

SUMMARY

RESEARCHED ABUSE, DIVERSION, AND ADDICTION-RELATED SURVEILLANCE (RADARS®) SYSTEM FIRST ANNUAL SCIENTIFIC MEETING:

NEW DEVELOPMENTS IN PRESCRIPTION DRUG ABUSE RESEARCH

The RADARS System First Annual Scientific Meeting: *New Developments in Prescription Drug Abuse Research* was held April 12, 2007, at the Hyatt Regency, Bethesda, Maryland. Registrants (n=70) included researchers and speakers, pharmaceutical representatives, federal research or regulatory agencies, and policymakers.

The meeting was organized in keeping with the RADARS System mission: to provide timely and geographically-specific data to the pharmaceutical industry, regulatory agencies, policymakers and medical/public health officials to aid in understanding trends in abuse, misuse, and diversion of prescription drugs in the United States. Current RADARS System drug classes include buprenorphine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone and tramadol.

Richard C. Dart, M.D., Ph.D., Director of the Rocky Mountain Poison and Drug Center (RMPDC) at Denver Health and Hospital Authority in Denver, Colorado, and Executive Director of the RADARS System, provided a warm welcome and meeting overview. The RADARS System, which was acquired from Purdue Pharma L.P. by RMPDC January 1, 2006, completed its 5th year of data collection in December 2006.

The focus of the annual meeting was the release of 2006 Annual Report and to stimulate discussion of issues raised by RADARS System data. Each presentation was followed with a question and answer session to promote exchange of ideas between attendees. Panel discussions focused on risk management plans, intervention once a signal site is identified, and therapeutic use versus addiction. A summary of each presentation and discussion is provided below. Posters from 2006 RADARS data were available for review in the meeting room, and participants were provided with the five most recent issues of *RADARS System News* as well as “Quantifying morbidity associated with the abuse and misuse of opioid analgesics: A comparison of two approaches” recently published in *Clinical Toxicology*. A complete list of RADARS System related publications is provided in the Appendix.

Report of RADARS System 2006 Data

RADARS System data offer multiple perspectives through the use of four unique signal detection systems that collect and provide data rapidly, with geographical specificity (three digit zip code level), address the rural nature of prescription opioid abuse, and include coverage/data of non-abuser victims.

Goals of the RADARS System are as follows:

- Identifying sentinel events involving the misuse, abuse and diversion of prescription drugs nationwide
- Measure rates of misuse, abuse and diversion of prescription drugs

- Provide experienced and expert analysis and interpretation of the data

Nationally, RADARS System 2006 data demonstrate increasing trends in rates per 100,000 persons for the Key Informant Network and Poison Center Systems and a slight decreasing trend in rates per 100,000 persons for the Opioid Treatment Center System. The Drug Diversion System rates per 100,000 persons appear relatively stable over time. Trends in rates per 1,000 persons filling a prescription for the Key Informant Network System appear to be increasing while those from the Drug Diversion and Opioid Treatment Center Systems appear to be decreasing. Using population rate per 100,000 persons, hydrocodone and oxycodone are consistently the most abused, misused and diverted. Per 1,000 persons filling a prescription, a proxy for drug availability, buprenorphine, methadone, and hydromorphone are the current drugs of choice. Geographic areas with increased activity identified by the RADARS System include Appalachia, New England, and Florida.

In addition to detecting signals, RADARS System research can be used to interventions as in the case of Kentucky's Operation UNITE (Unlawful Narcotics Investigations, Treatment and Education).

Recent RADARS System research also indicates poison center call rate per 100,000 persons is higher in rural than urban areas while heroin rates tend to be higher in urban than rural areas.

While no single signal detection system covers the entire United States, 92% of the country is covered by at least one system. In 2006, 93% of these covered zips reported at least one case of prescription drug abuse, misuse or diversion. After five years, the RADARS System is maturing well and two new focused signal systems are close to coming online.

Product specific data are provided only to RADARS System clients for their use in satisfying regulatory requirements and providing interventions to address the challenge of prescription opioid abuse.

Key findings from the annual report:

- No community is immune to prescription drug abuse.
- Prescription drug abuse is widespread, affecting nearly all areas of the United States.
- Levels of abuse are high and still increasing in some areas, though may be flattening out in other areas.
- No one drug can be blamed. RADARS System data indicate that abusers typically take advantage of multiple opioids.

RADARS System Signal Detection Systems

Drug Diversion System

James A. Inciardi, Ph.D.

*Center for Drug and Alcohol Studies, University of Delaware Research Center
Coral Gables, Florida*

The Drug Diversion System (DD), comprised of 300 reporting investigators (primarily from police departments and drug task forces), has been reporting nationwide data to the RADARS System on drug seizures since 2002.

Dr. Inciardi described the “Black box of drug diversion”: how cases are actually occurring – what are the sources of acquiring opioid-based prescription drugs? The answer to this question depends upon whom you ask. The primary sources reported by DD are doctor shopping and patient theft or forgery; other data collection systems report friends or family, and dealers as the primary source. There is a need to research the secondary source – where friends, dealers, etc. are getting the drugs they supply to others. It is suggested that this can be accomplished with studies of the following subgroups: pain patients, dealers and brokers, traders, friends or family, and prescription abusers on the street and in treatment (both public and private pay programs).

Key Informant Network System

Theodore J. Cicero, Ph.D.

Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri

The Key Informant Network System (KI), comprised of 345 informants (primarily clinicians, epidemiologists, and treatment counselors) across the nation, has been reporting data to the RADARS System on abuse and misuse since 2002.

An internal study of validity was done to diagnose the accuracy of reporting by key informants. The study recruited key informants and patients to complete questionnaires; results were then compared between the groups. Outcomes found KI diagnosis of abuse to be very accurate. Appropriate interpretation of KI data includes that the reported three-digit zip is that of the key informant not of the patient. Discussion brought to light the problem of where intervention should then take place – at the locale of the key informant or of the patient?

Poison Center System

Richard C. Dart, M.D., Ph.D.

Rocky Mountain Poison & Drug Center, Denver Health and Hospital Authority, Denver, Colorado

The Poison Center System (PC), currently comprised of 43 of 60 U.S. poison centers, has been reporting data to the RADARS System on abuse and misuse since 2003. Data collection is product specific; standardized data collection and established quality control measures are used.

Pediatric exposures are captured by PC. Analysis of exposures in children (<6 years old) lead to the following results:

- 9240 exposures in young children were reported in a 3.5-year period from January 2003 to July 2006.
- Hydrocodone and oxycodone exposures predominate per 100,000 persons presumably due to their wide availability.
- Per 1,000 persons filling a prescription, buprenorphine is the most likely to end up in hands of a child.
- Buprenorphine is significantly more likely to be associated with a medical effect of any kind – whether mild (like drowsiness) or major (like hospitalization),

- Methadone is significantly more likely to be associated with death or major effect.
- Deaths were associated with exposures to hydrocodone, methadone, or oxycodone.

In some cases, a single opioid unit can kill a small child. New approaches are needed to prevent any exposure in children. Case notes suggest exposures can result from neglect and attempts to sedate children. Suggestions were made to compare this data with that of other drugs (prescription and illegal).

Opioid Treatment Centers System

Mark Parrino, M.P.A.

American Association for the Treatment of Opioid Dependence, Founder and President

The Opioid Treatment Center System is comprised of 76 treatment programs (predominately in rural areas) from 34 states and has been reporting data to the RADARS System since 2005. Data is collected via anonymous questionnaires from patients entering treatment.

Among the population of those entering treatment programs an urban-rural discrepancy is evident. Trends show that the proportion of patients from rural areas using prescription opioids is higher than the proportion using heroin in the 30 days prior to admission. In urban areas, the proportion of patients using heroin is higher than that of prescription opioids. People tend to use whatever drugs are easily available – no one drug is the problem; it is necessary to look at the broad picture and devise standards for risk management.

Questions arose about a patient’s preference between buprenorphine and methadone. Buprenorphine is available at approximately 35% of program sites. Although it is a schedule III drug, federal government mandates it be treated as schedule II within treatment centers. Currently there is no evidence of patient preference or difference in treatment outcome between the two drugs.

Panel Discussion: Risk Management Programs

Moderator: Richard C. Dart, M.D., Ph.D.

Rocky Mountain Poison & Drug Center, Denver Health and Hospital Authority, Denver, Colorado

Panel Members: Sidney H. Schnoll, M.D., Ph.D.

Vice President, Pharmaceutical Risk Management, Pinney & Associates

Nathaniel Katz, M.D., M.S.

Analgesic Research

Annette Stemhagen, Dr.P.H, FISPE

Vice President, Epidemiology & Risk Management, United BioSource Corporation

Edgar H. Adams, Sc.D.

Executive Director, Epidemiology, Covance, Inc.

The goal of the panel was to highlight current and emerging issues, the future of risk management plans, and how legislation affects these plans.

Risk management as defined by the FDA is an iterative process of assessing a product’s benefit-risk balance, developing and implementing tools to minimize its risks while preserving benefits,

evaluating tool effectiveness and reassessing the benefit-risk balance, and making adjustments, as appropriate, to the risk minimization tools to further improve the benefit-risk balance.

Evaluating the benefits and risks associated with pharmaceutical products has become an increasingly important issue. On September 22, 2006, the Institute of Medicine (IOM), a charter of the National Academy of Sciences, per request from the FDA, released its findings in *The Future of Drug Safety: Promoting and Protecting the Health of the Public*.

The IOM report found that contrary to the public health mission of the FDA and the pharmaceutical industry's responsibility to the users of its products, accountability and transparency is not consistently demonstrated to the public by communicating safety concerns in a timely and effective fashion. Recommendations from the IOM report include that risk management programs should become a requirement of drug approval by the FDA and that the FDA needs to be more authoritative in its leadership role, provide consistent direction, and enforce compliance.

Risk management is an ongoing process of assessment, confrontation, intervention, communication, and evaluation. Prescription opioid abuse is a public health problem that transcends any individual drug. Risk factors are common among all drugs.

Risk management for controlled substances requires access to new data sources. New approaches need to be developed to assess data and new types of interventions may need to be developed.

Discussion focused on the lack of, and need for, standards, specifically:

- What is an acceptable risk-benefit ratio for drug abuse?
- Should Risk Minimization Action Plans and Risk Management be made broader, class specific?
- The need to identify active government agencies and identify/create a centralized entity.
- The need for a clear articulation of the accountable/responsible agency at a national level.
- Interaction is needed between the pharmaceutical industry, whose focus is product specific, and of public health agencies, which focus on broader levels of prevention, treatment, and education.

Online Pharmacies: Opioid Purchasing, Dependence, and Treatment of Withdrawal

Edward Boyer, M.D., Ph.D.

Children's Hospital, Boston Massachusetts

Online sources of opioids provide an easy, inexpensive way to obtain prescription opioids – often times without a prescription. Both domestic and international online pharmacies, online consultation services, and email sources provide links to obtaining drugs of interest. Patients use online sources as they typically can get what they want (dose and quantity) without hassle of talking with and traveling to see a physician all for an affordable price.

A survey of online purchasers revealed that many members have enormous opioid requirements; however, they do not consider themselves addicts. Addicts, in their minds, cannot function

because they use drugs. In contrast, the surveyed online purchasers believe they are able to work, take care of children, and be active because they liberally use opioids.

Treatment of withdrawal is done through opioid “holidays” (decreasing or abruptly stopping medication) or more commonly through replacement therapy. Buprenorphine or kratom is most commonly utilized in replacement therapy as methadone carries a stigma of being a drug for “junkies”. Research is being conducted on identifying and understanding the active ingredient(s) of kratom.

Questions arose as to why the RADARS System does not identify the Internet as a strong source of prescription drugs. Studies indicate that source depends on the population surveyed; while friends/family and dealers may be the primary source of prescription drugs, friends/family and dealers may be receiving their supply via the Internet. Also of interest was whether drugs provided via the Internet are really what they claim to be, particularly those which are schedule II. From what information is available, the delivered drugs are usually, but not always exactly what they claim to be and schedule II drugs are difficult to get online, particularly through domestic sites.

Sources of Diverted Prescription Opioid

Nathaniel Katz, M.D., M.S.

Analgesic Research

Source is dependent upon the questioned population and questions asked. Frequent users tend to go through different sources than one time or new users. There are different ways to assess source - percent of people who get drugs from each source (friends/family, theft, dealer, Internet etc.) or percent of drugs diverted by each source (manufacturer, distributor, pharmacy, patient).

Analysis of data from the opioid treatment centers system indicates that older patients are more likely to obtain their drugs from doctor prescription or the Internet in comparison to the younger population who are more likely to use dealers, friends or family, and theft as their primary sources.

To fill in the gaps of the primary and secondary sources of diverted prescription opioids, and thus identify the problem to solve, funding and collaboration of data is necessary.

Discussion brought up previously unmentioned sources of diversion such as destruction facilities and the immeasurable potential of misuse and abuse that is inside household medicine cabinets. Dr. Schnoll recommended that next time you visit someone to take a look inside his or her medicine cabinet for a snapshot of this problem.

Panel: Interventions: After the Signal Site is Identified

Moderator: Sidney H. Schnoll, MD, Ph.D.

Vice President, Pharmaceutical Risk Management, Pinney & Associates

Panel members: James A. Inciardi, Ph.D.

*Center for Drug and Alcohol Studies, University of Delaware Research Center
Coral Gables, Florida*

Meredith Smith, Ph.D., M.P.A.

Director, Risk Management & Health Policy, Purdue Pharma L.P., Stamford, Connecticut

After a signal site is identified, an in-depth assessment is needed to determine if the signal is an indicator of a significant and persistent problem. Determination of whether the problem can even be addressed through an intervention is then made followed by development of interventions targeting physicians, patients, or the community as a whole.

Intervention options include: media declarations, legislation, scheduling, treatment such as methadone maintenance, drug-free outpatient programs, residential therapeutic communities, 12-step and other self-help groups, risk reduction protocols and prescription drug interventions. Treatment is the most widely implemented and most effective intervention.

Increasingly, data show that individual substance abuse behaviors are expressed within the context of broader social and physical conditions of the neighborhood or local community. A quick and economical way to understand community dynamics and longevity of the problem and what might be done to disrupt the cycle of prescription drug abuse is needed. With this in mind, ecological factors of communities including economics, social values/norms, quality of life, and law enforcement, need to be considered and incorporated into intervention strategies.

Incorporating ecological factors can potentially help in many ways:

- Generate insight into community dynamics,
- Help evaluate “signals” of opioid analgesic abuse,
- Suggest where and how to intervene,
- Prevent negative unintended intervention results.

To complete the cycle of risk management, evaluation of interventions is necessary. Methods of measurement of intervention effectiveness need to be devised and standardized.

Field researchers from Purdue Pharma L.P. were able to reply to the question of how communities respond to interventions. Response varies by community, but it usually takes time to develop trust from the people and for them to not feel threatened. Response can depend upon the level of desperation and funding available and/or needed. In general, communities are appreciative of a raised awareness of resources if nothing else.

The question of what effort level is required to invest in a signal site was discussed as well. Unfortunately rapid assessment is not possible everywhere. Effort level is determined individually for each community and may be influenced by willingness of collaboration from local entities, community reaction, and community involvement.

Panel: Therapeutic Use and Addiction

Moderator: Kenneth Hoffman

Substance Abuse and Mental Health Services Administration

Panel Members: George E. Woody, M.D.

University of Pennsylvania, Philadelphia, PA

Steven D. Passik, Ph.D.

Associate Attending Psychologist, Memorial Sloan Kettering Cancer Center, New York, NY

Risk management should be carried out without hurting the majority of patients who use prescription opioids appropriately to manage pain. Prescribers should be educated so that prescribing and management practices can be tailored to individual patients. Prescribing and monitoring practices should be adjusted as a function of risk factors (family history of substance use disorder, high levels of psychiatric symptoms, tendency to self-medicate psychiatric symptoms, antisocial behavior, etc.) and adjusted as necessary.

There is a positive correlation between aberrant behavior and addiction (out of control, compulsive drug use). Surveillance systems and medical practitioners can detect patients whose therapeutic use has led to addiction.

Universal precautions, such as urine toxicology and risk factor assessment are needed for everyone; however, a major problem is insurance coverage. Patients with dual diagnosis who need treatment for pain and addiction must be willing and open in working with their physician. There are no known studies documenting the future of patients banished from pain management.

Final Discussions

Recurring themes throughout the day are summarized below:

- Drug abuse is a multi-faceted problem that cannot be solved by a single person or entity.
- Signal Definition: need a solid definition of what a signal is and how to determine the significance (indicator of new or persistent problem) and intensity of the signal.
- Risk Management Programs: standardization of risk management programs is necessary and perhaps needs to be done both at a drug class level and at a product specific level (accountable and responsible parties need to be identified).
- Intervention: the role of the pharmaceutical industry and public health agencies and their interaction needs to be defined (accountable and responsible parties need to be identified).
- Fresh Perspectives in Looking at and Collecting Data: consider differences in pain populations, the characteristics of populations being prescribed different opioids, and investigate diversion sources by surveying new populations.

Appendix: Publications (current as of 04/04/2007)

Manuscripts

Bailey JE, Barton PL, Lezotte D, Lowenstien SR, Dart RC. The Effect of FDA Approval of a Generic Competitor to OxyContin® (Oxycodone HCl Controlled-Release) Tablets on the Abuse of Oxycodone. *Drug and Alcohol Dependence*. 2006; 84:182-187.

Cicero TJ, Dart RC, Inciardi JA, Woody GE, Schnoll S, Munoz A. The Development of a Comprehensive Risk-Management Program for Prescription Opioid Analgesics: Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS). *Pain Medicine*. 2007; 8:157-170.

Cicero TJ, Inciardi JA, Munoz A. Trends of Abuse of OxyContin® and Other Opioid Analgesics in the United States: 2002-2004. The Journal of Pain. 2005; 6:662-672.

Hughes AA, Bogdan GM, Dart RC. Active Surveillance of Abused and Misused Prescription Opioids Using Poison Center Data: A Pilot Study and Descriptive Comparison. Clinical Toxicology. 2007; 45:144-151.

Inciardi JA, Goode JL. OxyContin® and Prescription Drug Abuse. *Consumers' Research*. 2003; 7:17-21.

Inciardi JA, Surratt HL, Kurtz SP, Burke JJ. The Diversion of Prescription Drugs by Health Care Workers in Cincinnati, Ohio. *Substance Use and Misuse*. 2006; 41:255-264.

Inciardi JA, Cicero TJ, Munoz A, Adams EH, Geller A, Senay EC, Woody GE. The Diversion of Ultram®, Ultracet®, and Generic Tramadol HCl. *Journal of Addictive Diseases*. 2006; 25:53-58.

Smith MY, Dart RC, Hughes AA, Geller A, Senay EC, Woody GE, Colucci S. Clinician Validation of Poison Control Center Intentional Exposure Cases Involving Prescription Opioids. *American Journal of Drug and Alcohol Abuse*. 2006; 32:465-478.

Smith MY, Schneider MF, Wentz A, Hughes A, Haddox JD, Dart RC. Quantifying Morbidity Associated with the Abuse and Misuse of Opioid Analgesics: A Comparison of Two Approaches. *Clinical Toxicology*. 2007; 45:23-30.

Smith MY, Woody G. Nonmedical Use and Abuse of Scheduled Medication Prescribed for Pain, Pain-related Symptoms, and Psychiatric Disorders: Patterns, User Characteristic, and Management Options. *Current Psychiatry Reports*. 2005; 7:337-343.

Wright IV C, Kramer ED, Zalman M-A, Smith MY, Haddox JD. Risk Identification, Risk Assessment, and Risk Management of Abusable Drug Formulations. *Drug Alcohol Dependence*. 2006; 83:S68-76.

Abstracts

Bailey JE. Demographic Difference in the Misuse and Abuse of Oxycodone Formulations: Poison Center (PC) Surveillance. Drug Information Association (DIA) Annual Meeting. Philadelphia, PA. June, 2006.

Dart RC, Hughes AA. Reporting for the RADARS® System Poison Control Centers. Public Health Disparities in Rural Areas: High Rates of Prescription Opioid Abuse. The American Public Health Association Conference. Philadelphia, PA. December, 2005.

Dart RC, Hughes AA. Adolescent Prescription Opioid Abuse and Misuse: Surveillance by Poison Centers. The College of Problems of Drug Dependence Conference. Scottsdale, AZ. June, 2006.

Graham A, Smith MY, Haddox JD, Wright C. Reducing the Potential for Diversion of Prescription Opioids: Tested Interventions. The College on Problems of Drug Dependence Conference. Orlando, FL. June, 2005.

Haddox JD, Schnoll SH. The Standards for Risk Management Plans for High Abuse Potential Medications. The College on Problems of Drug Dependence Conference. Washington, DC. April, 2005.

Abstracts (continued)

Haddox JD, Smith M, Wright C. Characteristics of Nonmedical Users of Dilaudid. The College on Problems of Drug Dependence Conference. Orlando, FL. June, 2005.

Haddox JD, Smith MY, Colucci S, Rosenblum A, Fong C, Maxwell C, Parrino M. Pain as a Reason for Seeking Admission to Methadone Treatment. The College of Problems of Drug Dependence Conference. Scottsdale, AZ. June, 2006.

Hughes AA, Bogdan GM, Bond R, Dart RC. Increase in OxyContin[®] Abuse or Media Hype? *Journal of Toxicology: Clinical Toxicology*. 2002;40:656-657.

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Smith MY, Irish W, Wang J, Haddox JD, Dart RC. Relative Rate of Opioid Analgesic Abuse in Communities in the U.S. The College of Problems of Drug Dependence Conference. Scottsdale, AZ. June, 2006.

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