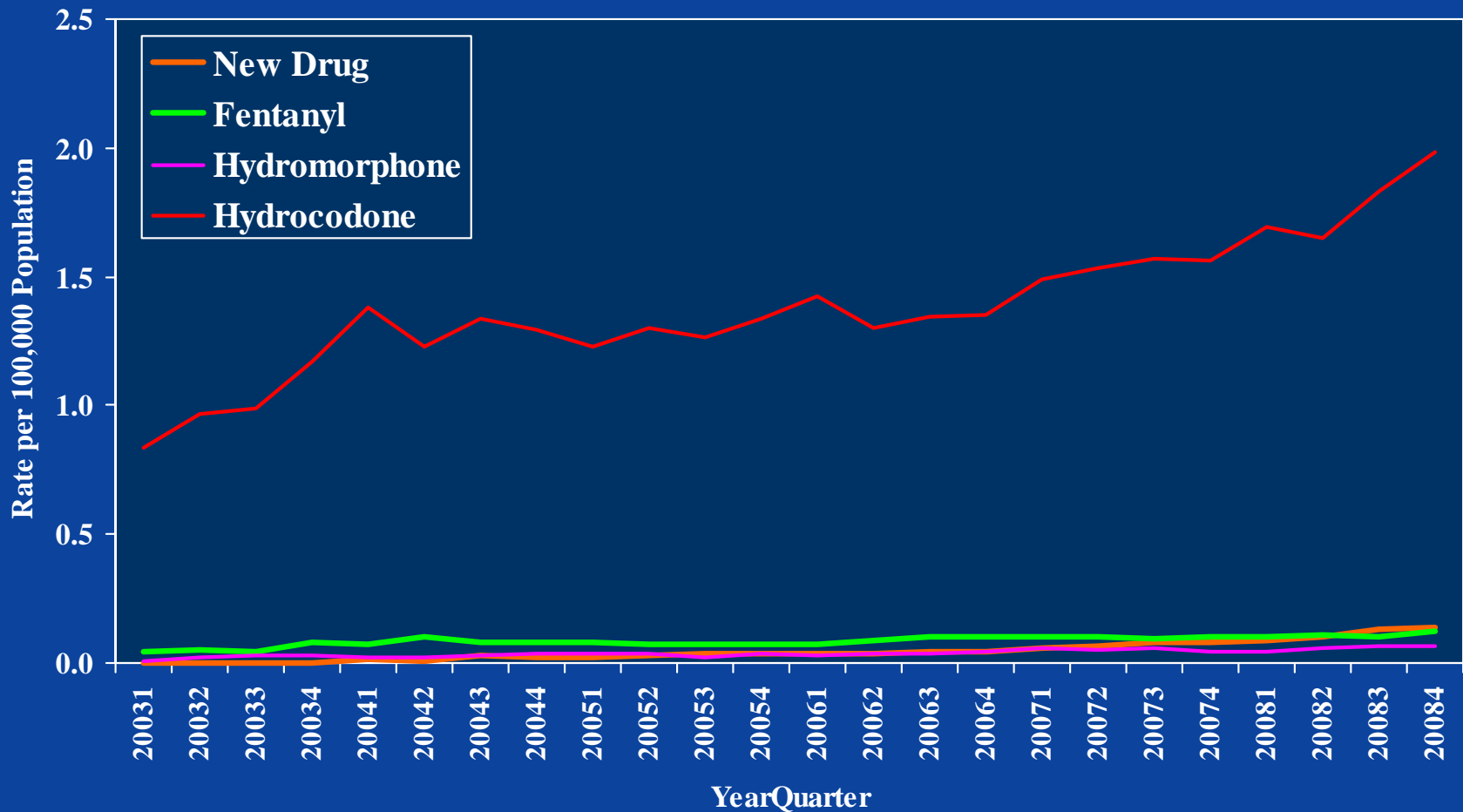
Rate
per 1000 URDD



How Does Abuse Compare to Other Opioids?

Poison Center Intentional Exposures

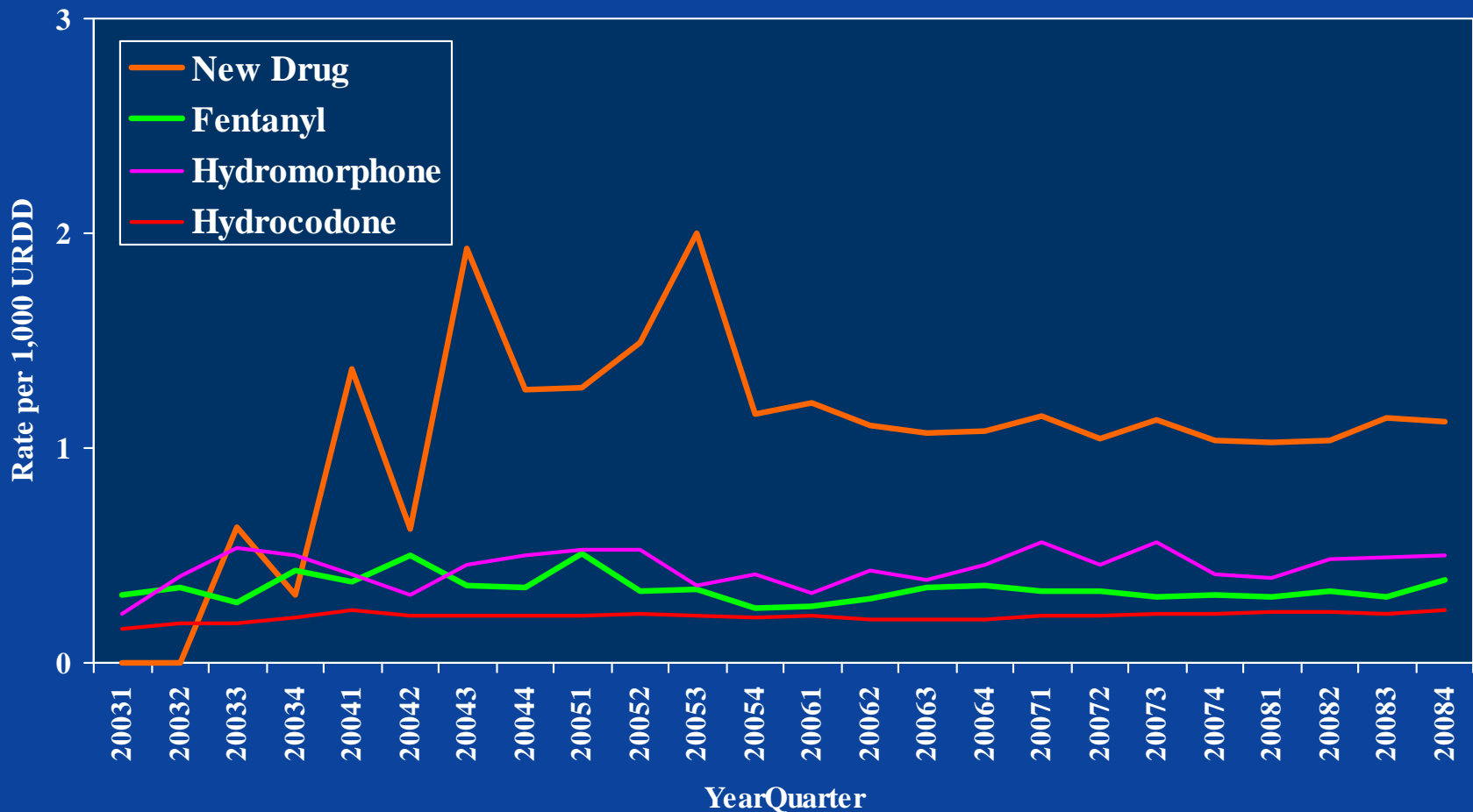
Rate per 100,000 population



How Does Abuse Compare to Other Opioids?

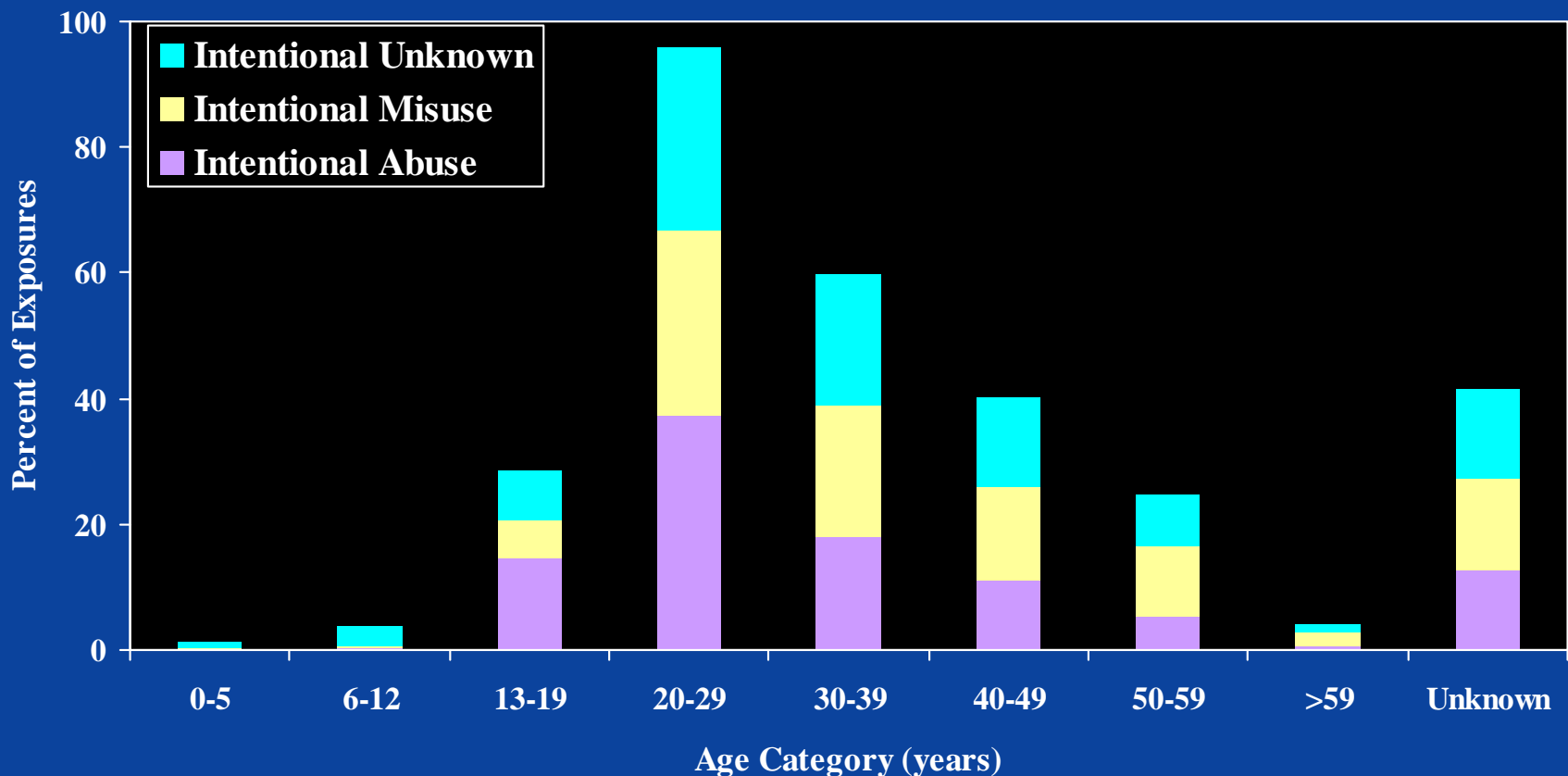
Poison Center Intentional Exposures

Rate per 1,000 URDD



Who Abuses The New Product?

New Drug Rates for all RADARS® System centers, 2003-2008

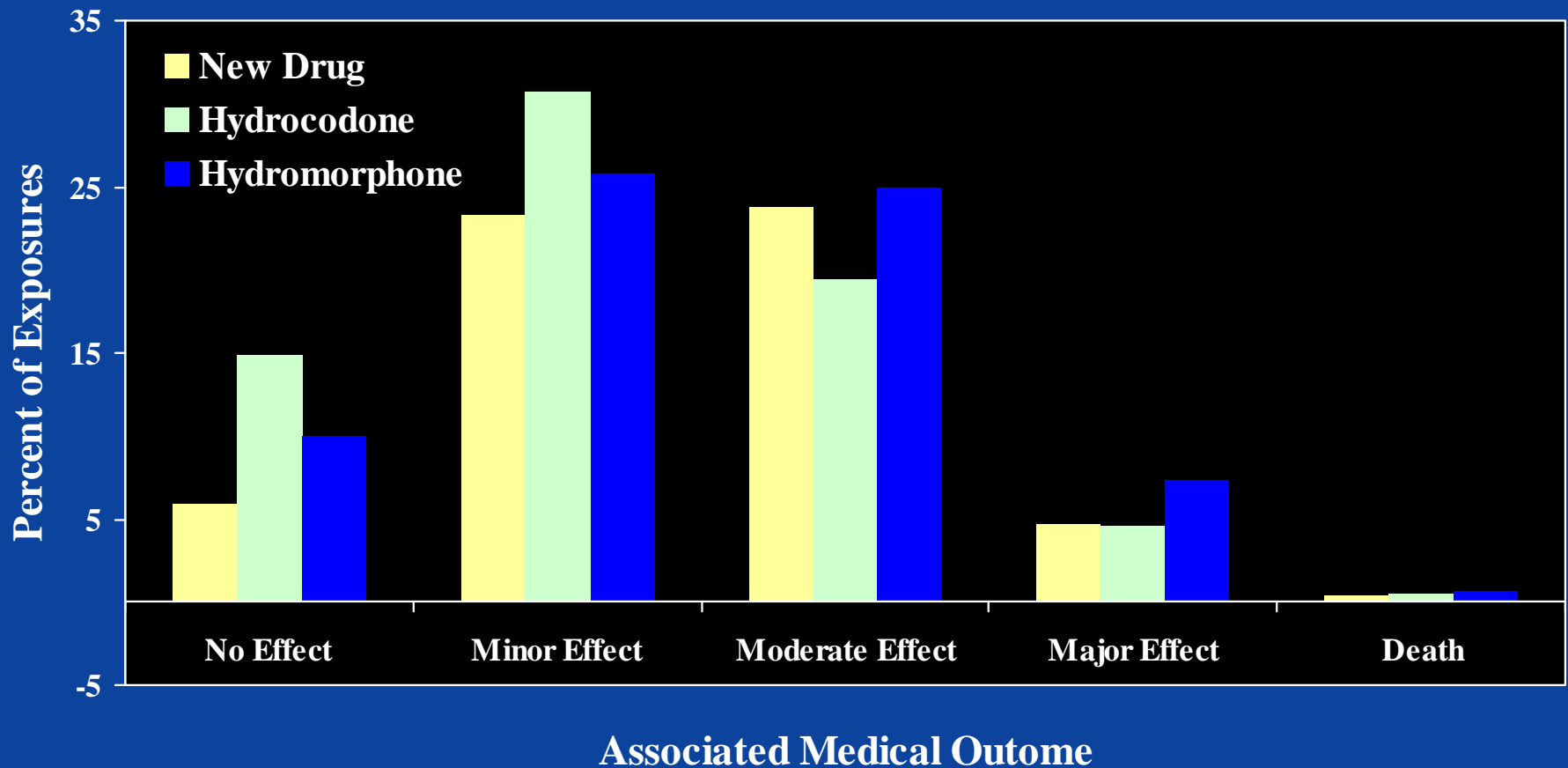


Intentional abuse: Intentional improper or incorrect use of a substance ... likely attempting to achieve a euphoric or psychotropic effect. All recreational use is included.

How Does Abuse Compare to Other Opioids?

Associated Medical Outcome

Percent of Intentional Exposures, 2003-2008

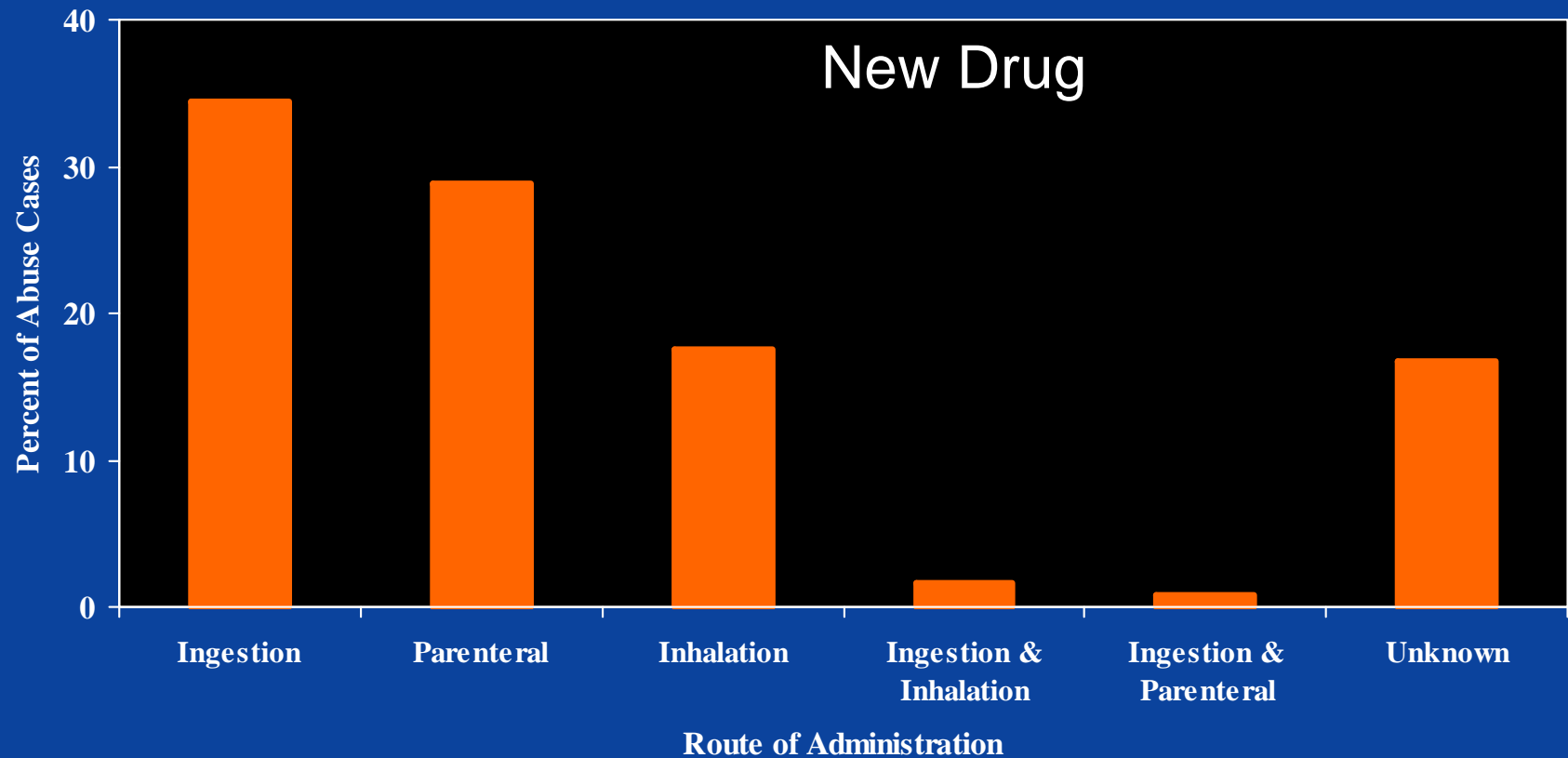


Route of Administration

- Many opioid medications are abused by a non-oral route of administration
- Route of administration data is provided by four RADARS System programs
 - Survey of Key Informant Patients (SKIP)
 - College Student Survey
 - Poison Centers
 - Opioid Treatment Programs

Does Tampering Occur?

Route of Administration, RADARS[®] System Poison Centers



College Survey, 1Q 2009

Routes of Administration

	N	Swallow %	Chewed %	Inhaled %	Inject %	Derm %
New Drug	20	55.0	40.0	40.0	10.0	0
Fentanyl	22	22.7	63.6	27.3	4.6	22.7
Hydrocodone	139	90.7	16.6	18.0	0.7	0
Hydromorph.	24	62.5	33.3	25.0	12.5	0
Methadone	23	73.9	39.1	17.4	13.0	0
Morphine	29	58.6	34.5	20.7	13.8	10.3
Oxycodone	103	79.6	23.3	25.2	3.9	0
Stimulants	190	85.8	21.1	20.5	2.6	1.1
Carisoprodol	24	95.8	16.7	12.5	0.6	4.2

How is the Product Abused?

RADARS® System Poison Centers, Rates for all centers

1. Per caller: Person I know is crushing up New Drug, warming it in spoon and shooting up with it. He is acting really agitated, shaking and really hyperactive.. What should I do?
2. S; Dr want PC opinion... 53 y/o F took ?? amts of fentanyl and morphine that was for son's PCA pump for pain (son has cancer) and injected self IV. EMS found unresponsive with resp 6 , IV, naloxone admin , pt AAO x 3 on arrival

How is the Product Abused?

RADARS[®] System Poison Centers, Rates for all centers

- Caller: sister is a heroin addict and she is prescribed with generic hydrocodone/apap and she grabbed a tablet scraped it and added water and shoot it up. She is currently asx. caller wants to know what to do.
- ER: have adult female that scraped and injected a fentanyl patch. Unk concentration..Came into ER lethargic and hypoventilating. Narcan and woke up.
- EMS call: medics on scene w/ 17 yo that supposedly injected XX oxycodone 3-4 hrs ago and has taken a few Oxycodone/Apap throughout the day. Currently awake and alert. Medics see some kind of trigeminy on the monitor. PCC rec transport.

Are There Vulnerable Populations?

- Underrecognized Toll of Prescription Opioids in Children (Annals Emerg Med: Sept 2008)
 - 2003-2006
 - Any call for a child < 6 years and 1 opioid drug
 - Buprenorphine
 - Fentanyl
 - Hydrocodone
 - Hydromorphone
 - Methadone
 - Oxycodone
 - Oxymorphone
 - Tramadol

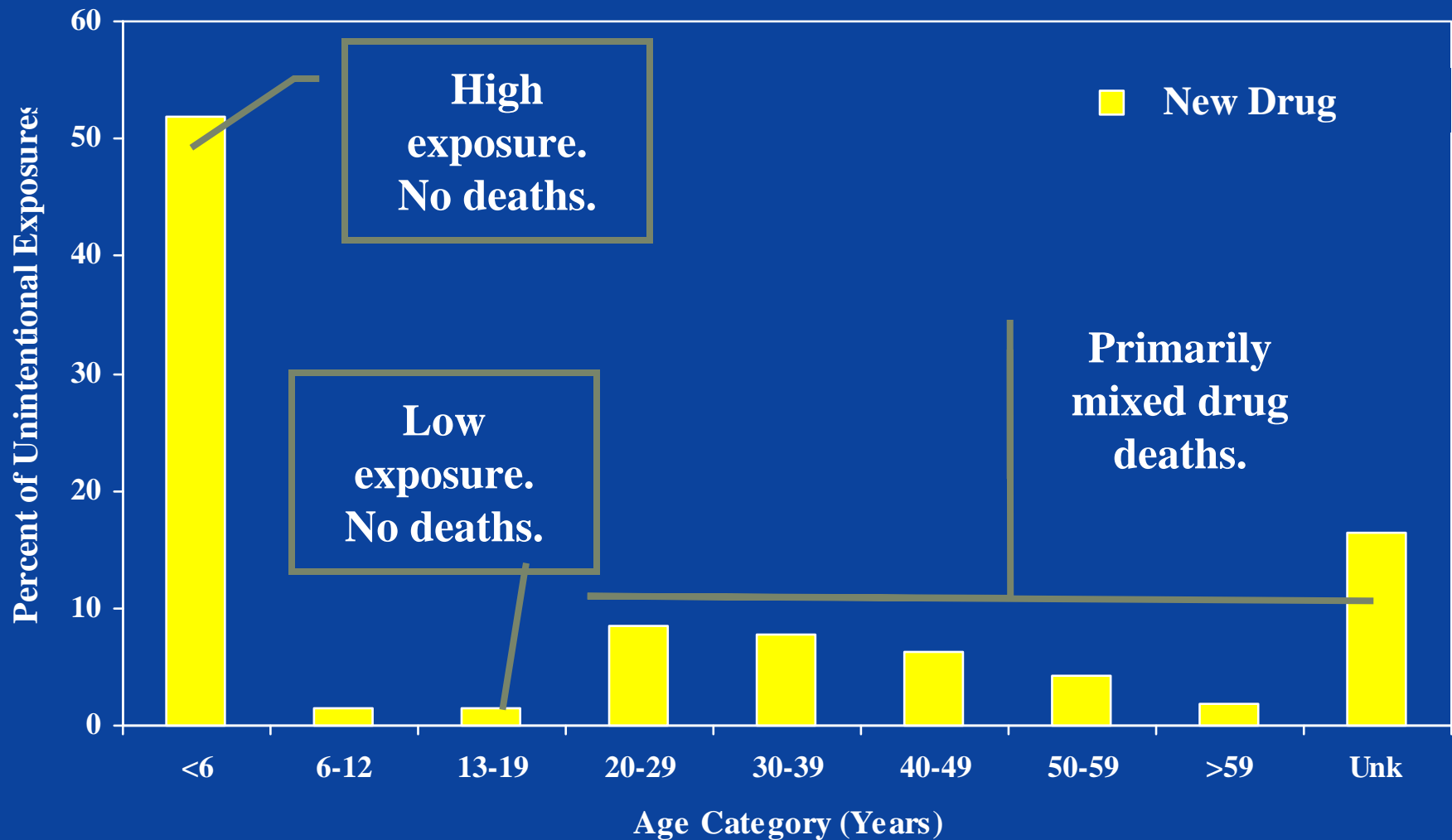
Pediatric Opioid Exposures

Results

- 9,240 exposure mentions involving 9,179 children.
National - at least two fold higher
 - Age range newborn to 5.5 years
 - Ingestion (99%), unintentional (>99%)
 - 92% occurred in the child's home (92%)
 - 8 deaths
- National 2006 AAPCC data – 9 of 29 (31%) deaths in child < 6 yrs 9 deaths were associated with an opioid drug

New Drug: Children are Affected

Poison Center Unintentional Exposures, 2003 – 2008



Recommendations - 1

- Surveillance must play a role in evaluating abuse deterrence/resistance.
- Some firm decisions or foundational concepts should be developed now.
- A claim for abuse resistance should be limited to a specific context.
 - i.e. reducing experimental abuse in young adults
- Other surveillance systems should be developed to assess potential claims

Recommendations - 2

- We need to compare total abuse among drugs.
- Selection of comparator drug could depend on specific label. For example, if the abuse resistant drug is an controlled release product intended to treat chronic pain, it could be compared to OxyContin.
- Mosaic approach
 - At least 3 populations should be included: Abusers, Children, Experimenters
 - Comparison to at least two other drugs – label and actual use
- Since time plays a role, needs to be ongoing.

THE END