



### In This Issue

The RADARS<sup>®</sup> System Interviews Dr. Nathaniel Katz: Prospective on Opioid Abuse and Abuse Deterrent Formulations

Identifying Seasonality Trends in RADARS System Poison Center Pediatric Stimulant Exposures

RADARS System 5th Annual Scientific Meeting

Recent RADARS System Publications and Presentations

Upcoming Meetings of Interest

Contact Information

Mission Statement

RMPDC and DHHA

## The RADARS<sup>®</sup> System Interviews Dr. Nathaniel Katz: Prospective on Opioid Abuse and Abuse Deterrent Formulations

Nathaniel Katz, MD, MS, is a neurologist and Adjunct Assistant Professor of Anesthesia at Tufts University School Medicine who is internationally recognized as an expert in pain management and analgesic clinical trials. He has conducted numerous clinical investigations of treatments for pain, involving pharmaceuticals, non-pharmaceutical analgesics and devices, with a particular focus on opioids and risk management.



**RS:** How does your current work and professional affiliations impact abuse deterrent formulation of prescription opioids?

**Dr. Katz:** I have worked with most manufacturers of abuse deterrent opioids helping them figure out what their goals actually are, how they can be addressed with formulations, and how the effects of these formulations can be evaluated. In addition I have had an academic interest in this area for about a decade. Primarily in the context of the Tufts Healthcare Institute's Program on Opioid Risk Management, which I have the privilege of serving as Director, we have managed to produce a number of useful publications, which I believe have helped guide thinking in this area.

**RS:** Can you describe the limitations to premarketing studies in relation to opioid abuse?

**Dr. Katz:** Actually, a lot more can be done pre-marketing than has been acknowledged. Types of studies that can be performed pre-marketing include:

- *In vitro* extractability/tamperability
- Preclinical pharmacology (when appropriate)
- Human abuse liability / pharmacology
- "Kitchen chemistry" studies
- Evaluation of abuse-related endpoints in clinical trials performed for pain (which are rarely collected and evaluated methodically)
- Randomized controlled clinical trials (or observational studies) conducted in pain patients with primary abuse-related endpoints (I don't think this has been done, but there is nothing preventing such studies).

The major type of studies that cannot be done pre-marketing are epidemiologic studies of abuse (which include most surveillance systems), and street pricing and other "ethnographic" studies. This is a real limitation, since abuse-related behaviors are likely to evolve when modulated in "real-world" settings. However, much more could be done pre-marketing than is currently being done.

**RS:** What are the challenges in measuring the consequences of non-medical opioid use?

**Dr. Katz:** The consequences of non-medical opioid use include:

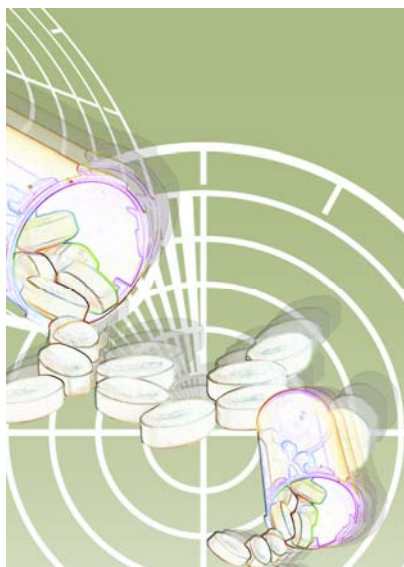
- Fatal overdoses
- Non-fatal overdoses
- Addiction
- Drug-related diseases, such as HIV disease and hepatitis
- Pediatric exposures and overdoses
- Criminal activity, such as doctor shopping, patients selling medications, etc.

### Did You Know?

On February 25, 2011, FDA released a draft guidance for the distribution of medication guides in situations where a drug or biological product is administered by a health professional

Please type the following into web browser

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM244570.pdf>.



Once you look at this list of consequences the measurement challenges become more obvious. In order to measure any of these events, you need two things: (1) product specificity, and (2) accurate and comprehensive event ascertainment. There are only a few sources of data that meet both requirements.

**RS:** What do you see as the current limitations to existing data collection systems? What gaps in data can we feasibly fill?

**Dr. Katz:** There are a number of opportunities to fill these data gaps. One major opportunity is to modify the National Survey of Drug Use and Health so that it provides more refined information on prescription drug abuse, which is essential to inform public health policy.

**RS:** What data are needed to evaluate the shifts in abuse patterns that may be associated with new abuse deterrent formulations?

**Dr. Katz:** In my experience there is a great deal of confusion on this issue. There are two types of data one can look at: product specific abuse data and general prescription opioid abuse data. Several databases are available in which abuse-related events can be linked to specific products, such as the RADARS-PC database or the Inflexxion ASI-MV-Connect database. These data can be used to examine hypotheses related to specific products, which take a form like: *product A is abused less than product B*. The second more general type of data can be used to address non-product-specific hypotheses, which take a form like: *when product A was introduced into an area, the rate of prescription opioid overdoses increased*. The major confusion is to mix these two, for example to expect that introducing a small penetration product into an area will result in general changes in prescription opioid abuse-related indices.

An additional major challenge is whether epidemiologic studies can ever overcome confounding by indication. Patients perceived to be at risk for abuse are more likely to be prescribed abuse-deterrent opioids than patients not perceived to be at risk for abuse. Most diverted prescription opioids appear to come from patients prescribed the medication. Therefore, abuse-deterrent opioids will naturally have a *higher* incidence of abuse than standard opioids, just based on the population to whom they will be prescribed. This will contaminate product-specific abuse rates seen in epidemiologic studies. The only cure for this may be conducting large randomized, controlled trials with abuse as the primary endpoint.

Dr. Katz serves as President of Anesthetic, Critical Care, and Addiction Products Division of Analgesic Research, served as Clinical Advisor of Ionix Pharmaceuticals Limited, served as an Associate Editor of the Clinical Journal of Pain, and Associate Editor (Pain) for the Encyclopedia of Neurological Sciences, and served as a Staff Neurologist in the Pain Management Center of Brigham & Women's Hospital. Dr. Katz founded the Pain & Symptom Management Program at Dana Farber Cancer Institute, and the Pain Trials Center (a clinical analgesics research unit) at Brigham & Women's Hospital. He is a member of the Advisory Board at TheraQuest Biosciences, LLC, and a member of Medical and Scientific Advisory Board of Neurogesx, Inc. Dr. Katz has served as Chairman the Advisory Committee of Anesthesia, Critical Care and Addiction Products Division, United States Food and Drug Administration, served as Chair of the National Initiative on Pain Control, and served as Chair of Inflexxion's [www.painedu.org](http://www.painedu.org). He completed his neurology residency at Tufts-New England Medical Center and a pain management fellowship in the Department of Anesthesia at Brigham & Women's Hospital. Dr. Katz received his medical degree from the Medical College of Pennsylvania and his M.S. in Biostatistics at Columbia University.



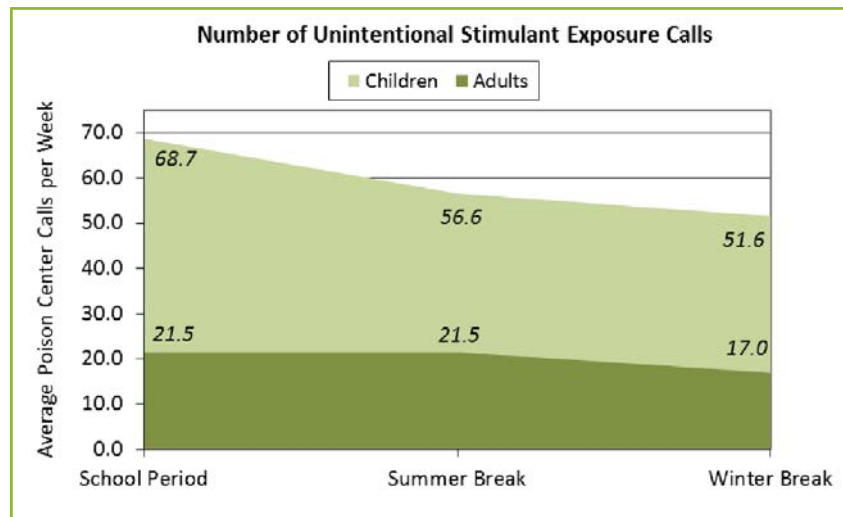
## Identifying Seasonality Trends in RADARS System Poison Center Pediatric Stimulant Exposures

Diagnoses of attention deficit disorder (ADD) and attention deficit hyperactivity disorder (ADHD) in children have been steadily increasing in recent years. Consequently, stimulant prescriptions used to treat ADD/ADHD in children have also increased. The amount of stimulant medication prescribed to children increased substantially from 1990 – 1995, with methylphenidate increasing 2.5 times. Prescribing practices and the use of stimulant medications may be season-dependent due to identification of attention-related issues resulting from school teachers and administrators.

Because the use of stimulants by children for ADD/ADHD likely fluctuates dependent on when school is in session, RADARS System researchers tested to see if unintentional exposures to stimulant medications parallel school sessions. An analysis of RADARS System Poison Center (PC) data was conducted to determine if the frequency of unintentional stimulant exposures was related to higher call volume in children during traditional school sessions than when school is not in session. Exposure data extracted from spontaneous calls to PCs from the public about stimulant exposures was examined to determine seasonality. PC calls are reviewed weekly by the RADARS System, with extracted data collected in a central database.

Seasonal variations in unintentional stimulant exposures were analyzed by aggregating historical weekly unintentional stimulant exposure call count data (July 2007 to October 2010). PC call counts were examined for children 6-12 years and for adults over 30 years. Calls were assigned to time periods that reflect common school sessions, based on when the call to the PC occurred. Weekly frequencies were categorized as Fall, Winter, Spring, or Summer timeframes based on typical school terms, in accordance with the case start date. Fall and Spring categories were further grouped together as the traditional School Period. Adults were included as a comparison group to examine overall seasonal differences against potential school related differences.

Analysis was conducted with Poisson regression with adjustments for population and a measure of retail availability (Unique Recipients of Dispensed Drug). Over the time period assessed, the number of calls per week involving children decreased by 17 % (from 69 to 57) between the regular school session and the summer session. This decrease was not seen in adults.



More specifically, PCs answered an average of 68.7 calls per week (Wald 95% CL 66.9, 70.6) about unintentional pediatric stimulant exposures during times when children are commonly in school; calls averaged 56.6 (52.3, 61.3) per week during the summer time when children are not commonly in school, and 51.6 (46.1, 57.6) per week during the winter term when children are commonly on winter break. PCs answered an average of 21.5 calls per week (95% CL 19.8, 23.3), 21.5 (17.1, 27.1), and 17.0 (12.2, 23.7) involving unintentional adult stimulant exposures for the School Period, Summer and Winter periods respectively. An interaction term suggests a similar reduction in unintentional stimulant exposure calls was not observed among adults during the Summer term ( $p < .001$ ).

An overall pattern of fewer unintentional pediatric stimulant exposure cases Winter and Summer breaks was identified. A similar decline was observed among adults, but only in the winter. These findings suggest seasonal changes in pediatric unintentional stimulant exposure calls are related to the school schedule and that this pattern is different from adults.

### RADARS System 5<sup>th</sup> Annual Scientific Meeting

The RADARS System is holding its Fifth Annual Scientific Meeting on April 28, 2011 titled, *Abuse Deterrent Formulations (ADFs) of Prescription Drugs*. The meeting will be held at the Hyatt Regency in Bethesda, MD. We are excited about the scheduled topics of discussion. Invited speakers, including Dr. Nathaniel Katz and Dr. Thomas McLellan, will be covering topics such as:

- A Report of 2010 RADARS System Data
- How RADARS System Can Support Abuse Deterrent Formulations
- Street Price Data Analysis
- An Industry Perspective of ADFs
- Abuse Deterrent Formulations - Policy and Regulatory Issue

### Recent RADARS System Publications and Presentations

- Dasgupta N, Bailey JE, Cicero T, Inciardi JA, Parrino M, Rosenblum A, Dart RC. Post-marketing surveillance of methadone and buprenorphine in the United States. *Pain Medicine*. 2010;11(7):1078-1091.

### Upcoming Meetings of Interest

- American Society of Addiction Medicine, April 14-17, 2011. Washington, District of Columbia.
- Association of Clinical Research Professionals, April 29-May-3, 2011. Seattle, Washington.
- American Association of Occupational Health Nurses, April 29-May 5, 2011. Atlanta, Georgia.
- American Psychiatric Association, May 14-18, 2011. Honolulu, Hawaii.
- European Association of Poison Centres and Clinical Toxicologists May 24-27, 2011. Dubrovnik, Croatia.
- American College Health Association, May 31-June 4, 2011. Phoenix, Arizona.
- International Society for Pharmaceutical Engineering, June 6-9 2011. Washington, District of Columbia.
- National Association of State Alcohol and Drug Abuse Directors, June 7-10, 2011. Indianapolis, Indiana.
- Council of State and Territorial Epidemiologists, June 12-16, 2011. Pittsburg, Pennsylvania.
- American Medical Association, June 16-18, 2011. Chicago, Illinois.
- American Pain Society, May 19-21, 2011. Austin, Texas.
- College on Problems of Drug Dependence, June 18-23, 2011. Hollywood, Florida.
- Drug Information Association, June 19-23, 2011. Chicago, Illinois.
- American Public Health Association, June 23-25, 2011 Chicago, Illinois.
- American Society of Interventional Pain Physicians, June 24-29, 2011. Arlington, Virginia.

## Did You Know?

The number of oxycodone doses distributed in Florida jumped 25 percent in 2009 to 523 million, up 100 million from 2008. By comparison, the No. 2 state for the drug was Pennsylvania at 267 million pills; the national supply rose 11 percent that year.

## 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 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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