



RADARS[®] System Fifth Annual Scientific Meeting
Abuse Deterrent Formulations of Prescription Drugs
Thursday, April 28, 2011
Hyatt Regency (Bethesda, Maryland)

The RADARS System Fifth Annual Scientific Meeting was organized to address the assessment of the impact of abuse-deterrent prescription drug formulations, using various approaches for data-based decision making and a multiple-perspective approach.

Attendees (n=94) included researchers and speakers, pharmaceutical representatives, federal research/regulatory agency representatives and policymakers.

Richard C. Dart, MD, PhD, Director of the Rocky Mountain Poison & Drug Center (RMPDC) at Denver Health & Hospital Authority in Denver, Colorado, and Executive Director of the RADARS System, presided over the meeting. After a brief overview of RADARS System annual data from 2010, the meeting focused on strategies and methods of assessing the impact of abuse-deterrent prescription drug formulations. A summary of each of presentation is provided below.

Report of RADARS System 2010 Data

Richard C. Dart, MD, PhD

Executive Director

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

The RADARS System is comprised of six programs – Drug Diversion (DD), Poison Center (PC), Opioid Treatment (OT), Survey of Key Informants' Patients (SKIP), College Survey (CS) and Impaired Health Care Worker. Of 3-digit zip codes in the US, 99% of these are covered by at least one RADARS System program, with over 90% covered by two RADARS System programs. The RADARS System published 7 manuscripts in 2010, and presented 10 scientific presentations/posters.

When Rank Ordered by population, oxycodone rates are the highest-ranked opioid class in four of five RADARS System programs (hydrocodone is first in Poison Center); hydrocodone is ranked second in four of five programs. When Rank Ordered by URDD, methadone rates are the highest-ranked in all five RADARS System programs.

Overall opioids population rates for all RADARS System programs show increasing slopes, with overall opioid URDD rates for all RADARS System programs showing increasing slopes in DD, PC, OT and SKIP with the slope in CS more stable. The RADARS System all opioids US Signals map 2010 shows virtually all US 3-digit zip codes had an opioid signal in 2010. Stimulant population rates are generally trending upward across the RADARS System programs, while stimulant URDD rates are generally stable over time. In comparing immediate-release and extended-release opioids, immediate-release rates are higher in CS and DD and are more stable in the other RADARS System programs. PC opioid exposure medical outcomes for 2010 show immediate-release opioids tend to result in less-serious events, while extended-release opioids tend to have more serious effects.



Pain Management, Prescription Overdose, and Physician Responsibility

Tom McLellan, MD

Professor – Department of Psychiatry

Director, Penn Center for Substance Abuse Solutions

There is a common tendency to think about drug issues in silos of abuse or diversion. Since 1997, pain management societies have issued guidelines and recommended expanded use of opioids. By 2008, there was a 350% increase in pain management clinics, a 1000% increase in methadone and an 878% increase in oxycodone. A staggering increase in unintentional deaths has been noted over time, especially since 1996. An examination of opioid sales and opioid-related deaths shows similar trends over time. In 2006, geographic regions such as Appalachia and the western US showed higher overdose deaths, perhaps as a function of policies.

Overall increases in physician arrests, overdose deaths and overdose reporting were noted by 2008. This has yet to result in increasing attention. Pharmaceutical overdose death is the Number Two cause of accidental death in many states. An example is drugged driving (NHTSA Roadside Survey 2007): on Friday/Saturday nights, road check cheek-swabs (only valid within 3-4 hours of drug use) were administered to 6000 drivers, detecting illegal drugs in 11% (mostly marijuana) and medications in 5% (most commonly opioids). This is a public health/public safety concern.

In two studies of overdose, a question is: what is the source of overdose? And further, who bears the responsibility? Hall et al (2008) found a 550% increase in opioid overdose deaths (1999 – 2004) in West Virginia, resulting in an alarming death rate. Predictors were found to be middle age, low SES, mental health/substance abuse histories, prior history of overdose incident and the presence of benzodiazepine prescription; overdoses tended to occur within 5 days of original/refilled prescription. Only 36% of those who died had a prescription for an opioid.

Dunn et al (2009) found all patients had a primary care doctor, good records and minimal doctor shopping. Death rates were lower but found the same predictors as the Hall study. The majority of deaths occurred the night of the first prescription or refill. Many of these things, the healthcare system can address.

Physician response

The American Academy of Pain Medicine and the American Pain Society issued clinical guidelines for opioid therapies – these are sensible, feasible, and data-based recommendations. Screening, patient contracts (single prescriber, single pharmacy – effective for true patients), patient/family education, urine screening (although not usually done in practice), limited dosing (most serious among dentists – creates storage problems and next-day call-backs), use of PDMPs (good evidence that states using PDMPs have less problems).

Government response

The Department of Justice/Health and Human Services are testing PDMPs; the Department of Justice uses the Hal Rogers system, which is fundamentally different from PDMPs (only 10% of physicians use it). Few states share data



which is problematic because 30% of US populations live near state lines. This effect could be obviated with use of the Electronic Health Records System. Since 2009, more active collaboration within Federal departments (ONDCP, DOJ, HHS) has occurred. Recently the FDA proposed an extension of REMS which is not yet finalized but represents an effort to bring together the pharmaceutical industry and regulatory agencies. When a doctor renews his/her license, a test would be given but consider the feasibility of such testing. There is some debate over who will pay for and contribute to educational content. DEA has worked with FDA, CDC, and ONDCP to focus efforts on Pill Mills. Lists of 100 most prolific prescribers in US have been created (95 of the 100 are located in Broward Co. Florida).

Opioids are essential medications for pain treatment. We know that opioids work, the population is getting older, and many non-opioids have come off market recently. What is not clear is what proper doses are, how long people should take them, and for what kinds of pain. The right policies will not reduce access, scare doctors or improperly assign blame/responsibility. The right policies will however provide better training/education for physicians, increase responsibility of patients, and improve system responses (electronic health records will help).

Overdose is the first issue and the second issue is diversion/addiction. Healthcare reform will affect the treatment of substance use disorders, and such reform includes a primary benefit for treating substance use disorders. Beware of unintended consequences such as increased heroin abuse. All of this reinforces the importance of considering the full range of issues related to opioid use.

ADF Case Study – Street Price Analyses

Nabarun Dasgupta, MPH

Researcher - University of North Carolina – Chapel Hill

The RADARS System

The street price of opioids is a topic of broad social interest and is a good example of market dynamics. Law enforcement acknowledges the importance of having access to street price data, and there is interest from some regulatory agencies. Broader questions can be addressed with street price data, and FDA advisors have specifically requested street price data. These data can inform and have been cited in drug scheduling decisions (e.g. buprenorphine).

There are few published studies on drug prices – some studies on cocaine and heroin, but few with epidemiological data. Street price is not just a function of drug but also where a person is in the addiction pathway. At three basic phases price varies:

- Early – price not as important – females have less control over price paid (partners often help with procurement)
- Continuation/addiction – lower prices may help facilitate more frequent use
- Entering treatment – a commonly-cited reason for entering treatment is the habit became “too expensive”

Generally, people are willing to pay more when in throes of addiction.



The main question: will ADFs have lower street price? There are four general approaches in ADF technology: physical, agonist/antagonist, prodrug, and aversive agent. There has been recent debate over proper acronym for ADFs – perhaps should be tamper-deterrent or tamper-resistant – and which approach is best, and how to compare approaches.

The Street Price Questionnaire (SPQ) was initiated in 1st quarter 2010, and has a good US distribution of reporting Key Informants (within the RADARS System Drug Diversion program). Data for both stimulants and opioids are captured via Street Rx.com, which uses the idea of crowdsourcing for prescription drug street pricing. Major organizations use crowdsourcing (e.g. CNN); the National Drug Intelligence Center uses SENTRY for public reporting directly to NDIC. Street pricing on the internet is not a new concept.

The SPQ created a platform for entering information on street prices and for accessing data on street prices, using a Google Maps interface. Data are submitted by DEA, local/state law enforcement. Security measures are in place which prevent excessive identical submissions and fake drug names; a visual verification of drugs is requested at the time of data entry. Information on mental health drugs and cholesterol medications are collected as well. Those who submit data can rank the price paid. The study is currently in a soft launch phase, and has collected approximately 1500 submissions since 11/1/2010.

New OxyContin data suggest prices reported in the RADARS System Drug Diversion Program and Street Rx system are very similar, with a 20-30% decrease in street price of new OxyContin formulation when compared to the old formulation. Buprenorphine data also show similar results between the RADARS System Drug Diversion Program and Street Rx, with a 15-20% difference between Suboxone and Subutex. Vyvanse data also show differences between Vyvanse and amphetamine salts street prices. The nature of the deterrence approach (physical barrier, agonist/antagonist, and prodrug) determines the price difference between non-ADF and ADF formulations.

An Industry Perspective on ADF Assessment

David Brown, PhD, MPH, MA
World Wide Safety Strategy
Pfizer, Inc.

With regard to FDA requirements for ADF-related claims on drug labels, there are two hurdles to mount: demonstrating safety and efficacy at approval and conducting long-term epidemiological studies demonstrating a reduction in abuse-related outcomes. What is the best way to bridge the distance between these hurdles while meeting prescriber and patient needs, positively impacting public health and remaining business-competitive?

The underlying principles of an ADF include deterring abuse as a key goal, recognizing that it is not possible to eliminate all abuse (e.g. oral consumption). Researchers must understand mechanisms for abuse and the population of abusers. In the case of low population exposure products, it is difficult to determine “reduction” in abuse because of limited



patient exposures/market penetration. The depth of market penetration is important; low market penetration results in low power to conduct epidemiological studies.

A goal of the planned epidemiology program is to reduce abuse by tampering, leading to reduced overdose, addiction, and death; essentially, modifying behavior to improve outcomes. Questions an epidemiology program should ask are: what are the appropriate study endpoints? What is the best study design? Is there reliable baseline information against which to evaluate effect size? What is a meaningful effect size? What are the appropriate comparators?

Proposed studies and related evaluation criteria to determine the effectiveness of an ADF product include:

- Abusers in treatment; statistical significance
- College students; directionally supportive
- General population (calls to Poison Centers); directionally supportive
- Experiences opioid abusers; contextualize cross-sectional studies 1,2 and 3
- Not all studies will achieve statistical significance

An effective ADF may result in abuse populations too small for meaningful assessment. Confounding by indication or by prevention efforts should be controlled.

Paul Coplan, DSc, MBA
Executive Director, Risk Management & Epidemiology
Purdue Pharma, LP

Abuse of OxyContin often begins orally, with a progression of abuse to snorting and injection as the preferred administration routes. The reformulated OxyContin tablets are similar in shape and color to the original tablets and are more difficult to manipulate and to inject. Hypothesized benefits of the new formulation include bioequivalence, reduced breaking/crushing and reduced abuse via crushing, snorting and injecting.

Various post-marketing studies have been designed to assess the reformulation, with the principle of each being to look for a decrease in rates of adverse effects compared to other opioids. Reductions in tampering, demand, abuse in the community and clinical endpoints will also be evaluated.

Data preceding introduction of reformulated OxyContin shows the number of prescriptions for extended-release oxycodone have increased since 2000 but not nearly as much as immediate-release oxycodone. Routes of abuse vary by drug, and OxyContin routes of abuse over time are relatively stable. RADARS System Poison Center trends in oxycodone (immediate-release, OxyContin, and generic extended-release) show the majority of exposures are to immediate-release oxycodone. RADARS System Drug Diversion trends in oxycodone are stable for generic extended-release, but increase in immediate-release oxycodone. In general, the reformulated OxyContin is expected to shift administration routes away from those associated with more frequent and dependent abusers. Multiple studies are required to demonstrate effects of the reformulation.



Damon Smith, BSc, PhD, CPM
Senior VP of Research and Development
Labopharm, Inc.

Three questions for the medical and pharmaceutical industries:

- By focusing solely on the abuse population, are we ignoring the legitimate patient in terms of access, formulation, or price?
- Are regulatory hurdles a disincentive to industry to develop new formulations? How to achieve a return on investment? How to get new products to the consumer quickly?
- Will price be driven upward for legitimate patients? Acetaminophen as an example – the FDA may broaden those regulations to address overdose. How to manufacture good products to the patients while maintaining low prices?

Edgar Adams, ScD
Executive Director of Epidemiology
Covance

The generally-accepted knowledge about opioids is non-medical use/abuse of analgesics is increasing, with pain as the Number One symptom reported in doctors' offices. REMS and abuse/tamper resistant opioids may or may not be the answer, considering most patients take medications via the intended route and do not become addicts. Over time, various mechanisms have been implemented to deter abuse/tampering. In evaluating the public health benefit of ADFs, consider if addicts switch to different drugs or formulations; possible increases in morbidity due to attempts to circumvent the ADF; precipitation of withdrawal in naltrexone/naloxone release; and possible reluctance on the part of physicians to prescribe appropriately.

Panel Discussion: Industry Perspective on ADF Assessment

Moderator: Sid Schnoll
Panel: David Brown, PhD, MPH, MA
Damon Smith, BSc, PhD, CPM
Paul Coplan, DSc, MBA
Edgar Adams, ScD
Carl Roland, PharmD

Question: What are companies doing with marketing reps to cut down on prescriptions/overprescribing?

- Sales force for OxyContin distributed packets on REMS to physicians and pharmacists
- Using established system of risk management
- Website called oxycontinrems.com
- Online training program with confirmation form to track how many have completed this
- Population of "legitimate patients" – a continuum which has a focus on one particular part of the continuum – perhaps missing needs of larger population – perhaps access/service



- Who are we trying to serve – trying to serve all constituencies

Question: What is the sense of proportions of various groups (appropriate use patients, comorbid patients, abusers)?

- MDs are not well trained on scheduled medications, addiction seen as voluntary – most don't understand; primary care, 10-minute patient visit
- Price – drugs will not be included on state formulary lists if prices are high – significant dilemma to keep price as low as possible – how to get new/better products to patients who need them
- In-vitro studies – determine extractability/crushability after product has been introduced
 - These studies are predictive but no real correlation – likely no increase in cMax – speaking to broader patient population, no benefit to doing extractions or long-term grinding studies – crushing studies seem to correlate – there's value but unsure how to talk to a doctor about this
 - Development of ADF – in vitro extraction followed by in vivo pharmacokinetic studies followed by epi studies – monitoring of websites with discussion of methods for extraction
 - Reduction in liking for Subutex vs. Suboxone – translates to pricing difference between drugs
- Oral abuse data (SAMHSA) – multiple pills, crushing/chewing – can't address multi-pill abuse – developed technology to address unintended routes and chewing/crushing – multi-pill abuse resistance is possible – new delivery system – trying to address opioids mixed with benzodiazepines (using new technology)

Question: Is the new version of OxyContin being delivered to Canada or Europe?

- Komer study points to using a likeability study – HealthCanada is reviewing new OxyContin formulation – approval more closely linked to reimbursement considerations – Europe has not filed application for new OxyContin – opioid abuse not perceived to be a problem in Germany – Windsor, Ontario had a 95% increase in sales for OxyContin
- Subutex vs. Suboxone – naloxone via IV route – some patients get a fair amount, some get little absorption – are GI symptoms legitimate? Switch to monoformulation?

Question: The notion of industry developing new formulations – is there evidence that companies choose not to develop new formulations based on lack of incentives?

- Economic model has changed, effecting decisions on return-on-investment – formulations can be developed which speak to broadest populations
- Possibly thresholds for market penetration
- Single-entity products could be considered

Evaluation of ADFs Using RADARS[®] System Data

Richard C. Dart, MD, PhD

Executive Director

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

Are ADFs an effective innovation or marketing gambit? Recent natural experiments may provide some answers.

Consider the example of buprenorphine as an early ADF. Nearly the whole market is Suboxone (buprenorphine combined with naloxone), which provides a comparison to Subutex due to easily-identified differences (e.g. tablet



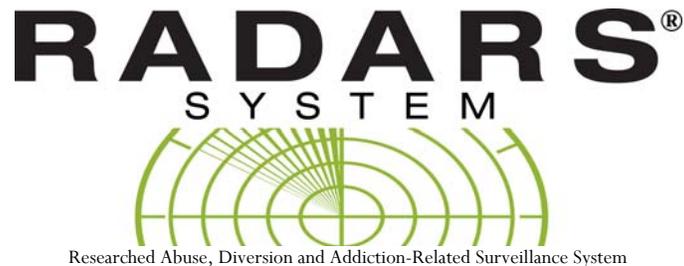
appearance). In evaluating the impact of ADFs, it is important to compare two denominators: both population rates and rates by Unique Recipients of Dispensed Drugs (URDD) are helpful in understanding product-specific abuse potential. URDD for buprenorphine products are increasing dramatically.

Within RADARS System programs, Drug Diversion shows population rates rising since about 2005 – total buprenorphine is rising, with the majority as Suboxone (85%). With regard to URDD rates, when a prescription is filled for Subutex, the drug is more likely to end up on the street due to more desirability over Suboxone. In Poison Center, intentional exposures population rates show a rise in calls involving total buprenorphine, with URDD similar to Drug Diversion. In Opioid Treatment, population rates show a rapid slope with dip around 2009 – a general increase, mostly Suboxone. URDD rates show the same phenomenon with Subutex rising. SKIP population rates are increasing along with URDD.

As evidenced by comparing population and URDD rate trends, using population rates only would lead to incorrect conclusions about trends. In College Survey, population rates for total buprenorphine are highest but buprenorphine is not popular with college students, and URDD rates are one-tenth the rates seen in other RADARS System programs. The Street Price Questionnaire shows a 17% premium for Subutex over Suboxone. Medical outcomes in Poison Center for buprenorphine (when compared to methadone, oxycodone and hydrocodone) are associated with fewer major effects and deaths. In pediatric exposures (children under age 6) there were no deaths reported to the RADARS System Poison Center even after many thousands of exposures – most deaths involved methadone and oxycodone. There is debate over getting high vs. treating underlying withdrawal and concern about buprenorphine as drug of abuse. However, the data are clear – Subutex is preferred, people pay more for it, and it is abused more than Suboxone.

The OxyContin reformulation took 3-4 months before complete market penetration of the new formulation was achieved. Substitution of a product should result in diverging trends. Within RADARS System programs, Drug Diversion shows population rates increasing for immediate-release, extended-release and total oxycodone. The URDD rates are similar to buprenorphine, and the more desired drug is extended-release. The majority of the volume is immediate-release, but there is more desire for extended-release – the upward slope of URDD indicates as market expands, diversion increases. In Poison Center, URDD the values are very flat with a slight increase for extended-release, hinting that values are going in right direction. In SKIP, both population and URDD rate trends are flat in general, with extended-release preferred in treatment programs. In College Survey, lower levels – similar picture as seen in buprenorphine. In all systems, extended-release rates are decreasing. In the Street Price Questionnaire there is a 26% premium for old OxyContin, evidence that the new product is less desirable and abused less.

Poison Center alternate administration routes for OxyContin have decreased slightly. Intentional abuse OxyContin rates decreased in 4Q10. SKIP routes indicate in 3Q10 – 1Q11, other routes decreased while swallowing the drug intact increased slightly. SKIP reports nearly 60% would switch to heroin (when asked), which reinforces concern that people may switch to less-desirable options unless we control other options as well. So far, these data support the hypothesis.



Research Challenges – Proving Abuse Deterrence

Nathaniel Katz, MD, MS

President

Analgesic Solutions

Different types of studies can be used to answer questions about relative abuse of different medications, and there is potential for Randomized Controlled Trials (RCTs) in evaluating relative abuse trends. Different levels of evidence are afforded with each study design, yet there are no examples of clinical trials for pain. As researchers, we must define what we are trying to prove. More serious administration routes result in more serious health events and even long-term health effects (e.g. HIV). Researchers must consider different types of studies based on drug being studied, which may be less dependent on product-level and route-level data with established drugs. New entrant drugs to the market require product-level and route-specific data, as there is limited historical data.

Studies have documented risks for developing substance abuse and risk factors. Patients at higher risk have higher abuse rates – confounding by indication in epidemiological studies can be neutralized by randomization. In Massachusetts in 2001, doctor shopping for OxyContin spiked dramatically, an example of where lack of historical controls caused concern over potential bias.

Randomized Controlled Trials for assessment of abuse provide advantages such as the reduction/elimination of confounding by indication. RCTs can be done pre-marketing with reasonably-sized groups. However, disadvantages like unknown sample sizes and event rates, and highly-variable sample size ranges should be considered. Different drugs may require different approaches, considering factors such as market penetration and the type of ADF. Incentives for new ADF development remains an unresolved policy issue. Epidemiological studies are important, and RCTs may be a feasible way to study product-specific abuse in both pre-marketing and post-marketing settings.