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Evaluation of Abuse Deterrent Opioid Analgesic Formulations

The abuse and non-medical use of both legal and illegal psychoactive substances is a global public health problem with large economic, societal and personal health costs¹. The nonmedical use of opioid pain relievers is now recognized to be at "the center of a major public health crisis of addiction, misuse, abuse, overdose and death"².

Many prescription opioid nonmedical users tamper with the products to improve their high. Often, the drug is taken by alternate routes typically associated with abuse (e.g. snorting and injecting). Abuse deterrent formulations (ADFs) are intended to prevent tampering for abuse purposes and minimizing the consequences associated with alternate routes of administration while simultaneously ensuring drug availability for appropriate medical treatment³.

Due to the many ways individuals abuse prescription opioids, different abuse deterrent formulations are needed to effectively reduce abuse behaviors. There are several approaches to abuse deterrence:^{4,5}

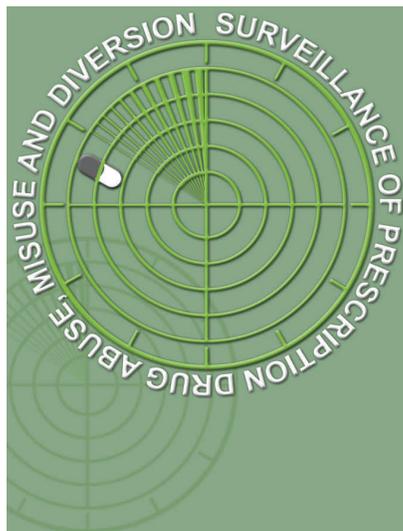
- An aversive agent or opioid antagonist can be incorporated into the product, which makes it undesirable (e.g. agonist/antagonist combinations)
- Physical barriers to tablet crushing or extraction of the active ingredient (e.g. time-release matrixes, coatings that collapse during extraction process, and osmotic-release oral systems [OROS]) can be included in the formulation.
- A mu-agonist opioids can be used (i.e. and agonist-antagonist), which pharmacologically prevents or reduces harmful consequences of abuse behaviors
- Use of pro-drugs that require metabolism to their active form

The Food and Drug Administration (FDA) has scheduled an Advisory Committee Meeting to discussing the design and conduct of postmarketing epidemiological studies for two currently marketed products with abuse deterrent mechanisms, OxyContin[®] and EMBEDA[®].

Regulatory News

The FDA will be holding an Advisory Committee meeting on Abuse Deterrent Formulation in October 21-22, 2010 - Please type the following into web browser

<http://www.fda.gov/AdvisoryCommittees/Calendar/ucm227383.htm>

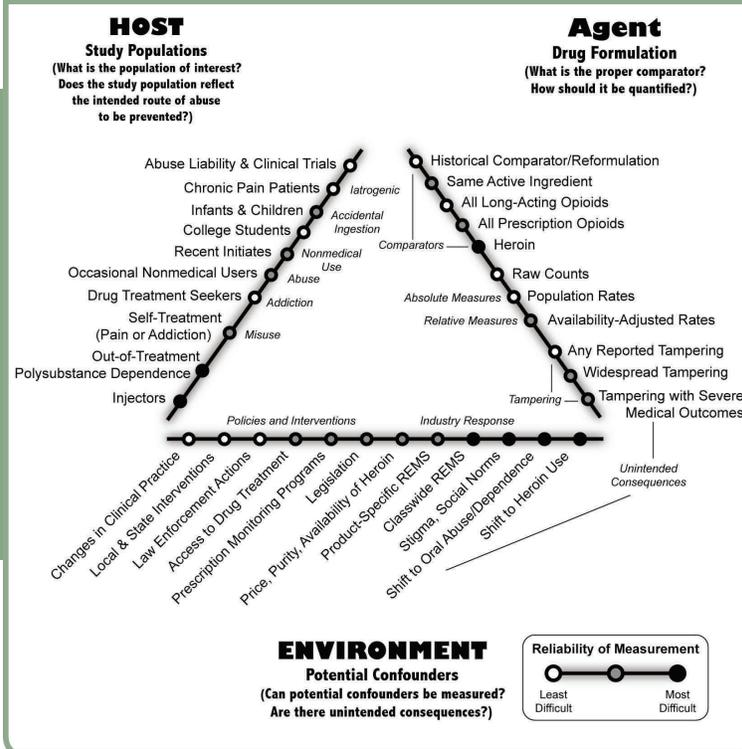


EPIDEMIOLOGIC TRIANGLE

For many decades, public health authorities have drawn the parallel between the spread of drug abuse phenomena and the spread of infectious agents.⁶ The epidemiologic triangle is routinely used to conceptualize the evaluation of the complex interaction between the host, the agent and the physical environment. We have extended this approach to provide a framework for evaluating the effect of extended-release opioids for the management of chronic pain.

EVALUATION OF ABUSE-DETERRENT FORMULATIONS

Epidemiologic Triangle of Measurement Considerations



Agent: Drug Formulation

A single ADF product cannot be expected to prevent abuse of other products, licit or illicit. Each marketed ADF will require a unique evaluation plan, based on the mechanism of abuse-deterrence that has been engineered into the product.

What is the proper comparator?

Five broad categories of comparators are possible:

1. In the case of a reformulated product, a pre- / post- product launch comparison is possible;
2. All products with the same active ingredient may be useful if the objective is to isolate the effect of a single modification (mechanical, pharmacological) in relation to existing drugs;
3. All long-acting opioids is reasonable if product is to be evaluated in the context of chronic pain patients;
4. All prescription opioids may be relevant if the concern is with prescription opioid abuse in general;
5. Heroin could be meaningful for general public health if there is reasonable suspicion that heroin is available concurrently during the evaluation of the ADF.

In some cases, it may be appropriate to use more than one category of comparator. Drug-specific data collection in RADARS System Programs allows for all five types of comparators to be readily assessed.

How should it be quantified?

Two types of quantitative scales should be used in tandem for the evaluation of ADFs to achieve confidence in the results of the evaluation:

1. Relative effect measures compare two drugs (e.g. ADF versus one comparator) and are often calculated using "abuse ratios" where the numerator comes from events in a surveillance system and the denominator is a measure of drug dispensing. These ratios of abuse ratios allow for the comparison between different prescription opioids, while adjusting for differences in the volume of medical use of the drugs.
2. Absolute effect measures can be calculated to gauge the broader impact on public health and are often calculated using study numerators and fixed general population denominators. Differences between drugs are calculated to judge the overall magnitude of the ADF on the population (e.g. the number of injection-related events that are theoretically avoided).

The intended outcome of ADFs would result in a decrease in the availability-adjusted rate for ADF opioids, indicating that the use of these drugs has become safer, without a corresponding increase in the population rate for non-ADF controlled drugs.

What kinds of outcomes should be evaluated?

Three types of outcomes are of interest in evaluating a drug that is formulated to discourage tampering by crushing and snorting/injecting:

1. Any reported street modification recipe or case report detailing tampering documented soon after the product is launched. These are likely to arise from anecdotal reports and may not lend itself to quantification. These cases are signals to be studied and hypotheses to be explored in more quantitative data sources. Poison center call notes may capture some of these events.
2. If tampering occurs in many different areas, prospective studies may be able to quantify broad patterns of "widespread" tampering, even if tampering is infrequent. These are the types of events that can be quantified using case-control and prospective studies methods, including data from the RADARS System.
3. Tampering with severe consequences are most likely to be detected in case reports if major public health harms result from concerted efforts to defeat the tampering deterrence (e.g., intra-arterial injection of particulates may create embolic events). RADARS System poison centers may be part of the surveillance efforts to detect problems quickly if they start to occur.

Host: Study Populations

What is the population of interest?

Does the study population reflect the intended route of abuse to be prevented?

The suite of studies to evaluate purported abuse deterrent properties must include populations other than intended medical users enrolled in clinical trials (e.g. nonmedical users [dependent and non-dependent] and children) who can only be studied ethically in observational studies. There is a spectrum of population-outcome pairs that could be studied in order to determine how a formulation may prevent tampering or abuse. While there are many potential population-outcome combinations of interest, six common choices are detailed below:

1. Incidence of iatrogenic addiction in chronic pain patients. This is unlikely to be feasible in small or short-term observational studies. Even a well-controlled randomized trial will not provide sufficient evidence to evaluate abuse deterrence due to lack of validated outcomes, exclusion of patients for whom an ADF is likely to be prescribed, likelihood of high dropout rate, and poor external validity.
2. Accidental ingestion in infants and children.
3. Tampering and nonmedical use among college students and recent drug use initiates.
4. Tampering and nonmedical use among occasional nonmedical users. National household surveys can capture some of this information.
5. Recent tampering among drug treatment seekers.
6. Injection frequency and practices among out-of-treatment injectors. This population is collectively likely to have the greatest amount of experience with tampering and consequences of tampering and can be recruited from service providers who serve these communities. Due to the higher mortality and morbidity rates likely associated with injecting, preventing injection drug use may be one of the most important public health benefits of ADFs.

The RADARS System provides data for children, new initiates, and persons that tamper with products prior to drug abuse.

Environment: Potential Confounders

Can potential confounders be measured?

Are there unintended consequences?

The onus is on the researchers to disprove the alternative hypothesis that differences in abuse between ADFs and traditional formulations are due to broader secular and social trends, instead of the properties of the ADF. Therefore, adequate control for the social environment and secular trends must be undertaken. Explicitly stating the potential confounders and creating proxies for their measurement allows for sensitivity analyses to determine the impact that potential confounders may have on the observed results. There are several important potential confounders to consider:

1. A formulation that prevents all types of abuse is not likely to be feasible. Since all drug formulations release drug, any one product can be abused without tampering by simply taking more tablets of that product orally. Evaluation of all routes of abuse should be assessed in relative and absolute terms to detect any shift from one route of abuse to another for the same product.
2. If there are large-scale changes in clinical practice because of the marketing of the ADF, the use of secondary data sources such as administrative claims data may be limited. For example, the patients who are more likely to experience an abuse outcome are more likely to receive an ADF opioid for analgesia, compared to an individual without those preexisting conditions.
3. Interventions at the local and state levels and by law enforcement may not be known to researchers at the national level. Location-based potential confounding needs to be in the interpretation of data on ADFs.
4. The individual effects of broader secular trends influenced by changes in societal norms, risk evaluation and mitigation strategies, heroin and other diverted prescription drug availability, etc. are difficult to quantify. However, these trends must be taken into account when data are interpreted to prevent from drawing undue causal inferences.

REFERENCES

¹United Nations Office on Drugs and Crime. (2009). *World Drug Report 2009* [Online]. Retrieved June 1, 2010 from the World Wide Web: http://www.unodc.org/documents/wdr/WDR_2009/WDR2009_eng_web.pdf.

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³Food and Drug Administration, Center for Drug Evaluation and Research (2010). Guidance for Industry, Assessment of Abuse Potential of Drugs [Online]. Retrieved on June 1, 2010 from the World Wide Web: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

⁴Comera SD, Ashworth JB, Foltin RW, Johanson CE, Zacny JP, Walsh SL, The role of human drug self-administration procedures in the development of medications, *Drug and Alcohol Dependence* 96 (2008) 1–15.

⁵Wick JY, Drug-Abuse Deterrent Formulations, *The Consultant Pharmacist*, 2009, 24(5), 356-365.

⁶Falk D, Yi H-y, Hiller-Sturmhöfel S. An Epidemiologic Analysis of Co-Occurring Alcohol and Drug Use and Disorders *Alcohol Res Health* Vol. 31, No. 2, 2008: 100-110.

Recent RADARS System Publications and Presentations

- Inciardi JA, Surratt HL, Cicero TJ, Rosenblum A, Ahwah C, Bailey JE, Dart RC, Burke JJ. Prescription drugs purchased through the internet: Who are the end users? *Drug and Alcohol Dependence*. 2010; 110(1-2):21-9.
- Smith MY, Rosenblum A, Parrino M, Haddox JD, Fong C, Colucci S. Validity of self-reported misuse of prescription opioid analgesics. *Substance Use and Misuse*. 2010;45:1509-1524.
- Zosel A, Bailey JE, Buchholtz C, Ross E, Dart RC. Methadone-associated deaths by formulation as reported by the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS[®]) System. The College on Problems of Drug Dependence Annual Meeting. Scottsdale, AZ. June, 2010.

Did You Know?

On July 14 the RADARS System resubmitted comment to FDA Docket on REMS - Please type the following into web browser

<http://www.radars.org/LinkClick.aspx?fileticket=kPISdcxobok%3d&tabid=1114>

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Upcoming Meetings of Interest

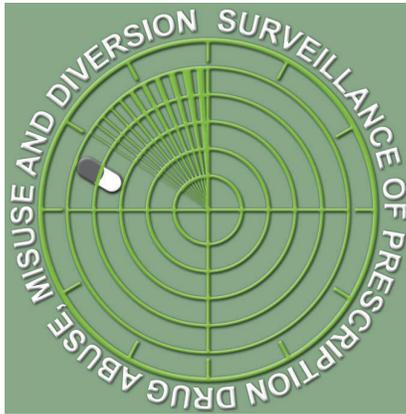
- National Public Health Information Coalition, October 10-13, 2010. San Diego, California.
- American Public Health Association, November 6-11, 2010. Denver, Colorado.
- North American Congress of Clinical Toxicology, October 7-12, 2010. Denver, Colorado
- DIA Excellence in Pharmacovigilance: Clinical Trials and Post Marketing, October 25, 2010. Vienna, Austria.
- National Association of State Controlled Substances Authorities, October 19-22, 2010. Charleston, South Carolina.
- National Association of Drug Diversion Investigators, November 16-19, 2010. Indianapolis, Indiana.

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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