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International Presentations by Richard C. Dart, MD

Global Addiction & European Opiate Addiction Treatment Association (EUROPAD) Joint Conference

May 7-10, 2013

Pisa, Italy

Diversion, misuse and trafficking of methadone and buprenorphine

Dr. Dart began the presentation with an overview of the RADARS System mosaic and outlined some of the challenges of prescription drug abuse surveillance including:

- clandestine behavior
- geographical variability
- rapid changes
- multiple age groups
- product specificity (15 active pharmaceutical ingredients (API) for opioids and stimulants and dozens of specific products)

According to RADARS System data by program:

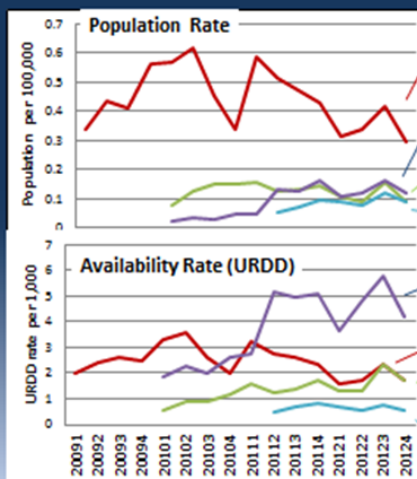
- Drug Diversion: buprenorphine diversion exceeded methadone diversion in 2011 (CESAR Fax presented a similar trend around 2010).
- Opioid Treatment and Survey of Key Informants' Patients: methadone endorsements are higher than buprenorphine, but are decreasing. Buprenorphine single ingredient shows the largest increase in endorsements among buprenorphine products (single ingredient tablets, combination tablets and combination film). The single ingredient tablets rates of diversion also are increasing.
- StreetRx (internet crowd-sourcing): the price of buprenorphine is significantly higher than methadone.

Did You Know?

On April 27th, the DEA held the 6th "National Prescription Drug Take-Back Day" in which over 370 tons of expired and/or unwanted drugs were collected.



Survey of Key Informant Patients Past 30 Day Endorsements, 2009-2012



Methadone high, but decreasing
Bup-Single Ingredient Increasing
Bup-Naloxone Combination Increasing Flat
Bup-Naloxone Film Strip Increasing slightly
Bup-Single Ingredient Increasing Dramatically
Methadone Slight Decrease
Bup-Naloxone Combination Increasing
Bup-Naloxone Film Strip low, flat

Cont.

In conclusion, prescription opioid abuse in the US may be plateauing, but still causes 16,000 deaths per year. Buprenorphine abuse is increasing quickly, perhaps due to generic availability. Methadone endorsements in treatment programs are decreasing, but it is the cause of more deaths than any other opioid.

European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) International Congress

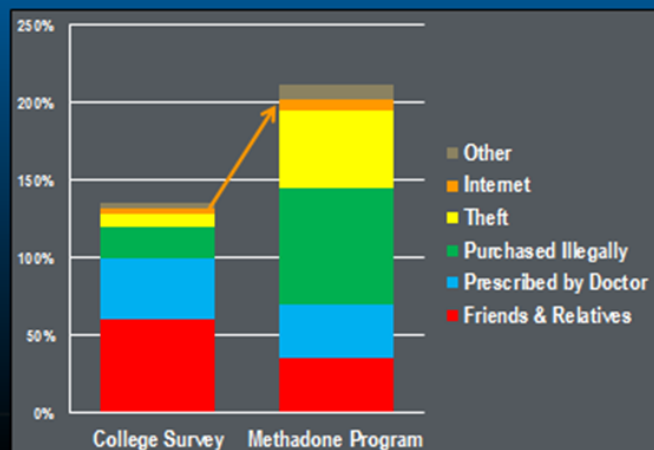
May 28-31, 2013

Copenhagen, Denmark

Prescription drugs purchased through the internet: Who are the users?

"The internet has become a pharmaceutical candy store stocked with addictive drugs, available at the click of a mouse" (Califano, 2007). But who is taking advantage of the situation, really? A study by Cicero, *et al.* (Pain Medicine, 2008) showed that although the internet seems to be an appealing source for the diversion of prescription opioid analgesics, there does not appear to be empirical evidence to support that hypothesis. The primary sources for abusers were dealers, friends or relatives and doctors' prescriptions; internet purchases accounted for less than 6% of responders. Increased enforcement by US agencies, including the Drug Enforcement Agency (DEA), has had a significant impact on availability of prescription opioids on the internet. Although many prescription drugs are purchased via the internet, stimulants in particular, abusers prefer other sources: "prescription drugs are cheaper on the street"; "there are too many 'rip offs'; and "big brother is watching". We will have to see wait and see the impact on abuse from developments like the Silk Road, an "anonymous market" which uses a Tor hidden service and peer-to-peer digital currency for payments to protect buyer & seller identities and Pfizer's move to sell Viagra® legitimately online.

RADARS® SYSTEM SOURCE OF ABUSED OPIOID, 2008



RADARS System Docket Submission to the FDA on March 29, 2013

Regarding FDA Dockets #FDA-2010-P-0526, #FDA-2010-P-0540, #FDA-2011-P-0473

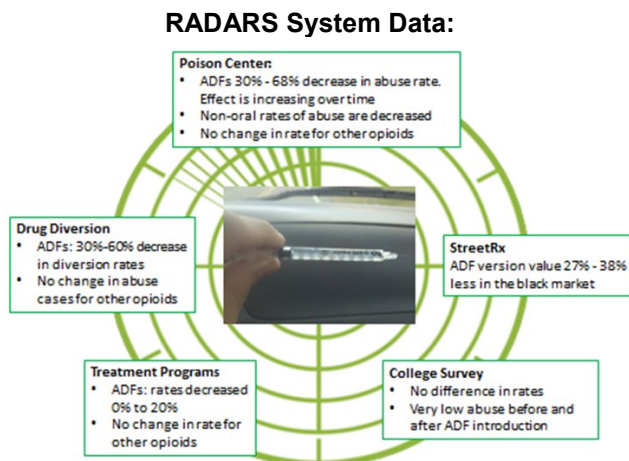
The dockets listed above refer to the determination if OxyContin® (oxycodone hydrochloride extended-release tablets) were voluntarily withdrawn from sale by Purdue Pharma for reasons of safety or effectiveness or reasons other than safety or effectiveness.

Abuse Deterrent Formulations of Prescription Opioid Analgesics: Changes in Abuse Indicators Following Introduction of Abuse Deterrent Formulations

Abuse deterrent formulations (ADF) of prescription opioids have been proposed to deter the diversion and abuse of these products. We examined rates of diversion and abuse before and after introduction of reformulated versions of OxyContin and Opana® ER compared to other opioids using the Researched Abuse, Diversion and Addiction Related Surveillance (RADARS® System), a national surveillance system for diversion and abuse of prescription opioids and stimulants. Results from multiple RADARS System programs as well as other sources indicate that the original formulations of opioid analgesics are less safe than the abuse deterrent versions.

3 Hypotheses presented to FDA:

1. Decreased interest in obtaining prescriptions to divert for abuse will result in fewer individuals filling prescriptions (i.e. the number of people filling prescriptions for OxyContin and Opana (URDD) would be lower following reformulation)
2. Rates of abuse & diversion of OxyContin and Opana would be lower following reformulation introduction. This decline would be different than changes in other prescription opioids and independent of changes in drug availability.
3. Use of these drugs through non-oral routes of abuse would decline relative to oral abuse as the new products were intended to deter crushing and solubilization of the drugs.



Hypothesis 1 Outcome

- Average URDD/quarter declined 15% for OxyContin & 31% for Opana ER following reformulation.

Hypothesis 2 Outcome

- For both products, DD rates were markedly decreased.
- PC Intentional abuse rates were lower following reformulation. The effect was observed after adjustment for availability of the drug (URDD) and was significantly different than trends for other opioids.
- Street price for OxyContin reformulation was significantly less than the original formulation. The street price for Opana ER reformulation was lower, but not significantly.
- Rates of OxyContin abuse declined in treatment programs per population.
- No other differences were observed in the OTP/SKIP or CS.

Hypothesis 3 Outcome

- It seems that the introduction of ADF reformulations of OxyContin & Opana ER resulted in the reduction of abuse of those products. Therefore, the original formulations are less safe than the reformulated versions.

Recommendation based on the analyses

It would be poor policy to approve new formulations of prescription opioid analgesics that can be easily crushed and solubilized for abuse when safer products are available.

FDA Citizen Petition Decisions — Abuse-Deterrent Formulations: Oxycodone® and Opana® ER

On April 16th, the FDA announced that it would not approve generic versions of OxyContin® referencing the original non-abuse resistant brand formulation. And, on May 10th, the FDA announced that it would not approve Endo's Citizen Petition to block generic versions of OPANA® ER using the original non-abuse resistant formulation, see the following for details on the announcements:

[FDA News Release 4/16/2013](#)

[FDA approves abuse-deterrent labeling for reformulated OxyContin](#)

The U.S. Food and Drug Administration (FDA) approved updated labeling for Purdue Pharma L.P.'s reformulated OxyContin (oxycodone hydrochloride controlled-release) tablets. The new labeling indicates that the product has physical and chemical properties that are expected to make abuse via injection difficult and to reduce abuse via the intranasal route (snorting). Additionally, because original OxyContin provides the same therapeutic benefits as reformulated OxyContin, but poses an increased potential for certain types of abuse, the FDA has determined that the benefits of original OxyContin no longer outweigh its risks and that original OxyContin was withdrawn from sale for reasons of safety or effectiveness. Accordingly, the agency will not accept or approve any abbreviated new drug applications (generics) that rely upon the approval of original OxyContin.

The agency review of this issue included an analysis of the following:

- Citizen petitions requesting that the agency determine whether original OxyContin was voluntarily withdrawn from sale for reasons other than safety or effectiveness;
- Comments submitted to the public dockets associated with these petitions;
- Information concerning original and reformulated OxyContin and the withdrawal of original OxyContin;
- Clinical data, peer-reviewed literature, and postmarketing adverse events associated with original OxyContin, reformulated OxyContin, and other ER oxycodone products;
- On-going postmarketing assessments of the impact of reformulated OxyContin on abuse.

[FDA Statement 5/10/2013](#)

[Original Opana ER Relisting Determination](#)

The U.S. Food and Drug Administration (FDA) responded to a petition and decided that the original formulation of Opana ER (oxymorphone hydrochloride) Extended-Release Tablets was not withdrawn from the market for reasons of safety or effectiveness. As a result, generic versions of the original formulation can continue to be approved and marketed.

The petition was submitted by Endo Pharmaceuticals Inc., the sponsor of original Opana ER and a reformulated version, also called Opana ER, which was designed with the goal of being more difficult to abuse and misuse. After an extensive, science-based review, FDA concluded based on the available data and information that the original formulation of Opana ER was not withdrawn from the market for reasons of safety or effectiveness. As a result, FDA has denied the manufacturer's petition. FDA conclusions include:

- Study data show that the reformulated version's ER features can be compromised when subjected to manipulation, such as cutting, grinding, or chewing, followed by swallowing.
- Reformulated Opana ER can be readily prepared for injection and prepared for snorting using commonly available tools and methods.
- The postmarketing investigations are inconclusive, and data also suggest the possibility that a higher percentage of reformulated Opana ER abuse is via injection than the original formulation.

FDA continues to encourage the development of abuse-deterrent formulations of opioids to help reduce prescription drug abuse and to positively affect public health. The science of abuse deterrence is relatively new, and both the formulation technologies and the analytical, clinical, and statistical methods for evaluating those technologies are rapidly evolving.

Ranking 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	TN	25.04	SD	6.64	SD	0.590
2	AL	24.03	WV	6.53	MN	0.522
3	WV	22.77	AZ	5.95	MD	0.444
4	KY	21.02	MD	5.35	NY	0.412
5	MS	20.56	MN	5.07	IA	0.393

Higher rates indicate higher risk. According to our 2012 Q4 RADARS® System data:

#1 for patients filling a prescription for opioids is Tennessee

- Tennessee has been #1 (24.29) for the last 2 quarters reported.

#1 for intentional abuse exposures for opioids based on population rate per 100,000 is South Dakota

- In our last report West Virginia was #1 (8.62)

#1 for intentional abuse exposures for opioids based on URDD rate per 1000 is South Dakota

- South Dakota also was #1 (0.59) in our last report.

** 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.*

Recent RADARS System Publications and Presentations

Manuscripts:

- Giraudon I, Lowitz K, Dargan PI, Wood DM, Dart RC. Prescription Opioid Abuse in the United Kingdom. *British Journal of Clinical Pharmacology*. 2013; In Press. Zosel A, Bucher Bartelson B, Bailey E, Lowenstein S, Dart R. Characterization of adolescent prescription drug abuse and misuse using the Researched Abuse Diversion and Addiction-Related Surveillance (RADARS®) System. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2013;52(2):196-204.
- Severtson SG, Bucher Bartelson B, Davis JM, Muñoz A, Schneider MF, Chilcoat H, Coplan PM, Surratt H, Dart RC. Reduced abuse, diversion, and therapeutic errors following reformulation of OxyContin® in 2010. *Journal of Pain*. 2013; In Press.

Abstracts/Posters/Platforms:

- Lavonas EJ. Prescription Drug Abuse: Colorado and National Data. Colorado In-State Policy Workshop, National Governors Association Policy Academy: Reducing Prescription Drug Abuse. Denver, CO. April 2013.
- Lavonas EJ, Severtson SG, Bucher-Bartelson B, Green JL, Cicero T, Kurtz SP, Rosenblum A, Surratt HL, Dart RC. Buprenorphine/Naloxone Film Diversion and Abuse Rates are Less than Tablet Formulations. ASAM Annual Medical-Scientific Conference. April 2013.
- Dart R, Severtson S, Patrick J, Webster J. Abuse, misuse, and diversion of hydromorphone since the introduction of the extended-release formulation (EXALGO®). APS Annual Meeting. May 2013.
- Lavonas E, Bucher Bartelson B, Severtson S, Davis J, Baker G, Vorsanger G, Dart R. Abuse and Diversion of Immediate-Release Prescription Opioids: 30 Months of Data from the RADARS® System. APS Annual Meeting. May 2013.
- Severtson S, Davis J, Le Lait M, Bucher-Bartelson B, Dart R. Use of both individuals filling prescriptions and population rates in assessing abuse potential of prescription opioids. APS Annual Meeting. May 2013.
- Surratt H, Kurtz, Cicero T, Dart R, Baker G, Vorsanger G. Street prices of prescription opioids diverted to the illicit market: data from a national surveillance program. APS Annual Meeting. May 2013.
- Dart RC. Diversion, misuse and trafficking of methadone and buprenorphine. Global Addiction and EUROPAD Joint Conference. May 2013.
- Bucher Bartelson B, Green JL, Desel H, Ochsenfahrt G, Sesana F, Milanesi G, Gunja N, Brown J, Gmerek B, Dart RC. Intentional and Unintentional Prescription Opioid Exposures in Italy, Australia, Germany and the United States. SPR Annual Meeting. May 2013.
- Dart RC. Prescription drugs purchased through the internet: Who are the users? EAPCCT International Congress. May 2013.
- Green JL, Desel H, Milanesi G, Sesana F, Brown JA, Gunja N, Kupferschmidt H, De Vries I, Campbell A, Thomas SHL, Thompson JP, Severtson G, Poppish L, Gmerek B, Dart R. Unintentional Pediatric Opioid Exposures as Reported to the Global Toxiconsurveillance Network (GTNet) from 2008-2010. EAPCCT International Congress. May 2013.
- Lavonas E, Severtson S, LeLait M, Lowitz K, Green J, Poppish L, Dart RC. Changes in Oxymorphone Abuse Rates Following Introduction of a Crush-Resistant Formulation. ICOO Annual Conference. June 2013.
- Surratt H, Kurtz, Cicero T, Dart R, Baker G, Vorsanger G. Street prices of prescription opioids diverted to the illicit market: data from a national surveillance program. ICOO Annual Conference. June 2013.
- Lavonas EJ, Bucher-Bartelson B, Severtson SG, Davis JM, Baker G, Vorsanger GJ, Dart RC. Abuse and Diversion of Immediate-Release Prescription Opioids: 30 Months of Data from the RADARS® System. ICOO Annual Conference. June 2013.
- Fonseca F, Green JL, Maremmani I, Touzeau D, Walcher S, Deruvo G, Somaini L, Martínez D, Roig J, Torrens M. Studying new trends of prescription drug use in Europe: The European Opioid Treatment Patient Survey. National Institute on Drug Abuse (NIDA) International Forum. June 2013.
- Rosenblum A, Fong C, Cleland C. Non-opioid substance use among opioid-dependent patients enrolling in opioid treatment programs: A latent class analysis. CPDD Annual Meeting. June 2013.
- Lowitz KA, Le Lait MC, Severtson SG, Dart RC. Evaluation of trends in abuse of stimulants in High School and College Age Persons Using RADARS® System Data. CPDD Annual Meeting. June 2013.
- Severtson SG, Le Lait MC, Bucher Bartelson B, Dart RC. Age trends in abuse calls to poison centers involving prescription opioids. CPDD Annual Meeting. June 2013.

New RADARS System Team Member – Annelies Hall, DVM, MBA

We are pleased to announce the appointment of our new Business Strategies Manager for the RADARS System – Annelies Olaerts Hall. Annelies is a veterinarian by training, but has worked in the health industry for the majority of her career with experience at multinational corporations like Pfizer and Nestle. After working in Brazil and the United Kingdom for the last 8 years, she recently relocated back to the US. Annelies brings vast experience in business development, strategic partnerships and development, international business and marketing. She is a welcome addition to the RADARS System team.

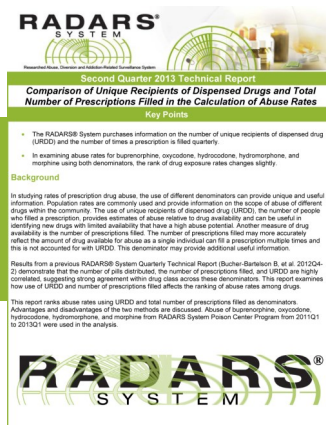


Some words from Annelies: *"I am very pleased to be joining this talented team and am eager to work with our existing subscribers to ensure we are meeting their needs and continue a long lasting relationship. I am also very enthusiastic to explore new partnerships and our growing international business."*

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RADARS System Quarterly Technical Report

RADARS System Technical Report #2013Q1-1

Comparison of Unique Recipients of Dispensed Drugs and Total Number of Prescription Filled in the Calculation of Abuse Rates

Please copy the web address into your web browser to view the pdf:
http://www.radars.org/Portals/1/2013Q1_QTR_urdd_vs_script_1q13_BBB.pdf

Conferences Attended

- Colorado In-State Policy Workshop, National Governors Association Policy Academy: Reducing Prescription Drug Abuse. Denver, CO. April 25, 2013.
- American Society of Addiction Medicine (ASAM) Annual Medical-Scientific Conference. Chicago, IL. April 25-28, 2013.
- Global Addiction & European Opiate Addiction Treatment Association (EUROPAD) Joint Conference. Pisa, Italy. May 7-10, 2013
- American Pain Society (APS) Annual Meeting. New Orleans, LA. May 8-10, 2013.
- Society for Prevention Research (SPR) Annual Meeting. San Francisco, CA. May 28-31, 2013.
- International Congress of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT). Copenhagen, Denmark. May 28-31, 2013.
- International Conference on Opioids (ICOO) Annual Conference. Boston, MA. June 9-11, 2013.
- National Institute on Drug Abuse (NIDA) International Forum. San Diego, CA. June 14-17, 2013.
- College on Problems of Drug Dependence (CPDD) Annual Meeting. San Diego, CA.

Did You Know?

On May 21st, a professor from the University of Kentucky was awarded a \$3 million dollar grant from the National Institutes of Health to test and market a naloxone nasal spray to counteract opioid overdoses.

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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 in the United States.

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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Questions or comments?

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