

The Development of a Comprehensive Risk-Management Program for Prescription Opioid Analgesics: Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®)

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ABSTRACT

Objective. Beginning in the late 1990's a marked increase in abuse of OxyContin® emerged, which led to the development and establishment of a proactive surveillance program to monitor and characterize abuse, named the Researched Abuse, Diversion and Addiction Related Surveillance (RADARS®) System. The main goal of RADARS® was to develop proactive, timely and geographically sensitive methods to assess the abuse and diversion of OxyContin®, along with a number of other Schedule II and III opioids with the aim of using this information to guide risk reduction interventions. Thus, its major focus was the detection of abuse of OxyContin® and other commonly prescribed opioid analgesics at the three-digit ZIP code level across the country utilizing a number of different detection systems.

Methods. The detection systems selected were: (1) Quarterly-surveys of drug abuse experts who are knowledgeable about cases of prescription drug abuse; (2) Surveys of law enforcement agencies that detect diversion of prescription drugs; and (3) Poison Control Center reports of intentional misuse or abuse of prescription opioids. Collectively, the three systems provide overlapping coverage of over 80% of the nation's 973 three-digit ZIP codes.

Results. Preliminary results indicate that prescription drug abuse is prevalent nationwide, but it seems to be heavily localized in rural, suburban and small urban areas. Our results also indicate that hydrocodone and extended and immediate release oxycodone products are by far the most widely abused drugs in the country, but the abuse of all prescription opioids seems to have grown over the 14 quarters since the inception of RADARS®.

Conclusion. The next step in these studies is to develop regionally specific, risk-minimization-strategies, which is the goal of all risk-management programs. If successful, RADARS® will serve as a prototype of such programs for any new drug approved that has measurable abuse potential.

Key Words. Prescription Drug Abuse; OxyContin®; Risk-management Program; Opioid Analgesic Abuse

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Introduction

Prescription opioid analgesic abuse has been a persistent national problem for decades, particularly in certain areas, most notably the Appalachian region of the United States [1-4]. Against the backdrop of a relatively low, but sustained, level of prescription opioid abuse nationwide for the past 40 years, there was a sharp increase in

prescription drug abuse beginning in late 1995 and extending to the present time [5–10].

While the reasons for this steady growth in prescription opioid analgesic abuse are largely unknown, prior research conducted by some of the current authors, examining trends in the abuse of tramadol and other more potent opioids [5,7], indicates that reasons most often given by recreational and addicted prescription opioid users include:

1. Prescription drugs are relatively easily obtained, as opposed to the great difficulty and perceived danger in obtaining heroin and other illicit drugs.
2. The purchase of illicit drugs on the street, such as heroin, was closely monitored by law enforcement officials and arrests were, therefore, far more likely for heroin than for legal drugs, such as opioid analgesics.
3. The use/abuse of prescription drugs is more socially acceptable among peers compared with heroin or cocaine.
4. The purity and the dosage of prescription medications are highly predictable and, consequently, they are much safer to use than illicit drugs.
5. When heroin is unavailable, these drugs serve as acceptable, although not preferred, substitutes.
6. These drugs can be useful as self-medications to relieve symptoms of heroin withdrawal or in an effort to detoxify.

It needs to be noted that the resurgence of abuse in the past decade was for the most part not detected in a timely manner by the Food and Drug Administration (FDA), which raises an obvious question: “Why did existing FDA systems fail?” Indeed, the FDA has long recognized the importance of postmarketing surveillance, and utilizes a complex set of databases to gather as much information as possible about the use, adverse events, misuse, and abuse of drugs. These databases include: the Drug Abuse Warning Network (DAWN), the Treatment Episode Data Set (TEDS), the Arrestee Drug Abuse Monitoring program (ADAM), the System to Retrieve Identified Drug Evidence (STRIDE), the National Forensic Laboratory Information System (NFLIS), the National Household Survey on Drug Use and Health (NHSDUH), Monitoring the Future (MTF), and the Toxic Exposure Surveillance System (TESS). The problem with all these databases is that they are passive, retrospective, and often anecdotal, and the data are not

analyzed or published for 18–24 months, thus hampering recognition of rapidly emerging problems [11–14].

The limitations of systems to monitor adverse events, including abuse, were clearly documented by an FDA task force that was charged with evaluating postmarketing surveillance of drug safety [15]. The catalyst for this task force was a four-fold increase in drug recalls over the period from 1993 to 2001: 1.56% of approved drugs for 1993–1996 compared with 5.35% for 1997–2001 [12]. The task force concluded, in the so-called Henney Report, that the monitoring systems currently in place failed to identify most adverse events before they evolved into full-blown, public health concerns. The most significant aspect of this report, however, was a mandate that the FDA work with drug sponsors to develop *proactive* risk-management strategies that would better protect the public by obtaining “real-time” evidence of emerging problems instead of historical trends, as is the case with most existing systems. With this timely data in hand, it was hoped that risk-minimization plans that would reduce or manage the abuse, i.e., a true risk-management program, could be implemented.

There was limited experience with risk-management programs within the FDA, but in 1994 a risk-management program for tramadol and ultimately its combination products was initiated as a voluntary, joint effort between Ortho McNeil Pharmaceutical, Inc. and the FDA [5,7]. The most unique and still unprecedented aspect of this program was that an Independent Steering Committee (ISC) was appointed, which had direct reporting lines to the FDA and Ortho McNeil Pharmaceutical, Inc., which ensured the committee’s independence. This program was unique and, for the better part of 6 years, there were rare and modest efforts to establish other postmarketing surveillance programs, most of which were not very successful judging by the dearth of any published information regarding them. With the impetus provided by the Henney Report, beginning in 2000 such programs were mandated by the FDA as a part of any new drug approval.

In this article, we will discuss a risk-management program initiated by Purdue Pharma, Inc., with the advise and consent of the FDA, to deal with a strong, marked increase in the abuse of OxyContin®, which occurred in the late 1990s. While the abuse was widespread [16], it was most heavily concentrated in certain areas with a history of prescription drug abuse, e.g., Appalachia and Maine.

The RADARS[®] System

To assist in the development of this risk-management program, Purdue Pharma determined that an External Advisory Board (EAB) of outside experts in addiction, law enforcement, drug regulation, and epidemiology would be helpful in guiding the design and direction of studies to understand the problem of OxyContin[®] abuse (see Acknowledgments).

The EAB recognized: first, that at a global level the proposed postmarketing surveillance program was intended to provide a sensitive system to detect abuse (i.e., *the risk* associated with using OxyContin[®]) in a geographically specific manner, which would then lead to focused studies of the characteristics, demographics, and drug-use patterns of abuse-prone individuals. From these focused studies unique intervention strategies would be developed to *manage* or reduce the abuse, which would make this a true risk-management program, not simply a postmarketing surveillance program.

The EAB also concluded that there were no universally accepted methods that could be easily adopted as a model for measuring abuse and diversion of prescription drugs, but concluded that the postmarketing surveillance program for tramadol provided a strong foundation upon which to build an enhanced effort [5–7]. In the tramadol program, a network of drug abuse experts (“key informants”) and, somewhat later, law enforcement drug diversion specialists, were assembled to proactively obtain evidence of abuse and diversion of tramadol with a geographic specificity down to the five-digit ZIP code. This effort resulted in more than a doubling of the number of cases of abuse and dependence detected by the FDA’s main data-gathering system, MedWatch [7].

The abuse patterns detected by this system suggested that tramadol abuse was evident sporadically across the United States, but tended to be transiently localized to fairly discrete loci with unique characteristics in each area. These observations were reminiscent of the earlier outbreaks of abuse of Robitussin and “T’s and Blues” [17–20] two decades ago that occurred in very limited geographic areas, each of which had unique and regionally specific characteristics [5–7]. The key informant system was also sufficiently sensitive and timely to pick up abuse and dependence on tramadol (Ultram) immediately after its release in 1995: within 2 days after its launch, evidence of abuse was detected in an isolated area of Florida

Table 1 Drugs evaluated by RADARS[®]

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- Hydrocodone
 - Hydromorphone
 - Morphine
 - Oxycodone immediate-release (IR) products (IR oxycodone)
 - Extended-release (ER) oxycodone products (including OxyContin)*
 - Methadone
-

* In the second calendar quarter of 2004, a generic version of extended-release oxycodone became available, and thus, from this date onward, OxyContin and the generics were grouped under ER oxycodone products.

[5]. This timely receipt of data, which pre-dated published DAWN mentions by 18 months, enabled the almost immediate detection of sites, which were identified as “target” areas, in which abuse seemed to be concentrated. This permitted more focused studies of abuse to determine the nature of the abuse problem and the characteristics of those abusing drugs. This, in turn, led to the implementation of successful intervention strategies [7].

Thus, this risk-management program was adopted as a platform for the new, more expansive Purdue Pharma program, dubbed Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS[®]) System. The main goal of RADARS[®] was to develop proactive, timely, and geographically sensitive methods to detect the abuse and diversion of OxyContin[®], along with a number of other Schedule II and III opioids, with the aim of using this information to guide risk-reduction interventions.

Signal Detection Studies²

After reviewing a large amount of data, the EAB concluded that the emergence of OxyContin[®] abuse was not an isolated event, but was part of a nationwide growth in prescription drug abuse, indicating that the OxyContin[®] problem needed to be considered in the context of abuse of the whole class of opioid analgesics [5–10]. Thus, the EAB selected other commonly prescribed Schedule II and III opioids to monitor for abuse; the drugs selected are listed in Table 1. Because OxyContin[®] lost patent protection in the second quarter of 2004 and generics came on the market, we will henceforth refer to OxyContin[®] and its generics as extended-release (ER) oxycodone products. Because abuse is detected in a variety of settings,

²The principal investigators of the signal detection studies were as follows: Key Informant (Theodore J. Cicero); Law Enforcement Drug Diversion Network (James Inciardi); and Poison Control Centers (Richard Dart).

the EAB determined that a number of systems should be put in place, two of which were used in the tramadol postmarketing study (numbers 1 and 2 below). Those selected systems were: 1) quarterly surveys of drug abuse experts and others who are knowledgeable about cases of prescription drug abuse in their catchment areas (i.e., key informants); 2) surveys of law enforcement agencies that detect diversion of prescription opioid drugs along with two other classes of commonly used medications that are subject to abuse (e.g., benzodiazepines and carisoprodol); and 3) Poison Control Center reports of intentional misuse or abuse of prescription opioids.

The EAB recognized that there were limitations to each of these data sources, but felt that information from these systems could provide a “signal” that abuse might be occurring in certain populations and in discrete ZIP codes, which might then warrant more focused efforts to validate the problem or strength of the “signal” and develop intervention strategies.

General Considerations for any Risk-Management Program

Risk-Benefit Analyses

The EAB felt that as a core principle of any risk-management program, the risk-benefit analysis mandated by the Controlled Substances Act (CSA) needed to be addressed in a specific manner. While abuse or any other adverse event is unfortunate, no drugs are free of adverse events and, indeed, any package insert contains extensive, often intimidating, lists of possible adverse events associated with the therapeutic use of the drug. The key then is to weigh the possibility of an adverse event against the therapeutic benefits of the drug, the so-called risk-benefit analysis. For most drugs, the risk-benefit analysis is positive and relatively easy to calculate: the benefits greatly outweigh the potential for mild adverse events. For others, the task is much more complicated.

Before proceeding to this discussion, it is important to emphasize that even with a low incidence rate, the raw number of adverse events rises as the number of persons exposed expands. For example, if only 0.01% of all individuals who are prescribed a drug develop an adverse reaction, the number of cases would be 100 if 1 million patients are prescribed the drug, or 1,000 if 10 million people are exposed. Thus, the sheer number of cases could distort a very low incidence rate which might otherwise be indicative of a very favorable risk-benefit ratio. Clearly, the only valid index of

a drug's risk-benefit ratio is the rate of an adverse event, which takes into account the total number of persons who are prescribed the drug.

Aspirin and related nonsteroidal anti-inflammatory drugs (NSAIDs) provide an excellent example of a favorable risk-benefit ratio where there are very serious adverse events and the absolute number of these adverse events (numerator) is high. These drugs have proven to be effective in the treatment of pain, inflammation, and fever, but they have a serious adverse event that occurs with some frequency—gastrointestinal (GI) bleeding. It is estimated that GI complications account for approximately 103,000 hospitalizations each year [21,22]. Death from GI bleeding occurs in an estimated 26,500 people per year [22]. Despite the potential for these serious, life-threatening adverse events, and their high number in absolute terms, NSAIDs remain FDA approved for over-the-counter use, due to their efficacy and relatively low incidence rate of GI problems, but with strong label warnings about the potential for GI bleeds.

The example of NSAIDs illustrates both how misleading raw numbers of adverse events can be and how difficult risk-benefit analyses are in many cases. More importantly, NSAIDs serve as a striking backdrop against which to contrast the weighting given to drug abuse as an adverse event in risk-benefit decisions regarding opioid analgesics.

Addiction is a clinical disorder, characterized by well-defined patterns of loss of control, craving, compulsive use, and continued use despite evidence of harm. Problems of prescription drug abuse can range from occasional use to addiction. Interestingly, prescription drug abuse or addiction to prescription opioids occurs to a great extent in persons who use these drugs for non-medical purposes. Thus, the risk-benefit analysis for opioid analgesics with an abuse liability, in a practical sense, needs to be recast: What level of abuse is acceptable in drug-abuse prone recreational and street drug abusers, who have often obtained the medications through deceit or from sources located outside the legitimate practice of medicine, given the benefits of these efficacious analgesics in the relief of pain for legitimate patients?

Complicating the delicate and difficult risk-benefit analyses inherent with all opioid analgesics is the fact that there are no accepted standards for determining what threshold level of abuse and diversion is acceptable, beyond which the incidence of abuse outweighs the benefits of pain

relief. This question remains essentially unanswered, despite an often heated debate encompassing much of the past four decades. What is clear, however, is that there needs to be an informed judgment, based on solid scientific data, about the risk–benefit ratio of opioid analgesics.

Determination of Rates

Directly related to the risk–benefit analyses, of course, is determining the rate of an adverse event, expressed generally as cases of the adverse events divided by the number of people benefiting from the therapeutic use of the drug. The problem with abuse as a risk factor is that this is not generally associated with therapeutic use of opioid analgesics, and hence, abuse is not a typical adverse event in the usual meaning of that term. In the case of abuse, the only accurate risk–benefit ratio would be the total abuse cases divided by all of those exposed to the drugs, either as a patient or as those who have obtained the drug illicitly (e.g., forged prescriptions, theft, drug dealers, etc.). Obviously, this denominator is elusive and will never be estimated with any degree of certainty. In the absence of available data on the total number of individuals exposed to prescription opioids, it is necessary to resort to the use of proxy measures to estimate exposure and, thereby, calculate rates. In the following sections, various denominators that can be used to estimate exposure are discussed.

Number of Cases of Abuse

Typically, abuse of any drug is most easily measured by the number of cases of abuse reported in large national databases, such as DAWN, TEDS, ADAM, STRIDE, NFLIS, NHSDUH, MTF, and TESS. This metric ignores the degree of exposure that can greatly distort the true magnitude of abuse. Nevertheless, the number of abuse cases does serve the purpose of giving an idea of the magnitude of drug diversion and abuse encountered by local law enforcement agencies, treatment centers, and emergency rooms. The EAB determined, therefore, that the number of cases needed to be calculated and the data expressed in this manner, realizing that this measure in isolation can distort the actual rates of abuse.

Exposure Corrected by Total Population

A rate of abuse can also be calculated using the number of abuse cases in a particular ZIP code divided by the 2000 Census-derived population numbers in those three-digit ZIP codes. The rationale for this approach is simple. It is likely

that five cases of ER oxycodone abuse in the New York City area with 8–10 million people might be considered a relatively modest rate of abuse, whereas if this same number of cases were observed in a city of 18,000, this rate would be viewed with considerably more gravity. Because the purpose of RADARS[®] was to identify geographic areas where abuse was disproportionately high, the EAB believed that this population-based metric was very useful, even with the restrictions inherent in noncorrection for exposure.

Number of Kilograms of Drug Dispensed as a Denominator

The number of kilograms distributed at the retail level can and has been used to estimate the degree to which selected opioid classes were used medically [2,23]. Although the number of kilograms distributed (which is derived from individual prescription data) can be estimated at the individual three-digit ZIP code level, a significant limitation in using this is that it does not adjust for variability in potency of different prescription opioids. That is, rates of abuse of a kilogram of the highly potent fentanyl will be very much higher by several orders of magnitude than a kilogram of immediate-release (IR) oxycodone. It is doubtful that this reflects the true relative rates of abuse and, thus, the EAB rejected this denominator.

Number of Prescriptions Dispensed

The number of prescriptions dispensed has been used as a denominator in calculating rates of abuse associated with prescription opioids [20]. Such data are readily available at the three-digit zip code level for most regions in the United States through various commercially available databases (e.g., IMS Health, Inc.). However, there are two significant limitations associated with using the number of prescriptions as a proxy for the “at risk” population: 1) substantial variability in how often individual prescriptions need to be filled and the size of the prescriptions; and 2) there is a lack of adjustment for the strength of the dose prescribed or for the duration of action. The EAB, therefore, rejected this denominator as well.

Number of Patients Prescribed a Prescription Opioid

The number of patients who are prescribed a specific drug has the advantage of expressing the denominator in units similar to those used in the numerator, thus reducing the likelihood of obtaining a biased estimate and threatening the internal validity of the rate [24]. In addition, using the

number of patients avoids certain problems inherent in the use of other alternatives, including non-adjustment for such factors as potency, size, and duration of prescription. Most importantly, using the number of patients as the denominator provides a much better estimate of the risk (i.e., abuse)—benefit (i.e., patients in whom pain is treated) ratio. To determine the number of persons who filled a prescription for a drug, we employed commercially available data for all marketed drugs based on a proprietary algorithm developed by Verispan, a commercial vendor of administrative and health care databases. Using this estimate, we solved the following equation in order to estimate the proportion of patients who are prescribed each of the RADARS® System opioids at the three-digit ZIP code level. This rate will be more fully explained in a forthcoming publication.

$$\frac{\# \text{ prescriptions in a 3-digit ZIP code}}{\# \text{ prescriptions in a given state}} = \frac{\# \text{ patients in a 3-digit ZIP code}}{\# \text{ patients in a given state}}$$

The EAB felt that this measure corrected for exposure better than all others and, therefore, served as an excellent index of the risk–benefit analysis.

Signals of Abuse

To establish a rate that would constitute a signal that certain geographic areas show disproportionately high abuse, the EAB determined that rates more than 5 cases/100,000 population or 10 cases/1,000 people filling a prescription would adequately serve as a standard for determining areas in which abuse is high.

The advisory committee realized that these signal levels were arbitrary, and that there was no scientific basis for establishing such a threshold below which abuse was not considered a problem, but above which there was a public health concern that needed attention. However, this decision was made based upon three independent lines of thought and reasoning:

First, and foremost, there is not a single study that would help define significant levels of abuse, because ours is one of the first studies in which relative rates of abuse have been calculated, and hence, our experience is unique and not informed by any existing literature.

Second, our extensive experience with the abuse of tramadol [5,7,16] has shown that the rate of

abuse of this unscheduled drug worldwide ranges from 0.05 to 0.15 cases per 1,000 patients who are prescribed the drug. We reasoned that Schedule II and III drugs should have incidence rates at least 10–50-fold higher. Thus, these levels were set as a reasonable threshold.

Finally, in our initial studies described below, using frequency distributions we established the values for the 90th percentile (i.e., 5 cases/100,000 population or 10 cases/1,000 patients who are prescribed the drug). All those signal rates in the top 10% were considered “out-liers” and therefore constituted a signal of disproportionately high abuse.

Based on these points, this definition of a signal site, at least in our initial studies, seemed to represent a logical starting point to determine which regions of the country had disproportionately high abuse rates. Nonetheless, we are cognizant of the fact that these rates, no matter how logical, are arbitrary and that our experience will help refine these numbers.

Components of RADARS®

Key Informant Network

Based upon the tramadol postmarketing study, a survey of “key informants” or drug abuse experts was chosen to gather data on the abuse of prescription opioids, including ER oxycodone, at a community level. The term “key informants,” borrowed from the fields of social and cultural anthropology [25], refers to clinicians, epidemiologists, treatment counselors, and other observers who are well-recognized experts in the field of substance abuse and pain medicine and are in a position to evaluate, treat, or otherwise know about new and emerging drug problems in their areas [5,7]. The types of key informants that the EAB asked to participate, the population covered, and the rationale for selecting them are discussed below.

Programs for Impaired Health Care Professionals

Health care professionals were one of the earliest populations who were found to abuse pentazocine, fentanyl, and tramadol [26–28]. They have easy access to prescription drugs, and are keenly aware of their reinforcing properties and, hence, programs designed for monitoring licensed professionals who develop substance-use disorders were identified as important sources of data.

Methadone Clinics

Methadone patients who do not completely divorce themselves from the drug culture may

engage in drug-abuse patterns that reflect diversion of prescription drugs to the street. Methadone programs also have discharges or dropouts who are replaced by new patients, who may reflect current patterns of prescription opioid and other drug abuse.

Private Residential and Other, Non-methadone Substance Abuse Programs

Patients in these programs normally consist of individuals who can pay for the treatment of their addiction. This population often is Caucasian and relatively affluent compared with those who are found in most methadone programs, and therefore, may be less likely to abuse illicit opioids and more likely targets for prescription drug abuse [5,7].

National Institute on Drug Abuse

The National Institute on Drug Abuse (NIDA) supports a number of comprehensive epidemiologic and treatment studies of drug-abuse populations, whose purpose is to detect the emergence of abuse and characterize abuse patterns, including those of newly available medications, and study treatment effectiveness. Hence, the principal investigators of NIDA grants dealing with epidemiological or treatment outcome were logical choices for inclusion as key informants.

Selection of Key Informants

The sample was not random, but rather individual programs, physicians, and drug abuse experts were selected from national databases by the EAB based upon information it had on their qualifications and experience with recognizing problematic substance use or abuse. The only other selection criterion was that informants from as many rural and small urban areas as possible would be recruited to provide coverage of the entire country. A total of 338 individuals in 208 of the nation’s 973 three-digit ZIP codes agreed to participate. The specialization and self-classification of all of the key informants is shown in Table 2.

Key informants were asked to fill out a quarterly questionnaire that posed several questions

regarding whether the informant had direct, first-hand knowledge and evidence of abuse of the targeted opioid drugs. For purposes of these studies, we used one of three criteria to define a case of drug abuse: 1) use to get high; 2) use in combination with other drugs to get high; and 3) use as a substitute for other drugs of abuse. Each informant was requested to provide as much information as possible about prescription opioid users—age, gender, reasons for use, etc. Valid cases were defined as those in which the informant had first-hand knowledge of the case. The informants were paid \$100.00 for each completed quarterly questionnaire.

Law Enforcement Drug Diversion Network

The purpose of the drug diversion network is to determine the extent of diversion of selected drugs in a national sample of police jurisdictions and to identify diversion “signal sites” for specific drugs. This program was established initially to screen tramadol diversion by a grant from Ortho McNeil Pharmaceutical, Inc., and is now funded by Purdue Pharma. A “signal site” is defined as any participating jurisdiction that registers a rate of 5 or more diversions of any given drug per hundred thousand persons within the three-digit ZIP code of the reporting agency, during any quarter of the calendar year. The drugs targeted in the survey include alprazolam (Xanax®), buprenorphine, carisoprodol (Soma®), diazepam, fentanyl, hydrocodone, hydromorphone, methadone, morphine, ER oxycodone, IR oxycodone, and since the second quarter of 2004, generic oxycodone ER tablets (ER oxycodone).

This study targets diversion investigators from all 50 states, the District of Columbia and Puerto Rico, and the U.S. Virgin Islands, including rural, suburban, and urban areas. Despite the extensive coverage, this is not a nationally representative sample. Of the more than 23,000 police and regulatory agencies in the United States, very few have officers assigned to pharmaceutical diversion. In fact, even among the thousands of municipal, county, and state police agencies that emphasize drug enforcement, few target prescription drugs. The Drug Enforcement Administration declined to participate. Nevertheless, the nationwide distribution of agencies is substantial, and is able to detect diversion of all the targeted drugs, including buprenorphine.

The participating sites were recruited through traditional chain referral/snowball sampling strategies. Initial recruitment began with the member-

Table 2 Areas of specialty of key informants

Impaired health professional programs	17
Pain management specialists	48
Addiction treatment specialists	148
Adult treatment programs	105
Adolescent treatment programs	55
University/research/prevention centers	34
Hospitals	30
Methadone specialists	23
Drug/family courts/other	12

ship list of the National Association of Drug Diversion Investigators (NADDI), and every law enforcement agency that had a NADDI member was contacted. Some agencies agreed to participate, while others refused. All agencies were asked for leads to other agencies that might be contacted. Referrals also came from RADARS[®] System EAB members and Purdue staff and by recruiting at regional and national NADDI meetings and training conferences.

The diversion-reporting sites' investigators who agreed to participate receive a questionnaire every quarter that elicits the following information:

1. The total number of *new* cases of diversion reported to and/or investigated by the diversion unit during the past 3 months. They must be new cases that were officially put "on the books" during the previous quarter. As such, only cases in which there is a new, *written* complaint or report are included. Continuing cases from the previous quarter that are still pending do not qualify.
2. For each of the drugs listed above, we request the number of cases logged in and the dosage form (tablet, liquid, patch, or other).
3. For the next five most diverted drugs, over and above the targeted drugs listed above, reporters are asked to provide the number of cases logged in, as well as the dosage form.

This procedure provides an exhaustive distribution of the types and numbers of diversion cases in a jurisdiction.

All participants in the survey report their data on the same instrument and in the same way. This requires some diversion units to change the way that their data are collected and recorded. In such cases, resources (such as computers) have been provided. Questionnaires are mailed, faxed, or emailed to the diversion investigators at the beginning of each calendar quarter. We review each returned instrument for completeness and accuracy, and when necessary, make repeated contacts with respondents for additional or corrected information. For unreturned questionnaires, repeated contacts are made by telephone, fax, mail, or email.

Participating diversion investigators are required to provide *all* of the data requested, and are paid a quarterly stipend of \$200 for their participation. For investigators whose department policies prohibit them from accepting a stipend, the payments are sent to either their agency or a charity of their choice. Some agencies do not

accept any type of payment, but participate nevertheless. Reporters who submit completed forms for *all* four quarters in the calendar year are paid an additional \$200.

Data are entered and verified by University of Delaware research staff using a program developed by Purdue Pharma. The complete database is maintained at the Coral Gables Office of the University of Delaware's Center for Drug and Alcohol Studies; however, many of the data are also sent to the central database for the RADARS[®] System, located at Washington University in St. Louis.

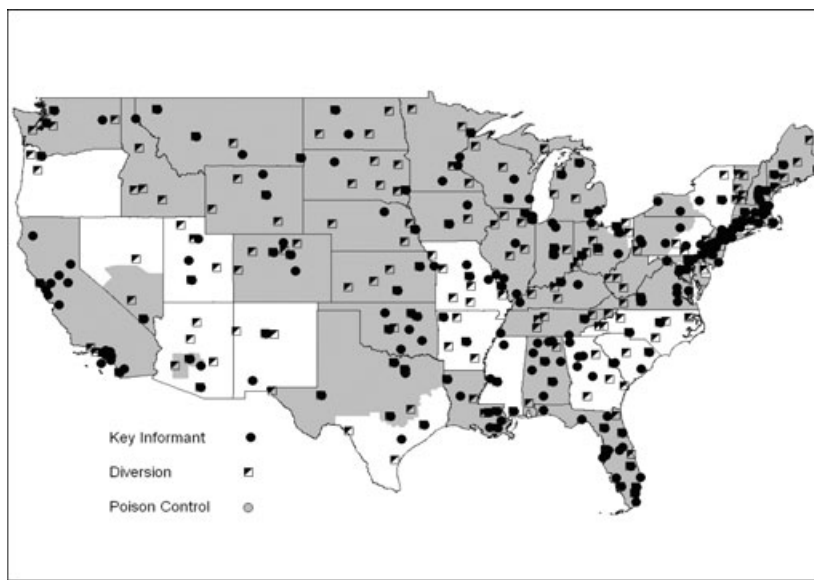
Poison Control Centers

A Poison Control Center is a specialized medical contact center that receives spontaneous reports from the public health care professionals and other public safety professionals, containing information regarding exposure to any poisonous substance. Each call to a poison center is managed by a trained poison specialist and has a medical director as well as pharmacists or nurses available. Every community in the nation has this service available 24/7, 365 days a year, by calling a toll-free number.

Poison centers provide several benefits for signal detection. First, they provide a perspective not included in the other signal detection systems, because the callers are typically patients or their health care providers. Second, all poison centers in the United States collect standardized information about each call and record this information in a computerized database. This information includes precise identification of the drug taken that includes dose and manufacturer.

The current participants in the RADARS[®] System are 15 geographically dispersed poison centers, serving a population of approximately 102 million people (Figure 1). Each center collects a standardized data set on each exposure call (the patient has actually injected or ingested the drug) or drug information call (information only, which includes pill identification calls). In the RADARS[®] System, a case is defined as any call from an individual involving intentional exposure to one or more RADARS[®] System drugs. Any exposure case that is assigned a reason code of intentional (patients knowingly injected or ingested substance) was considered a possible abuse or misuse case and was included in the analysis of types of events. The intentional exposure call category (suicide, abuse, misuse, and intentional unknown) was selected as a surrogate for possible abuse and misuse cases, because a few cases coded as suicide or intentional unknown are associated with abuse.

Figure 1 Coverage areas of the three detection systems. Poison Control Centers in gray shading can be most precisely defined, as their areas are designated by telephone service. For the key informant and diversion centers, the three-digit ZIP code of each informant is given. It is recognized that most of the informants actually have contacts with individuals in 4–8 ZIP codes other than their own, but this is highly variable and is difficult to establish. Thus, we have taken the conservative approach and mapped only their mailing ZIP codes.



After each case has been completed, the coordinator at each site focuses on verification of the substances involved and coding a reason for the exposure. Each case has all personal health identifiers removed, and the local Institutional Review Board approved data submission. Each participating center submits data weekly.

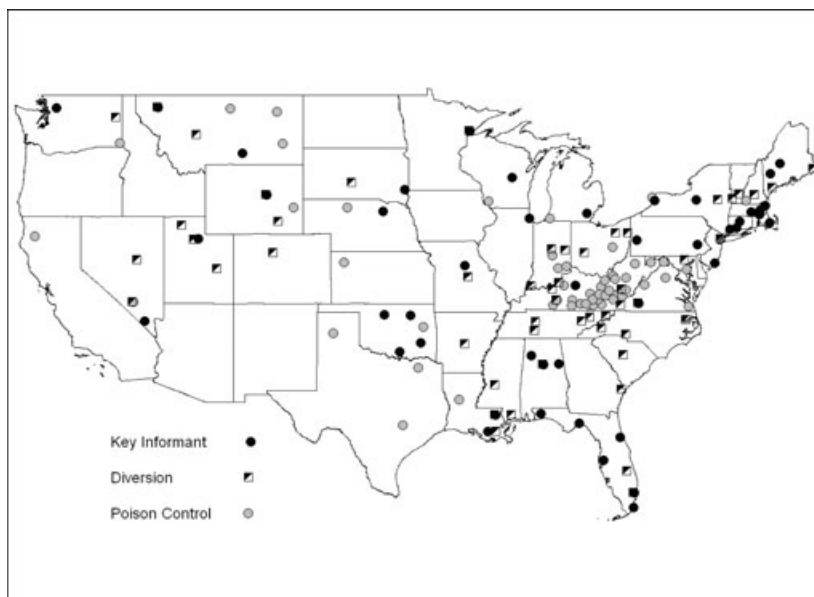
Initial Results from the RADARS® System

Figure 1 shows the coverage area of the three systems. Collectively, the three signal detection systems cover more than 80% of the nation’s 973 three-digit ZIP codes. This enables RADARS® to

detect problems of abuse in a timely fashion, no matter where they might occur, with a relatively high degree of precision. As mentioned above, we used a threshold of 5 cases of abuse/100,000 people in each three-digit ZIP code as a “signal” of disproportionately high abuse. The signal sites for all three systems for 2004 are shown in the map in Figure 2. Several observations are noteworthy:

First, prescription drug abuse is prevalent across the country, but appears to be unusually dense in the eastern portions of the United States. This may not be surprising given the demographics of the national population distribution, but, even in populous California, very little prescrip-

Figure 2 The signal sites (>5 cases/100,000 population) for all three detection systems mapped by three-digit ZIP codes. In many, perhaps most cases, the same ZIP code appeared in all four quarters in the third quarter of 2004 through the second quarter of 2005.



tion drug abuse seems to be detected despite extensive coverage by all three signal detection systems.

Second, while some large cities have problems with prescription drug abuse, most of the abuse is located in rural, suburban, and small metropolitan areas.

Third, there was an extensive overlap in cases of abuse detected by all three systems (e.g., 20% of the ZIP codes had signals identified by two or more systems), which indicates the sensitivity of our methods in localizing abuse. These data also stress that a number of regions (e.g., suburban and rural North East, Appalachia, and the upper Northwest) have very high rates of prescription drug abuse, measured by three different detection methods. These results should help focus regionally specific, detailed studies to understand the reasons for this disproportionate regional representation.

Finally, the distribution of signal sites of prescription opioid abuse is almost the opposite of that which would be seen with heroin.

Collectively, these data indicate that there are a number of target or signal areas of abuse that have been clearly and convergently identified by the key informant, diversion, and poison control networks. The next step is underway: to obtain as much information as possible to develop unique intervention strategies, individually tailored to each area.

In addition to the big picture view presented in Figures 1 and 2, the RADARS® systems can also be successfully used to detect the magnitude of

abuse and relative abuse levels of opioid analgesics. To illustrate these points, we will use data from the key informant network, because this network is the most well-established, a great deal of data were previously generated for tramadol, and we now have 14 quarters of data for a large number of drugs. The diversion and poison control data correlate extremely well with the key informant data described below, but are not presented here because of space considerations and the fact that they are less well-developed than the key informant network.

Figure 3 shows the total number of persons who filled a prescription for any of the six most commonly used opioid analgesics during the period from quarter 1, 2002 through the end of quarter 2, 2005. It is obvious that hydrocodone products are by far the most prescribed opioid analgesics in the country and their use is significantly expanding, reaching over 4 million people per calendar quarter by the end of the second quarter of 2005, which was nearly twice that found in 2002–2003. Next, by a substantial margin, were the remainder of the drugs, rank ordered: IR oxycodone > ER oxycodone > morphine > methadone > hydromorphone. Although the latter drugs were used much less frequently than hydrocodone, there was for the most part growth in prescriptions for all drugs over the course of this study. It is noteworthy that the introduction of generic ER oxycodone only modestly increased the total prescriptions for these products.

Figure 4 shows the abuse data expressed in three ways: first, as the raw number of abuse cases

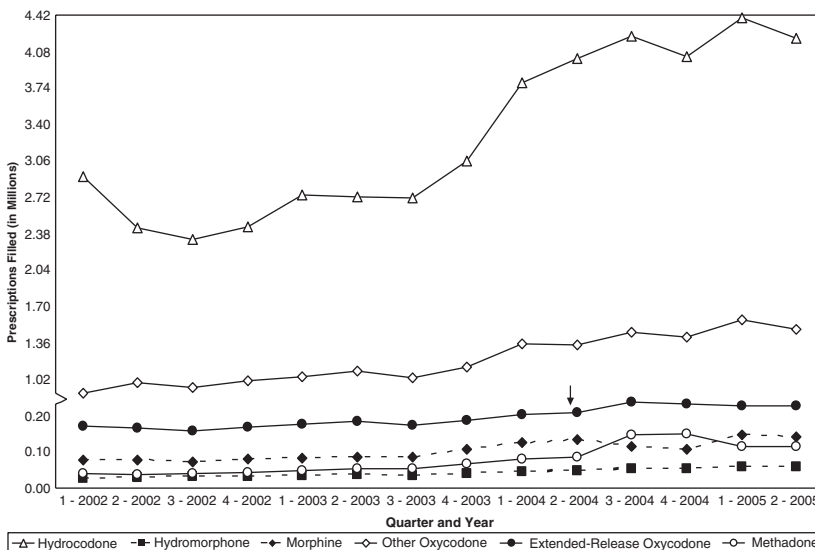


Figure 3 The total number of persons filling a prescription from January 1, 2002, through the end of the second quarter of 2005.

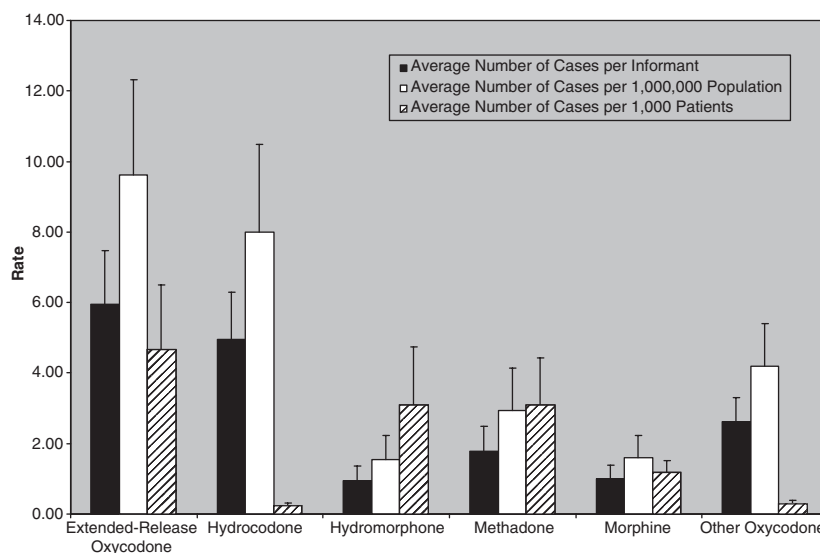


Figure 4 The average (mean \pm SEM) number of abuse cases per informant, per 1,000,000 population, or per 1,000 patients filling a prescription for the drugs was indicated on the X-axis.

per key informant for all 14 quarters from 2002 through the second quarter of 2005; second, as abuse ratios defined as cases/1,000,000 people in each ZIP code; and third, as abuse cases/1,000 persons filling prescriptions. Based on the first two metrics, it is evident that ER oxycodone and hydrocodone products are by far the most abused drugs of all those studied. The rest of the drugs were much less intensely abused and were rank ordered as follows: IR oxycodone > methadone > hydromorphone > morphine.

The rate data expressed as cases/1,000 patients show an entirely different rank ordering of abuse than the sheer numbers alone. In fact, only the ranking of ER oxycodone products was the same whether rates or sheer number of cases was used as the unit of measure. For all other drugs, the rates of abuse were very different than the numbers alone, particularly for hydrocodone and IR oxycodone products. These are the most frequently prescribed drugs (Figure 3) and, as a result, the denominator is very large resulting in a very low rate of abuse, which is in direct opposition to the rank order of drugs by abuse cases alone. Conversely, because of relatively limited exposure via prescriptions filled, the rates of methadone and hydromorphone are higher than the numerator data alone would indicate.

Discussion of Key Informant Data

The preliminary results of the key informant studies, which agree closely with the diversion and poison control data, indicate that the use of opioid analgesics, expressed as the number of persons filling prescriptions, is extensive in this country and

has grown at a fairly rapid pace in the period covered by this report: 2002–2005. Thus, the market for opioid analgesics now exceeds at least 6 million patients per quarter in 2005, which presumably means one of two things: first, the pool of patients requiring opioid analgesics for moderate to severe pain has increased; or second and more likely, the appropriate treatment of pain for existing patients has become more accepted. Notably, despite enormously bad publicity nationwide concerning the potential abuse of prescription opioid analgesics, particularly for ER oxycodone, physicians apparently are still willing to use all opioid analgesics in the treatment of pain. Given that there are estimates that over 40 million people suffer from pain that could be managed [29,30], there would appear to be room for even more growth. Furthermore, it is important to note that much of this increase in prescriptions from physicians would seem to reflect medically appropriate use, but this conclusion does come with a caveat: we used persons filling prescriptions as a proxy for pain patients. It is almost certain that a small percentage of these people are not in fact pain patients, but rather, prescription opioid users/abusers who forged prescriptions, doctor-shopped, or scammed doctors for prescriptions. We have no way of discerning which of these 6 million people may, in fact, not be therapeutic users of the drugs for which they have prescriptions, but it seems reasonable to conclude that it is a very small percentage of the total population.

The rank order of abuse found in this article shows that ER oxycodone products, hydromorphone, and methadone are the most intensely

abused prescription opioid analgesics when the data are corrected for degree of exposure and rates are calculated as cases/1,000 prescriptions filled. If, on the other hand, one uses the sheer number of abuse cases, hydrocodone ranks as high as ER oxycodone. This observation would very likely coincide with what legal authorities and professionals in treatment facilities would list as the number one drug of abuse in their community. However, this conclusion is based on the sheer numbers of abuse cases and fails to consider exposure, which in the case of hydrocodone products is huge, at more than 4 million people filling prescriptions in the second quarter of 2005. Given this degree of exposure, the rate of abuse—expressed as cases/1,000 persons filling a prescription—is quite low, which is directly relevant to the all-important risk (abuse)–benefit (appropriate analgesia) analysis, which is required in all assessments of a drug’s safety and efficacy. In this instance, the risk–benefit ratio is quite positive—a very low incidence of abuse relative to its prescribed use to ameliorate pain. This would seem to fully justify the designation of hydrocodone products as Schedule III drugs under the CSA, even though there are many more abuse cases than for most other drugs. There is a striking parallel between hydrocodone products and NSAIDs (see above), where the number of adverse events is very high, but their efficacy and very high exposure rates yields a positive risk–benefit ratio.

Despite the limitations in using numerator data alone, we concede that it is probably appropriate, as the FDA has concluded, that multiple measures of abuse should be used in evaluating the abuse potential of drugs, including the gross number of cases. Thus, we have also presented these data with the realization that the sheer number of abuse cases should not be used exclusively or inappropriately by regulatory agencies in scheduling decisions, which in turn may discourage physicians’ use of this important class of drugs for pain management.

There are limitations to our studies which need to be considered. Specifically, our process of selection of ZIP code–defined sites we monitored was nonrandom, but rather was based on recruiting the informants to participate, presumably because of their expertise and interest in studying abuse. Thus, our studies are biased to regions where prescription drug abuse was and is high, which might not necessarily apply to the nation as a whole. However, it needs to be stressed, as reported in our earlier studies [7], that the abuse of opioid

analgesics is nondetectable in over half of the three-digit ZIP codes we surveyed and the rates are very low in most others. Thus, our sample may not be as biased as it would appear.

Another potential limitation of our approach is the variability of response rates to the questionnaires, which could influence the results. With regard to this point, the response rate for the first 14 quarters in the key informant study was, on average, 67%. We eliminated all informants if they failed to respond to the survey in three or more consecutive quarters, and replaced them with new informants. Thus, all respondents had to have returned 11 of 14 questionnaires. In many cases, informants responded every quarter, but often their responses would be erratic. To accommodate this, we were careful to express all data as average responses per informant. In addition, we analyzed the data by frequency of responding for uneven reporting (see [5–7], for further discussion) and found no significant statistical differences in the trends depicted in the data. Nevertheless, the lack of consistent reporting is a troublesome, but probably insoluble, problem.

Conclusions

RADARS[®] was established in part to accomplish one stated purpose and one more subtle one. The stated purpose was to assess regionally specific patterns of abuse in a time-dependent fashion which would lead to characterization of abuse. This, in turn, would lead to the development of more focused studies to investigate the nature and characteristics of abuse. Based upon this knowledge, intervention strategies to reduce abuse or manage the risk of abuse could be developed. In so doing, this would make RADARS[®] a prototypic risk-management program. We believe that the data we have presented validate that the RADARS[®] detection systems can indeed measure quickly and sensitively pockets of regionally specific abuse. Furthermore, not only do the three systems overlap in many cases, but one or more extend to areas not necessarily covered by the others. We conclude that RADARS[®], therefore, can produce highly meaningful data on the regional distribution of prescription drug abuse.

The next steps beyond signal detection have not yet been taken, i.e., focused studies in key areas where abuse is overrepresented, which would lead to unique intervention strategies. As a result of these interventions, it is hypothesized that the abuse will decline. Should this occur, it would

appear that RADARS[®] would fulfill the requirements for the now mandated risk-management programs necessary for all new drugs.

As a matter of concern, it needs to be emphasized that the FDA requires risk-management programs for approval of all *new* drugs, but, for reasons unknown, it has not been able to enforce this regulation on generics. What this means, of course, is that once a product goes generic, meaningful abuse data will be impossible to obtain. Why do generics impede the development and implementation of risk-management programs? There are a number of reasons:

First, generic companies are generally resistant to cooperating with any endeavor to track abuse [7], because it is, in fact, costly to provide cases of abuse or data on sales. Furthermore, there is absolutely nothing to be gained by obtaining any data that might document an undesirable side effect and, hence, no reason to participate.

Second, although one could ask the original sponsor to purchase data on the generic, the cost is prohibitive. More importantly, why should the holder of the patent, with what is very often a brief period of exclusivity, shoulder the entire burden of the cost of the program?

Finally, there is considerable effort and associated costs involved in obtaining data from prescription drug abusers concerning whether they use a brand name or generic. Once again this raises the issue of who should be responsible for the costs involved in that effort.

The FDA must come to grips with this issue and mandate that not only the original sponsor, but all subsequent generic manufacturers must participate in a risk-management program. Without this mandate for generics, the entire purpose of risk-management programs, which are presumably intended to protect public health, would be largely unfulfilled.

The issue, of course, is: who should carry the burden for these costs? It is doubtful that NIDA or the FDA would have funding sufficient to meet these needs, nor should they. Pharmaceutical firms may be disinclined to fund intervention studies that could reduce sales of their drugs. In this connection, the authors would strongly support the concept of a recently proposed independent Center for Post-Marketing Studies [31].

The unstated goal of RADARS[®] was to provide systematic data that would refute claims of an “epidemic” of ER oxycodone abuse. From this perspective, our initial results have not met these anticipated outcomes. Collectively, our data sug-

gest that ER oxycodone abuse is now widespread and common in this country, with an upward trend, which needs to be carefully monitored. These results seem to support preliminary findings in federally supported surveys and extensive media coverage [7,13,29,30,32] that ER oxycodone abuse is substantial. However, it needs to be emphasized that this abuse seems to be part of a general pattern of increasing prescription drug abuse, because we found no ZIP code in which ER oxycodone was the sole drug abused and nearly all drugs showed upward trends of abuse over time [6,7,16].

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