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#### Abuse Deterrent Formulations – Updated RADARS<sup>®</sup> System Data

Researchers at the RADARS System continue to monitor the impact of abuse deterrent products on rates of prescription opioid abuse, misuse, overdose, death, and diversion. The impact of the reformulation of Opana<sup>®</sup> Extended Release (ER) and OxyContin<sup>®</sup> was studied.

The table below shows significant declines in intentional abuse exposures reported to poison centers participating in the RADARS System for OxyContin<sup>®</sup> and Opana<sup>®</sup> ER. The average of quarterly rates in year prior to the reformulation are compared to the average of quarterly rates post-reformulation.

	Population Rate	Unique Recipients of Dispensed Drug (URDD)
OxyContin	42.9% decline	30.9% decline
Opana ER	68.5% decline	54.0% decline

The above values are significantly different than the changes observed for other prescription opioids combined (IR oxycodone, IR oxymorphone, hydrocodone, fentanyl, morphine, methadone, hydromorphone, buprenorphine, tramadol, and tapentadol) during the same time period. These findings suggest that the introduction of opioid products reformulated to deter abuse corresponded with reductions in intentional abuse exposures to these products.

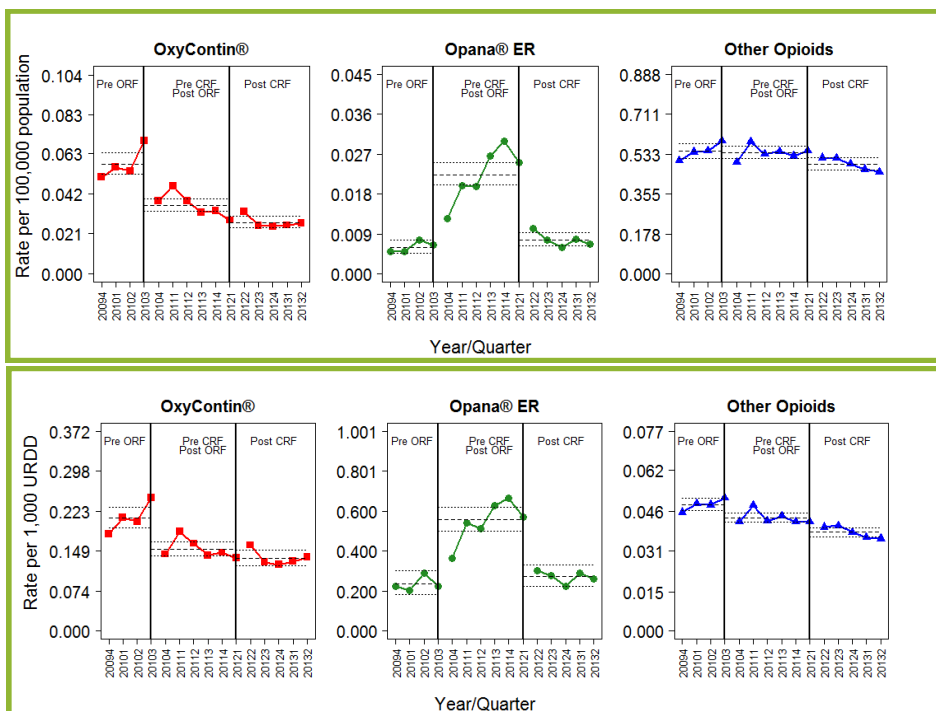
Continued monitoring is needed to determine whether these declines are sustainable, to observe patterns in the abuse of other prescription opioid products and to determine if abuse persists through intended routes of administration.

The figure below shows population and URDD rates since introduction of reformulated Opana ER and OxyContin. OxyContin was reformulated in 2010Q3 and Opana ER was reformulated in 2012Q1; the average rates of other opioids from 2009Q4 – 2013Q2 is provided for comparison.

#### Did You Know?

New York State's Internet System for Tracking Over-Prescribing (I-STOP) Law launched August 28, 2013 and works in conjunction with the Prescription Monitoring Program already in place.

CVS Caremark will use its database to identify and halt inappropriate prescribing of high risk drugs, including opioid painkillers. Details of the program were published online in a New England Journal of Medicine Perspective article on August 21, 2013.



## Crowdsourcing Black Market Pricing of Prescription Opioids.

Dasgupta N, Freifeld C, Brownstein JS, Menone CM, Surratt HL, Poppish L, Green JL, Lavonas EJ, Dart RC  
*Journal of Medical Internet Research*. 2013;15(8):e178. DOI:10.2196/jmir.2810.

Recently published in the *Journal of Medical Internet Research*, the study demonstrates the use of crowdsourcing to validate street prices of prescription drugs such as OxyContin®, Vicodin® and Dilaudid®. The study compares crowdsourced data from three sources:

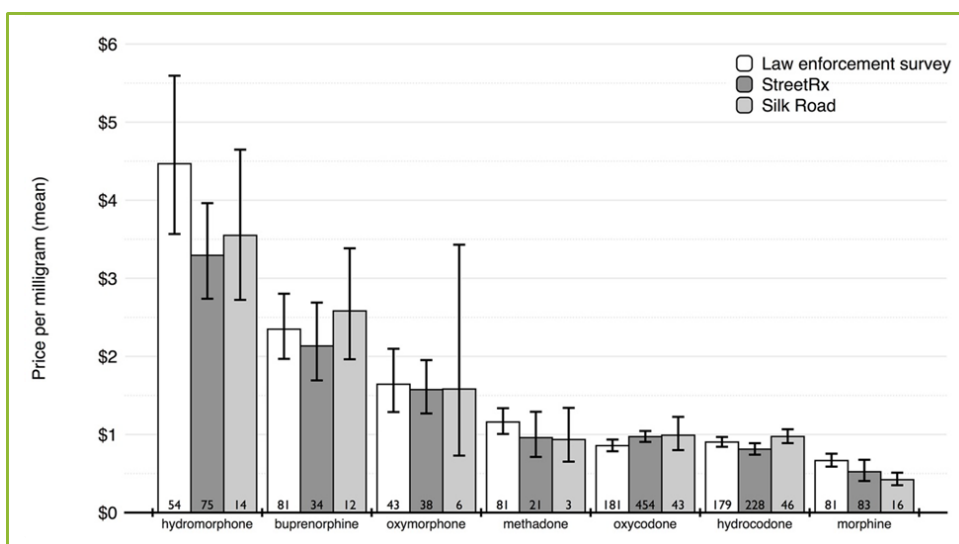
1. StreetRx ([www.streetrx.com](http://www.streetrx.com))
2. Silk Road, an online marketplace for illicit goods
3. Reference data from drug diversion investigators across the United States (collected on a quarterly basis from roughly 280 law enforcement agencies in 49 states)

"Crowdsourcing is a rapid and cost-effective way to gather information about sales transactions," said the study's lead author, Nabarun Dasgupta, MPH, PhD "We sought to determine whether crowdsourcing can provide accurate measurements of the street price of diverted prescription opioid medications."

The study finds the correlations between the data sources to be highly linear, suggesting that crowdsourcing and data mining are efficient ways to collect and project current street prices for prescription opioids that have been diverted to illegal markets.

These data can help model policy analysis and shed light on which new controlled pharmaceutical formulations have desirability relative to others when they hit the street.

Mean price per milligram of each opioid analgesic, between the data sources. Numbers at the bottom of each bar indicate sample size.



Crowdsourcing and data mining are efficient ways to collect data about street prices in an era of Internet-based social networks. These data can inform pharmaco-economic modeling and policy analysis, and may shed light on which new controlled pharmaceutical formulations have desirability relative to others when they hit the street. While this study represents an initial foray into collecting systematic economic data for modeling black markets for prescription drugs, the methodology could be extended in the future by connecting the data to health outcomes.

## Classification and definition of misuse, abuse, and related events in clinical trials: ACTION systematic review and recommendations.

Smith SM, Dart RC, Katz NP, Paillard F, Adams EH, Comer SD, Degroot A, Edwards RR, Haddox JD, Jaffe JH, Jones CM, Kleber HD, Kopecky EA, Markman JD, Montoya ID, O'Brien C, Roland CL, Stanton M, Strain EC, Vorsanger G, Wasan AD, Weiss RD, Turk DC, Dworkin RH

*Pain*. 2013; June 20. DOI: 10.1016/j.pain.2013.05.053. [Epub ahead of print]

As the nontherapeutic use of prescription medications escalates, serious associated consequences have also increased. This makes it essential to estimate misuse, abuse, and related events (MAREs) in the development and postmarketing adverse event surveillance and monitoring of prescription drugs accurately.

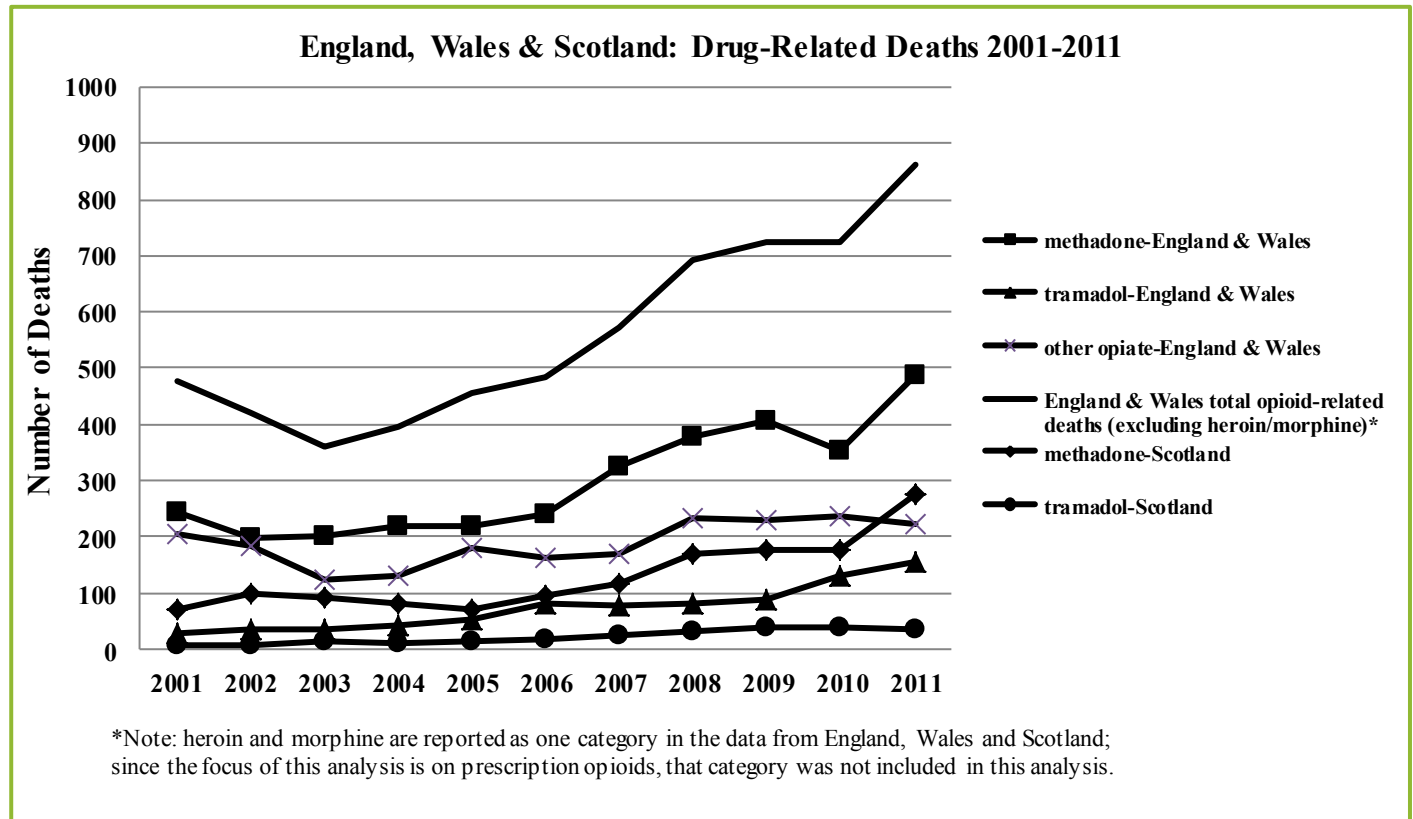
The Analgesic, Anesthetic, and Addiction Clinical Trials, Translations, Innovations, Opportunities, and Networks (ACTION) public-private partnership convened an expert panel to develop mutually exclusive and exhaustive consensus classifications and definitions of MAREs occurring in clinical trials of analgesic medications to increase accuracy and consistency in characterizing their occurrence and prevalence in clinical trials. The proposed ACTION classifications and definitions are designed as a first step in a system to adjudicate MAREs that occur in analgesic clinical trials and postmarketing adverse event surveillance and monitoring.

## Tramadol Reclassification in the UK

The United Kingdom's Advisory Council on the Misuse of Drugs recently recommended reclassifying tramadol to a Class C (Misuse of Drugs Act 1971) / Schedule III (Misuse of Drugs Regulations 2001) controlled substance due to growing concerns about the misuse of the product and increase in the number of deaths related to its use ([www.Medscape.com](http://www.Medscape.com)).

This mortality trend was noted in a letter to the *British Journal of Clinical Pharmacology*: Giraudon *et al.*, Prescription Opioid Abuse in the United Kingdom. 2013; Epub ahead of print:

*Tramadol presents interesting data in the UK: in 1996, England and Wales reported one death with the drug mentioned, but by 2011 there were 154 deaths. In Scotland, tramadol-related deaths increased from 8 in 2001 to 34 deaths in 2011.*



The complete Advisory Council recommendation can be found here:

[https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/144116/advice-tramadol.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/144116/advice-tramadol.pdf)

## FDA News – Safety Labeling Changes and Postmarketing Study Requirements

On September 10, 2013, the Food and Drug Administration announced class-wide safety labeling changes and new postmarket study requirements for all extended-release and long-acting (ER/LA) opioid analgesics intended to treat pain, recognizing that more information is needed to assess the serious risks associated with long-term use of ER/LA opioids.

FDA is requiring the drug companies that make these products to conduct further studies and clinical trials. The goals of these postmarket requirements are to further assess the known serious risks of misuse, abuse, increased sensitivity to pain (hyperalgesia), addiction, overdose and death.

The FDA is requiring a new boxed warning on ER/LA opioid analgesics to caution that chronic maternal use of these products during pregnancy can result in neonatal opioid withdrawal syndrome (NOWS), which may be life-threatening and require management according to protocols developed by neonatology experts.

In addition, the FDA is notifying ER/LA opioid analgesic application holders of the need for changes to the following sections of drug labeling: Dosage and Administration; Warnings and Precautions; Drug Interactions; Use in Specific Populations; Patient Counseling Information, and the Medication Guide.

For more detailed information visit: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm367726.htm>

## Recent Conference Attendance

### College on Problems of Drug Dependence (CPDD) Annual Meeting

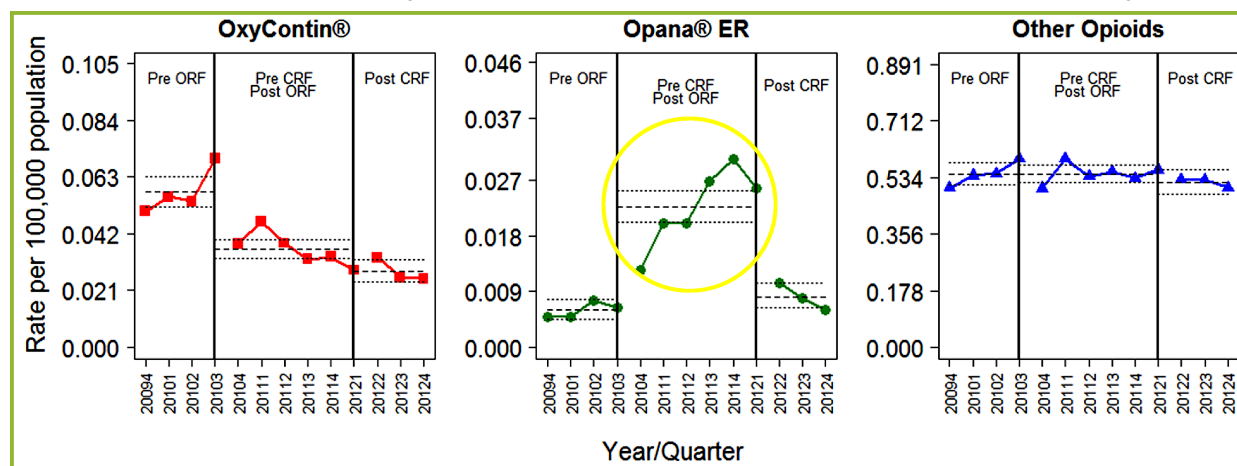
June 15-20, 2013 in San Diego, CA

#### Changing patterns of abuse reported to poison centers following introduction of reformulated extended release oxycodone

Dr. Richard Dart, MD, PhD

Dr. Dart's presentation at one of the workshops focused on an analysis of RADARS System data and the "natural experiment" for OxyContin® and Opana® ER involving the changeover to abuse-deterrent formulations (ADF). The figure below shows Poison Center Program Data for both products compared to other opioids pre- and post-reformulation.

- The Poison Center intentional abuse rate declined for both products after introduction of the ADF product; while the rates for other opioids stayed relatively steady
- In Drug Diversion and Treatment Programs, similar declines in diversion and abuse rates post-ADF introduction were seen
- The street value (dollars/mg) of the ADF formulations dropped compared to the value of the original formulations



#### Age trends in abuse calls to poison centers involving prescription opioids.

Severtson SG, Bucher Bartelson B, Dart RC

The availability-proneness theory suggests that drug abuse increases as the availability increases among individuals prone to abuse. The aim of the study was to examine the association between specific prescription opioid product availability and most frequent age of poison center intentional abuse calls mentioning those products in the past year.

- Prescription opioid classes that are more readily available are more likely to have an earlier peak age of mentions to poison centers
- The relationship between the number of intentional abuse cases and age differs across prescription opioid classes (age 11 to 69)

#### Evaluation of trends in abuse of stimulants in high school and college-age persons using RADARS® System data

Lowit KA, Le Lait, MC, Severtson SG, Dart RC

The purpose was to examine trends in stimulant use for high school and college age persons, comparing typical summer and in-school months using RADARS System Poison Center data.

- Seasonal trends for stimulant use for both high school and college age groups were evident
- College age persons showed higher rates of amphetamine use during in-school months
- High school age persons showed higher rates of methylphenidate use during in-school months

### National Governors Association (NGA) Policy Academy: Reducing Prescription Drug Abuse

April 18, 2013 in Denver, CO

Dr. Eric Lavonas, MD presented at the NGA Policy Academy on Reducing Prescription Drug Abuse. RADARS System data from the Poison Center and Drug Diversion Programs comparing opioid and stimulant rates in Colorado to national rates were shown.

### 2<sup>nd</sup> Practical Approach to Prescription Drug Misuse and Diversion

September 14, 2013 in Hamilton, Canada

The objective of this meeting was to bring together practitioners, pharmacists, law enforcement and the Canadian Centre on Substance Abuse, Pain Management and Addiction Medicine to develop a template to address prescription drug misuse. Dr. Annelies Hall, DVM attended of behalf of the RADARS System.

### **Centers for Disease Control and Prevention (CDC) PROTECT Meeting**

September 18-19, 2013 in Atlanta, GA

Dr. Jody Green, Ph.D is scheduled to present a review of key findings from the recently published manuscript "Root causes, clinical effects, and outcomes of unintentional exposures to buprenorphine by young children" *Journal of Pediatrics*, (Lavonas EJ, et al. 2013; online release August 29, 2013).

### **2013 Annual Meeting of the North American Congress of Clinical Toxicology (NACCT)**

September 27 - October 2, 2013 in Atlanta, GA

Once again, the RADARS System will present a diverse collection of original data at the 2013 NACCT Annual Meeting. This annual conference allows an opportunity for physicians, pharmacists, nurses, and scientists from around the world to participate in the sharing of knowledge on a wide variety of clinical toxicology topics and issues ([www.clintox.org](http://www.clintox.org)).

The following abstracts have been accepted for poster presentations:

- Lavery SA, *et al.* European and U.S. Patient Self-Reported Primary Drug and Percent of Endorsers Injecting at Treatment Intake
- Fischer LJ, *et al.* Geographic Description of Opioid Exposures in Pregnant Women within the US
- Winter EJ, *et al.* Micromedex® Clarification of Suboxone® Products Increases Coding Accuracy in the RADARS® System Poison Center Program
- Brown, KR, *et al.* Intentional Exposures to Opioids Reported by Health Care Workers
- Green JL, *et al.* Trends in Intentional and Unintentional Prescription Opioid Exposures Reported to Poison Centers (PC) in Australia, Germany, Italy, Switzerland and the United States, 2007-2012

In addition to the posters above, Dr. Eric Lavonas, MD was invited to speak and will present "Young child exposures to prescription medication: Do formulation and packaging matter?"

### **Nurse-Physician Advisory Taskforce for Colorado Healthcare (NPATCH) Meeting**

September 27, 2013 in Denver, CO

Dr. Richard Dart, MD, PhD is scheduled to present at the NPATCH 2013 Colorado Quad-Regulator Conference. NPATCH is affiliated with Governor's initiatives to reduce prescription drug abuse and is a part of the Colorado Department of Regulatory Agencies (DORA) (<http://cdn.colorado.gov/cs/Satellite/DORA-Reg/CBON/DORA/1251632229801>).

## **Upcoming Conference Attendance**

### **2013 American Association for the Treatment of Opioid Dependence (AATOD) Conference**

November 9-13, 2013 in Philadelphia, PA.

Dr. Green also will present at the World Federation for the Treatment of Opioid Dependence (WFTOD), which is a part of the 2013 AATOD Conference. The WFTOD officially started during the European Opiate Addiction Treatment Association (EUROPAD) conference in Ljubljana, Slovenia during July 2007 ([www.wftod.org](http://www.wftod.org)).

With Dr. Icro Maremmani, MD (EUROPAD, President WFTOD, Pisa, Italy), Dr. Green will chair the following Symposium: New Substances of Abuse in Europe: Results from a EUROPAD Pilot Study in Four European Countries.

### **Center for Lawful Access and Abuse Deterrence (CLAAD) National Prescription Drug Abuse Prevention Policy Consensus Meeting**

November 11, 2013 in Washington DC

Dr. Dart also will present "Evolving trends in substance abuse" at the CLAAD Policy Consensus Meeting. The meeting includes health care professionals, educators, legislators, law enforcement, insurers, private companies, journalists, academics and nonprofits that are in search of the best ideas for reducing prescription drug abuse while optimizing patient care (<http://www.claad.org/>).

### **Asia Pacific Association of Medical Toxicology (APAMT) International Scientific Congress**

November 21-23, 2013 in Dubai, United Arab Emirates

Dr. Green will present analyses of Prescription Drug Monitoring Programs and abuse deterrent formulations. The APAMT is an international association established by a group of medical toxicologists to promote chemical safety, poison control and treatment within the Asia Pacific region. (<http://www.asiattox.org/>).



## Rankings by State

Which states are most at risk for abuse, misuse and or diversion based on prescription and/or exposure trends? RADARS System data can help identify the top “at risk” states. Presented below are the top five “at risk” states based on three different analyses:

- (1) URDD Rate Prescriptions Filled = Unique Recipient of Dispensed Drug (URDD) per 100 Population: number of individual opioid prescriptions filled (excluding refills), calculated with data from IMS and 2010 US Census data.
- (2) Population Rate Intentional Abuse Exposures = Intentional exposures\* reported to RADARS System Poison Centers per 100,000 persons, calculated with 2010 US Census data.
- (3) URDD Rate Intentional Abuse Exposures = Intentional exposures\* reported to RADARS System Poison Centers per 1000 persons based on individual prescriptions for opioids (excludes refills), calculated with data from IMS and 2010 US Census data.

Rank	URDD Rate Prescriptions Filled		Pop. Rate Intentional Abuse Exposures		URDD Rate Intentional Abuse Exposures	
1	AL	24.57	WV	6.58	MN	0.565
2	TN	24.18	AZ	5.80	SD	0.490
3	WV	22.79	ME	5.73	AZ	0.396
4	KY	20.83	KY	5.38	MD	0.392
5	MS	20.25	MN	5.05	IL	0.378

Higher rates indicate higher risk. According to our 2013 Q1 RADARS System data:

#1 for patients filling a prescription for opioids is Alabama (24.57).

- Tennessee was #1 (25.04) for the last 3 quarters reported.

#1 for intentional abuse exposures for opioids based on population rate per 100,000 is West Virginia (6.58).

- In our last report South Dakota was #1 (6.64).

#1 for intentional abuse exposures for opioids based on URDD rate per 1000 is Minnesota (0.565).

- South Dakota was #1 (0.590) for the last 2 quarters.

*\* Intentional exposure is defined as a purposeful action resulting from the intentional improper or incorrect use of a substance where the victim was likely was attempting to gain a high, euphoric effect or some other psychotropic effect, includes recreational use.*

Quarter 2012	URDD Rate Prescriptions Filled		Pop. Rate International Abuse Exposures		URDD Rate International Abuse Exposures	
4	TN	25.04	SD	6.64	SD	0.590
3	TN	24.29	WV	8.62	SD	0.592
2	TN	24.67	AZ	7.30	MN	0.602
1	AL	22.52	WV	9.67	MN	0.706



## Change in Population Rate Calculation

The introduction of 2010 US Census data brought significant declines in population rates. In order to prevent abrupt declines, and adjust for population growth between releases of US Census data, RADARS System statisticians developed a method to estimate the US population at the ZIP Code tabulation area (ZCTA) level.

Beginning in the 1<sup>st</sup> quarter of 2013, population rates in quarterly reports are calculated using 2000 and 2010 US Census population estimates at the ZCTA level.

- Estimates assume a linear change in the population at the ZCTA level between 2010 and 2020, and that the change in population will be equal to the change observed between 2000 and 2010.
- Estimates for ZIP codes where no 2000 US population was observed are calculated using the national population growth (9.7% 10 year increase).

$$\frac{\left( \frac{(2010 \text{ US Census population})}{(2000 \text{ US Census population})} - 1 \right) \times \text{number of quarters since 2nd quarter 2010}}{40} \times 2010 \text{ US Census population}$$

The resulting number is then added to the 2010 US Census population for a given ZIP code.



### RADARS System Quarterly Technical Report

#### RADARS System Technical Report #2013Q3-1

#### Comparison of Drug Diversion Street Price and StreetRx Programs

Please copy the web address into your web browser to view the pdf:

[http://www.radars.org/Portals/1/2013Q1\\_StreetRx\\_QTR.pdf](http://www.radars.org/Portals/1/2013Q1_StreetRx_QTR.pdf)

## New RADARS System Manuscripts

### Manuscripts:

- Dart RC, Bucher Bartelson B, Adams EH. Non-medical use of tapentadol immediate release by college students. 2013. Clinical Journal of Pain. In Press.
- Dasgupta N, Freifeld C, Brownstein JS, Menone CM, Surratt HL, Poppish L, Green JL, Lavonas EJ, Dart RC. Crowdsourcing black market pricing of prescription opioids. 2013. Journal of Medical Internet Research. 2013; 15 (8):e178. DOI:10.2196/jmir.2810.
- Lavonas EJ, Banner W, Bradt P, Bucher-Bartelson B, Brown KR, Rajan P, Murrelle L, Dart RC, Green JL. Root causes, clinical effects, and outcomes of unintentional exposures to buprenorphine by young children. 2013. Journal of Pediatrics. In Press: online release August 29, 2013.
- Smith SM, Dart RC, Katz NP, Paillard F, Adams EH, Comer SD, Degroot A, Edwards RR, David Haddox, J. , Jaffe JH, Jones CM, Kleber HD, Kopecky EA, Markman JD, Montoya ID, O'Brien C, Roland CL, Stanton M, Strain EC, Vorsanger G, Wasan AD, Weiss RD, Turk DC, Dworkin RH. Classification and definition of misuse, abuse, and related events in clinical trials: ACTION systematic review and recommendations. 2013. Pain. In Press: published online 24 June 2013. DOI:10.1016/j.pain.2013.05.053.

## Did You Know?

The White House released a new anti-drug "toolkit" on August 28, 2013 with packets of information for prescribing physicians, patients, first responders, community members and overdose survivors to help stem an alarming rate of overdose deaths.

## Contact Information

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## RADARS System Mission Statement

The RADARS System provides timely, product specific and geographically-precise data to the pharmaceutical industry, regulatory agencies, policymakers and medical/public health officials to aid in understanding trends in the abuse, misuse, and diversion of prescription drugs.

## Rocky Mountain Poison and Drug Center and Denver Health and Hospital Authority

The RADARS System is a governmental nonprofit operation of the Rocky Mountain Poison and Drug Center (RMPDC), an agency of Denver Health (DH). The RMPDC has been in operation for more than 50 years, making it one of the oldest poison control centers in the nation. DH is the safety net hospital for the City and County of Denver and is the Rocky Mountain region's academic Level I trauma center and includes Denver Public Health, Denver's 911 emergency medical response system, nine family health centers, 12 school-based clinics, NurseLine, correctional care, Denver CARES, the Denver Health Medical Plan, and the Rocky Mountain Center for Medical Response to Terrorism, Mass Casualties and Epidemics.



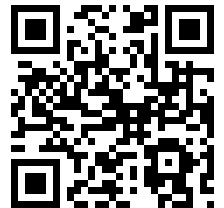
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