Evaluation of Risk Evaluation and Mitigation Strategy (REMS) Programs: Comments for Docket No. FDA-2009-N-0143

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RADARS® System
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BACKGROUND

The Food and Drug Administration Amendment Act of 2007 authorizes the FDA to require pharmaceutical companies submitting drug-related applications and with approved products on the market to submit a proposed Risk Evaluation and Mitigation Strategy (REMS). Further, the FDA has announced that companies producing certain extended-release and long-acting opioid products will be required to develop a single, class-wide REMS.

In this document we present a framework for REMS assessment based on nine principles derived from our experiences in post-marketing surveillance and evaluation of other public health interventions for problems with prescription controlled substances (see Appendix A). The RADARS® System can provide baseline data for many (but not all) of these indicators, and we intend to continue collecting data for the foreseeable duration during REMS implementation. However, additional data collection and analysis will be required for a thorough evaluation of the REMS, and these are beyond the scope of this submission to the docket. Following from the articulated principles, most of the data analyses presented in this submission compare REMS opioids to non-REMS prescription opioids monitored by the RADARS® System[1], although data on heroin are presented where appropriate.

The baseline data presented in this docket submission are intended to serve as a public *a priori* record of the extent and nature of the abuse, misuse and diversion of prescription opioids in the United States as of the end of 2009. Depending on the precise date of REMS implementation, we will update the data to reflect the most current baseline data available. Below, we present data on: 1) time trends and medical consequences of the misuse, abuse and diversion of REMS opioids versus non-REMS opioids, 2) pediatric exposures, 3) therapeutic errors, and 4) concurrent use of heroin and prescription opioids. We have assumed that readers will have a basic familiarity with the RADARS® System – additional information on the system has been published[2][3][4].

ABOUT THE RADARS® SYSTEM

The Researched Abuse, Diversion and Addiction Related Surveillance (RADARS®) System was initiated in 2002 and is owned and operated independently by Denver Health and Hospital Authority, a not-for-profit safety net hospital. The RADARS® System provides continuous surveillance of the abuse, misuse, and diversion of opioids and stimulants throughout the United States (www.RADARS.org) and is composed of six unique programs (Drug Diversion, Poison Center, Survey of Key Informants' Patients, Opioid Treatment, Impaired Health Care Worker,

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[1] REMS Opioids: Methadone, extended-release hydromorphone once launched, extended release morphine, extended-release oxycodone, extended-release oxymorphone, transdermal fentanyl. Non-REMS Opioids: Buprenorphine, hydrocodone, tramadol, immediate-release hydromorphone, immediate-release morphine, immediate-release oxycodone, immediate-release oxymorphone, transbuccal fentanyl, fentanyl injectable products.

[2] Schneider, M.F., Bailey, J.E., Cicero, T.J., Dart, R.C., Indiardi, J.A., Parrino, M., and Munoz, A. (2009). Integrating nine prescription opioid analgesics and/or four signal detection systems to summarize statewide prescription drug abuse in the United States in 2007. Pharmacoepidemiology and Drug Safety, (9), 778-790.

[3] Dasgupta, N., Bailey, J.E., Cicero, T.J., Inciardi, J.A., Parrino, M., Rosenblum, A., and Dart, R.C. (2009). Post-marketing surveillance of methadone and buprenorphine in the United States. Pain Medicine, (In Press).

[4] Bailey, J.E., Campagna, E., and Dart, R.C. (2009). The underrecognized toll of prescription opioid abuse on young children. Annals of Emergency Medicine, 53, 419-424.

and College Survey). These programs represent national data-collection systems, developed to capture information on individuals along various stages of the drug dependence pathway, and provide surveillance on national drug use trends (Appendices B, C, and D). In keeping with the Principle 2 in the framework (Appendix A), we also present data on opioid medications that are not included in the class-wide REMS proposal by FDA.

Quarterly rates for surveillance purposes are calculated by using counts from the six unique programs as numerators, and dividing them by the total population in the 3-digit ZIP code or the number of unique recipients of dispensed drug (URDD).

The URDD is the number of unique individuals receiving dispensed prescriptions for a drug in a given quarter in a given 3-digit ZIP code, provided by SDI (Plymouth Meeting, PA). SDI captures prescription reimbursement and payment information from numerous data suppliers including chain drug stores, claims processors such as switch houses, and other data aggregators. To a lesser extent SDI also captures prescription data from mail order pharmacies and specialty pharmacies. SDI estimates that roughly half of all retail transactions in the US are captured. URDDs are projected estimates derived from models used to estimate universe size, which employ a complex methodology that segments the US market into 814 projection zones and then further stratifies each zone by method of payment (e.g., third party, Medicaid, cash). This methodology is further supplemented by segmenting the market into 9 geographic census regions and, within these regions, stratifying by class of trade (e.g., pharmacy chains, independent pharmacies, mass merchandisers, food stores).

The two rates calculated during routine surveillance are the population rate and the URDD rate, as defined below.

$$\text{Population Rate} = N_{ptzd} / D_z$$
$$\text{URDD Rate} = N_{ptzd} / U_{tzd}$$

Where:

N = case count
D = population based on US census
U = unique recipient of dispensed drug

And where:

p = RADARS® System program
t = time, in calendar quarters
z = 3-digit ZIP code
d = drug formulation

The interpretation of the population rate is the absolute burden on public health incurred from the abuse, misuse and diversion of the drug. The interpretation of the URDD rate is the drug-specific unintended adverse consequences of medical availability, accounting for the amount of drug in use. *For the REMS evaluation both rates must be used in tandem; the intended outcome of the REMS would result in a decrease in the URDD rate for REMS opioids, indicating that the use of these drugs has gotten safer, without a corresponding increase in the population rate for non-REMS opioids, suggesting that a balloon effect has not shifted misuse, abuse and diversion to non-REMS opioids.*

SUMMARY OF FINDINGS

Given the interpretations of the two rates above, our analysis of RADARS® System data indicates that the opioid medications included in the REMS (i.e., long-acting and extended-release opioids) have higher rates of abuse, misuse, and diversion associated with them than non-REMS opioids monitored by the RADARS® System, when rates are calculated using the URDD denominator (Figure 1). By contrast, when the population denominator is used, in all of the RADARS® System Programs the outpatient use of non-REMS opioids in the general population is associated with greater levels of adverse unintended consequences than REMS opioids (Figures 6, 7). Pursuant to Principle 2 (Appendix A), these findings in part corroborate the FDA's decision to include these particular drugs in the REMS. However, the non-REMS opioids appear to exert a greater overall burden on public health than the REMS opioids. Figures and detailed descriptions are found in Appendix E

Specifically, in RADARS® System 2009 data, REMS opioids were associated with more tampering compared to non-REMS opioids (Figure 2), more severe medical consequences from acute poisoning exposure events (Figure 3), including pediatric exposures (Figure 4), greater levels of dependence symptoms (Figure 5), and more criminal diversion (Figure 6).

In keeping with Principle 5 (Appendix A), it should be noted that the abuse, misuse, and diversion of non-REMS opioids results in a greater absolute burden on public health when rates are calculated using population denominators (e.g., per 100,000 population per quarter). There are far greater numbers of cases of drug diversion and poison center calls for non-REMS opioids than REMS opioids (Figures 6 and 7). While the rates for the REMS opioids have mostly held steady during the previous decade, there is a moderately increasing number of poison center calls for non-REMS opioids (Figure 7).

While the REMS are intended to reduce the adverse consequences of long-acting and extended-release opioids, there may be a predictable shift to non-REMS opioids in medical practice and among street level users. In the fourth quarter of 2009, the proportions of use of prescription opioids to get high among enrollees to substance abuse treatment programs were: 9% REMS opioids only, 5% non-REMS opioids only, 26% REMS opioids and non-REMS opioids (Figure 9). There may also be a decrease in the amount of REMS opioids used in medical practice upon implementation of the REMS (Principle 4, Appendix A). Therefore it is important to measure the effects of the REMS using both URDD rates and population rates.

Reflecting Principle 8 (Appendix A), none of the REMS opioids are labeled for use in the pediatric population (less than six years-old), and exposures in this population are a specific cause for concern. Pediatric exposures involving non-REMS opioids occur with greater frequency than those involving REMS opioids; however, REMS opioids account for more serious medical outcomes (moderate effect, major effect, potentially toxic) than non-REMS pediatric opioid exposures (Figure 4). In 2009, the Poison Center Program of the RADARS System recorded 5,954 unintentional exposures to non-REMS opioids only and 831 unintentional exposures to REMS opioids alone or in combination with non-REMS opioids. Assessment of pediatric effects is crucial to understanding the effects of opioid products.

One intention of the REMS is to reduce therapeutic errors[5] among opioid patients. Elderly patients are the ones most likely to be prescribed REMS opioids, and are also suspected to be the most likely to make errors with medications; these types of events can be monitored through RADARS® System poison centers to determine if the REMS is having its intended effect, pursuant to Principle 8 (Appendix A). Since 2005, the proportion of poison center calls for therapeutic errors in older adults has steadily increased for non-REMS opioids and has increased for REMS opioids since 2008 (Figure 10).

In keeping with Principles 2 and 5 (Appendix A), there is a specific concern that there may be a shift to using heroin use among dependent non-medical prescription opioid users due to a lack of street availability of diverted REMS opioids, i.e., the balloon effect[6]. This phenomenon can be monitored using RADARS® System data from the Opioid Treatment Program, which collects information on recent use to get high among enrollees in drug treatment programs. In the fourth quarter of 2009, the proportions of opioid use to get high were as follows: 23% heroin only, 9% REMS opioids only, 8% REMS opioids and heroin (Figure 9). If a shift in these proportions towards more heroin use is observed after REMS implementation, the hypothesis of the balloon effect would be supported but would need to be interpreted in conjunction with other sources of data.

CONCLUSION

The baseline data presented in this submission are intended to serve as a public record of the extent and nature of the abuse, misuse, and diversion of prescription opioids in the United States before the implementation of the class-wide REMS. This document supports, but is independent of, the Industry Working Group's (IWG) REMS assessment plan. The RADARS® System will continue collecting data through the life cycle of the REMS.

Appendix A: Principles of REMS Assessment

The assessment of opioid REMS must follow basic principles of surveillance and public health as defined below. An evaluation framework that is designed to monitor both the intended consequences (reduction in the unintended consequences of outpatient opioid use) and potential unintended consequences of the proposed opioid REMS should be utilized.

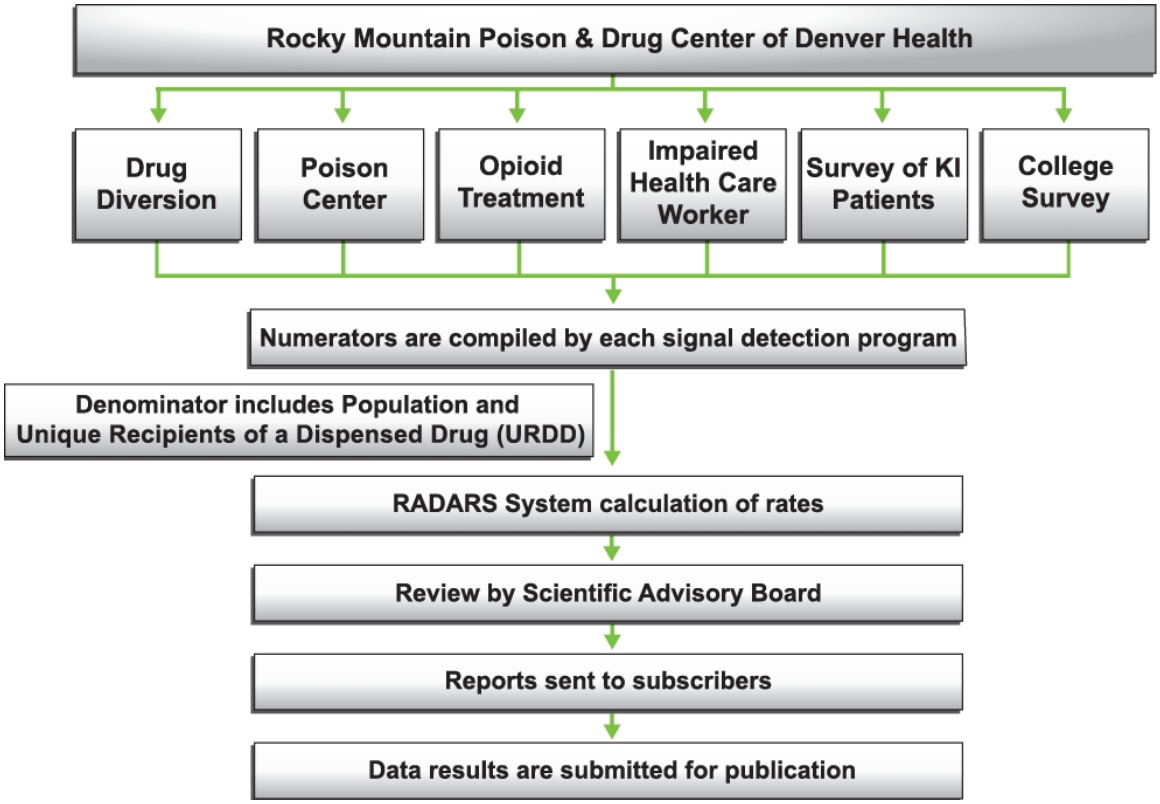
1. Evaluation should include the effects of opioid REMS on misuse, abuse, addiction, diversion and overdose
2. All types of opioid products must be included in the evaluation of the REMS: branded and generic as well as extended-release and immediate-release.
    a. As demonstrated in Figure 3, deaths are associated with intentional exposures to both REMS and non-REMS opioids (75 associated with REMS opioids or REMS and non-REMS opioids in 2009; 120 associated with non-REMS opioids). However, as demonstrated in Figure 3, the proportion of intentional exposures to

[5] Defined as an unintentional deviation from a proper therapeutic regimen that results in the wrong dose, incorrect route of administration, administration to the wrong person, or administration of the wrong substance.

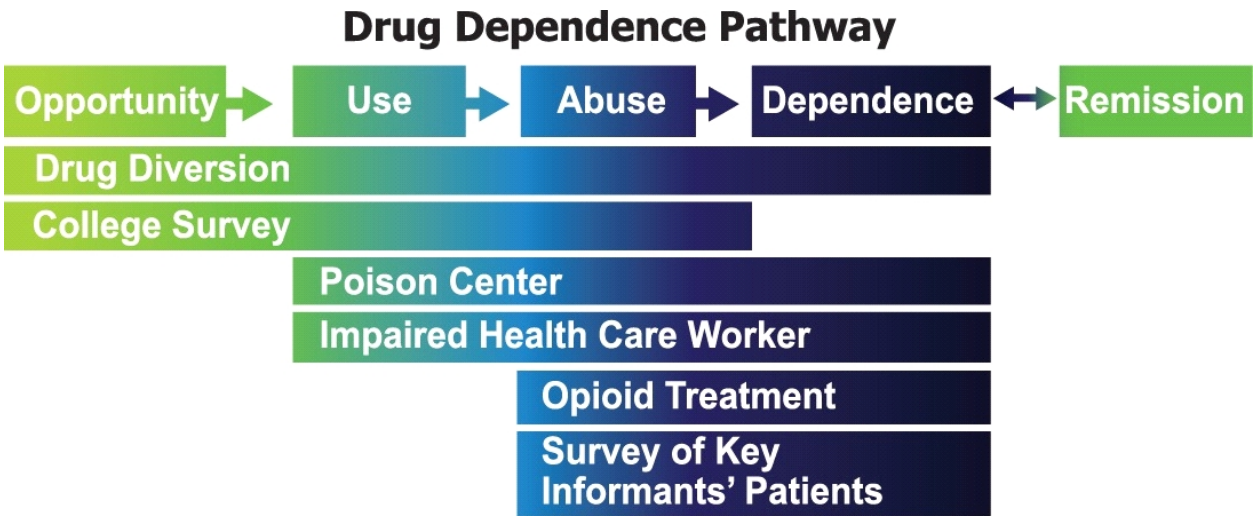
[6] Degenhardt, L., Roxburgh, A., van Beek, I., Hall, W.D., Robinson, M.K.F., Ross, J., and Mant, A. (2008). The effects of the market withdrawal of temazepam gel capsules on benzodiazepine injecting in Sydney, Australia. Drug Alcohol Review, 27, (2), 145-51.

REMS opioids or REMS opioids plus non-REMS opioids is higher than that for non-REMS opioids.
   b. Furthermore, illicitly manufactured opioids (e.g., heroin) should be included as a comparator.
3. The risks unique to specific formulations of prescription opioids must be measured separately (e.g. patch, tamper resistant, etc).
4. The evaluation should be comprehensive, including both the benefits and risks.
   a. Access to opioid medications by existing pain patients and appropriate potential candidates for opioid treatment must be evaluated.
   b. The prescribing of alternative forms of analgesic therapies and their attendant adverse events must be included (reinforcing the need to monitor immediate-release formulations).
   c. Quality-of-life and functioning must be measured in patients already receiving opioid pharmacotherapy; these factors must also be measured in patients with degenerative painful conditions who would have received extended-release or long-acting opioids in the absence of the proposed REMS (i.e., the counterfactual model of determining causality in epidemiology).
5. Multiple perspectives on the natural history of substance use disorders are needed to assess the proposed opioid REMS, measured separately but in parallel.
6. The impact of the opioid REMS on opioid treatment programs must be evaluated.
7. Assessments of opioid REMS must be conducted on pre-scheduled basis (required by Section 505-1).
8. Outcomes in specific populations must be monitored (e.g. young children, adolescents, etc). The effects of opioid REMS on patients *and* non-patients (e.g. abuse) must be included.
9. Evaluation must assess whether existing disparities in access to opioid pain medications by vulnerable minorities is not exacerbated.

Appendix B: **RADARS® System Structure**



Appendix C: RADARS® System Programs and the Drug Dependence Pathway

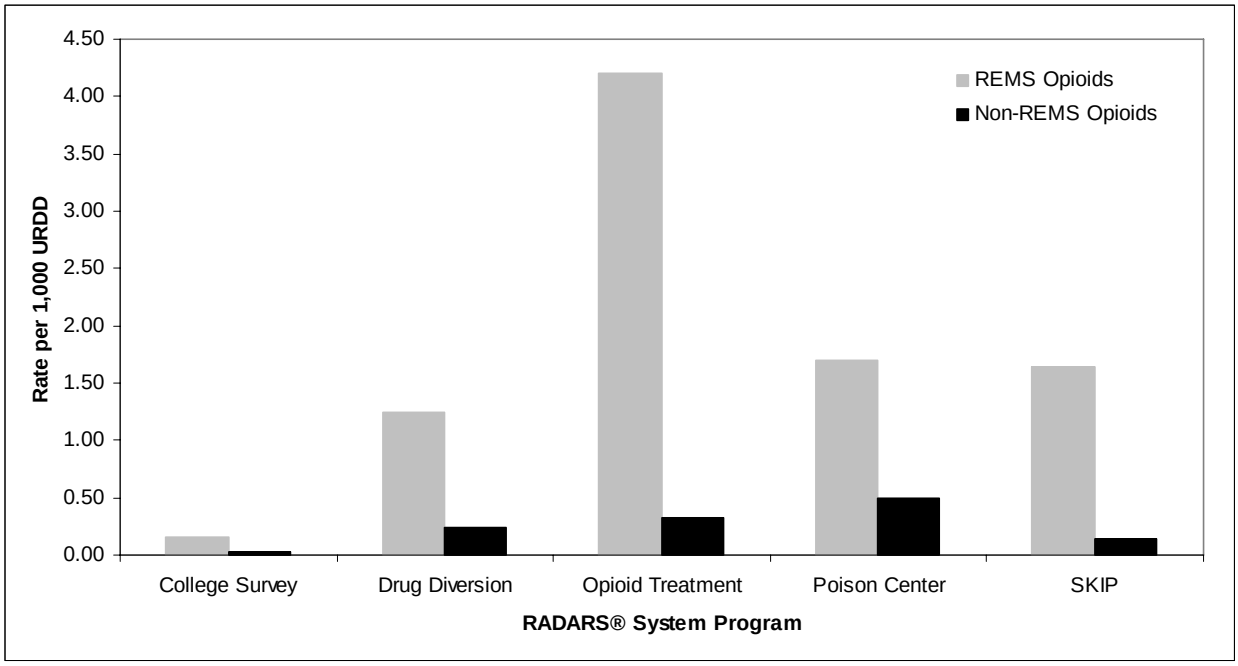


Appendix D: Characteristics of RADARS® System Programs, 2009 [1]IHCW surveillance program is a subset of DD, PC, OT and SKIP programs; [2]American Association of Poison Control Centers' National Poison Data System; [3]Drug Diversion reporters are the survey respondents. The age and gender of those diverting prescription drugs are not collected in the DD Program's quarterly reporting tools.

	Drug Diversion (DD)	Poison Center (PC)	Opioid Treatment (OT)	Impaired Health Care Worker[1] (IHCW)	Survey of Key Informants' Patients (SKIP)	College Survey (CS)
Year of Implementation	2002	2003	2005	2007	2008	2009
Target Population	Case mentions of prescription drug diversion	Children Adolescents Young Adults Adults Elderly	Opioid dependent persons seeking treatment at public & private opioid treatment programs	Health care workers	Opioid dependent persons seeking treatment at primarily private substance abuse treatment programs	College students
Case Definition	New instances of pharmaceutical diversion investigated by drug diversion units or reported to state regulatory boards	Spontaneous reports of intentional exposure mentions of acute medical events	Self-reported use of prescription or illicit opioids to "get high" in the past 30 days	Self-identified HCW reported in DD, PC, OT or SKIP Programs	Self-reported use of prescription or illicit opioids to "get high" in the past 30 days	Self-reported non-medical use
Frequency of Reporting	Quarterly	Weekly	Weekly	Quarterly	Weekly	Each semester and summer session
Type of Data Collection Tool	Standardized reporting tool	Standardized electronic record[2]	Standardized questionnaire	Subset of other surveillance programs[1]	Expanded OT questionnaire	Standardized web-based questionnaire
Geographical Coverage	295 informants in 50 states 614 3-digit ZIP codes	48 PCs in 44 states 788 3-digit ZIP codes	59 programs in 30 states 326 3-digit ZIP codes	Subset of other programs 477 3-digit ZIP codes	100 Key Informants in 46 states 203 3-digit ZIP codes	7,263 respondents in 50 states 768 3-digit ZIP codes
Mean Age, All Opioids, All Cases – Years (range)	N/A[3]	35.4 (0.01-120.0)	33.3 (17 – 73)	N/A	34.9 (18-82)	25.1 (18 – 43)
Percent Female, All Opioids, All Cases	N/A[3]	53.3	44.0	N/A	47.5	55.1

Appendix E: RADARS® System Figures

Figure 1. RADARS® System Program Rates per 1,000 URDD: 2009



SKIP: Survey of Key Informants' Patients

REMS Opioids: Methadone, extended release hydromorphone once launched, extended release morphine, extended-release oxycodone, extended-release oxymorphone, transdermal fentanyl.

Non-REMS Opioids: Buprenorphine, hydrocodone, tramadol, immediate-release hydromorphone, immediate-release morphine, immediate-release oxycodone, immediate-release oxymorphone, transbuccal fentanyl, fentanyl injectable products.

Quarterly rates for surveillance purposes are calculated by using counts from the six unique programs as numerators, and dividing them by the number of unique recipients of dispensed drug (URDD), which is the number of unique individuals receiving dispensed prescriptions for a drug in a given quarter in a given 3-digit ZIP code, provided by SDI (Plymouth Meeting, PA).

The College Survey Program is an online questionnaire collecting data from self-identified students attending a two- or four-year college, university or technical school at least part-time during the specified sampling period (three times a year corresponding with the end of Fall and Spring semesters and summer break). Each sample is equally distributed across the four geographic regions of the United States and is composed of self-identified students who have agreed to be contacted to complete online surveys. Approximately 2,000 respondents participate in each College Survey launch and are asked to report recreational drug use and non-medical use of prescription opioids, stimulants and muscle relaxants in the previous three months. Cases are assigned to the reported 3-digit ZIP code of the college student's residence during the sampling period.

The Drug Diversion Program is composed of 300 prescription drug diversion investigators or regulatory agencies who are surveyed quarterly and asked to report the number of new diversion cases in that quarter. Cases are defined as the number of new instances of

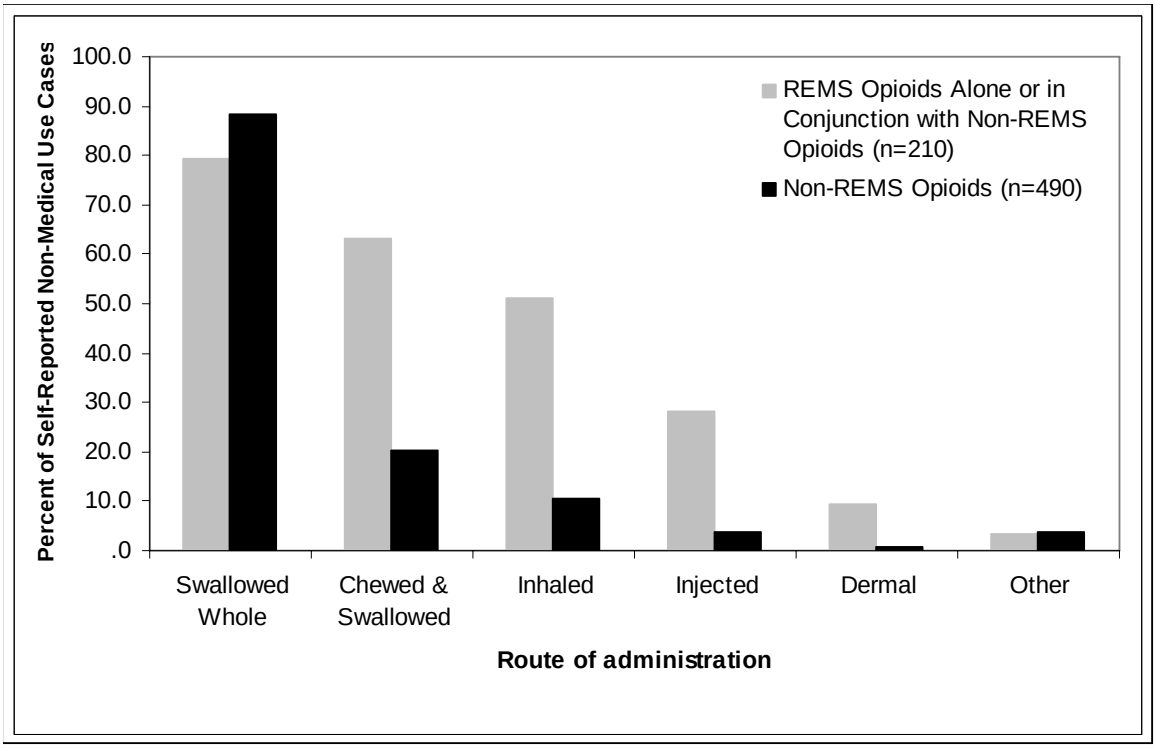
pharmaceutical diversion investigated by the diversion units or reported to the regulatory board during the previous quarter. These must be official cases initiated during the previous quarter. As such, only cases in which there is a new written complaint or report are included. Cases are assigned to the 3-digit ZIP code where the case occurred or, when the 3-digit ZIP code where the case occurred is unknown, are redistributed across the informant's jurisdiction.

The Opioid Treatment Program is composed of 75 participating methadone treatment programs (also known as opioid treatment programs). Patients who are enrolling at these treatment centers are asked to complete an anonymous questionnaire, which includes questions concerning the patient's drugs of choice, drug use in the past month, lifetime drug abuse, age at first use, and the primary source of the abused drugs. The survey also includes questions about demographics, pain, withdrawal and craving. Cases are defined as self-reported use of a prescription or illicit opioid to get high in the past 30 days. Cases are assigned to the reported 3-digit ZIP code of the patient's residence.

The Poison Center Program collects data on all exposures reported to participating poison centers (48 of 60 US poison centers). Spontaneous calls from the public and healthcare professionals are recorded by poison centers using a standardized, electronic data collection system. Participating poison centers send the coordinating center cases for the RADARS System drugs of interest on a weekly basis. Each case undergoes a rigorous quality control process. Abuse and misuse cases are defined as any intentional exposure (intentional abuse, intentional misuse, suspected suicidal, intentional unknown, and withdrawal) managed by participating poison centers for the products of interest. Cases are assigned to the reported 3-digit ZIP code of the exposed individual's residence.

The Survey of Key Informants' Patients Program (SKIP) Program is composed of patients in treatment facilities recruited by Key Informants (addiction specialists, treatment counselors, and others professionals at treatment centers) to complete an anonymous questionnaire which includes questions concerning the patient's drug of choice, drug use in the past month, lifetime drug abuse, age at first use, and the primary source of the abused drugs. Cases are defined as self-reported use of a product in the past 30 days. Cases are assigned to the reported 3-digit ZIP code of the patient's residence.

Figure 2. RADARS(R) System College Survey Program, Reported Administration Routes by Drug Type: 2009



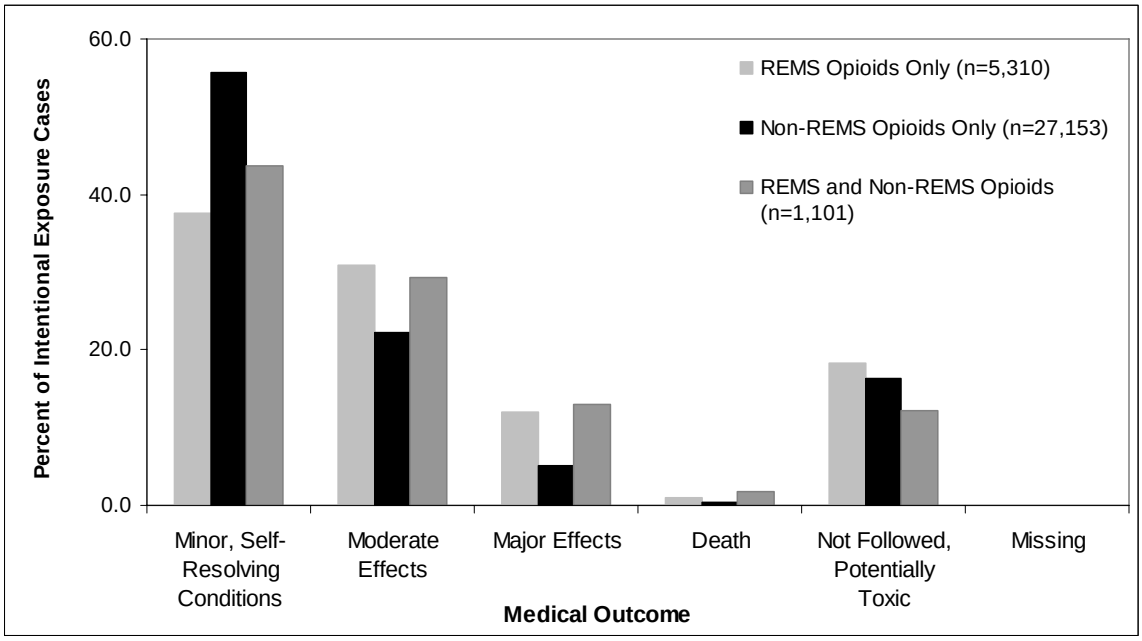
REMS Opioids: Methadone, extended release hydromorphone once launched, extended release morphine, extended-release oxycodone, extended-release oxymorphone, transdermal fentanyl.

Non-REMS Opioids: Buprenorphine, hydrocodone, tramadol, immediate-release hydromorphone, immediate-release morphine, immediate-release oxycodone, immediate-release oxymorphone, transbuccal fentanyl, fentanyl injectable products.

The College Survey Program is an online questionnaire collecting data from self-identified students attending a two- or four-year college, university or technical school at least part-time during the specified sampling period (three times a year corresponding with the end of Fall and Spring semesters and summer break). Each sample is equally distributed across the four geographic regions of the United States and is composed of self-identified students who have agreed to be contacted to complete online surveys. Approximately 2,000 respondents participate in each College Survey launch and are asked to report recreational drug use and non-medical use of prescription opioids, stimulants and muscle relaxants in the previous three months. Cases are assigned to the reported 3-digit ZIP code of the college student's residence during the sampling period.

Data represented above were collected in response to the following survey question: "You indicated that you used X prescription opioid drug during the last three months. From the list below, please select **all** answers that apply to the method in which you used X. If more than one method was used to take X, please **select all answers that apply**." Percentages shown may sum to greater than 100 percent as responses are not limited to one per participant.

Figure 3. RADARS® System Poison Center Program Intentional Exposures, Associated Medical Outcome: 2009



Intentional Exposures: Suspected Suicidal, Intentional Misuse, Intentional Abuse, Intentional Unknown, Withdrawal

Minor, Self-Resolving Conditions: no effect, minor effect, not followed – nontoxic, not followed – minimal clinical effects, unrelated effect, confirmed non-exposure.

REMS Opioids: Methadone, extended release hydromorphone once launched, extended release morphine, extended-release oxycodone, extended-release oxymorphone, transdermal fentanyl.

Non-REMS Opioids: Buprenorphine, hydrocodone, tramadol, immediate-release hydromorphone, immediate-release morphine, immediate-release oxycodone, immediate-release oxymorphone, transbuccal fentanyl, fentanyl injectable products.

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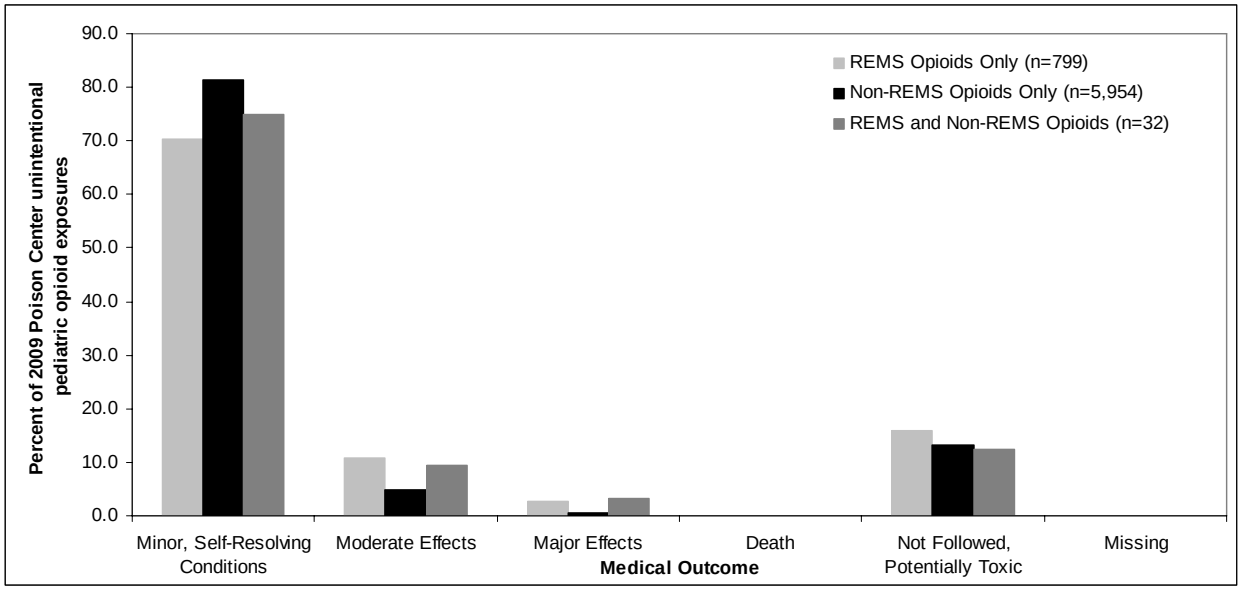
Figure 4. RADARS® System Poison Center Program Unintentional General Opioid Exposures, Associated Medical Outcomes in Young Children (<6 Years): 2009



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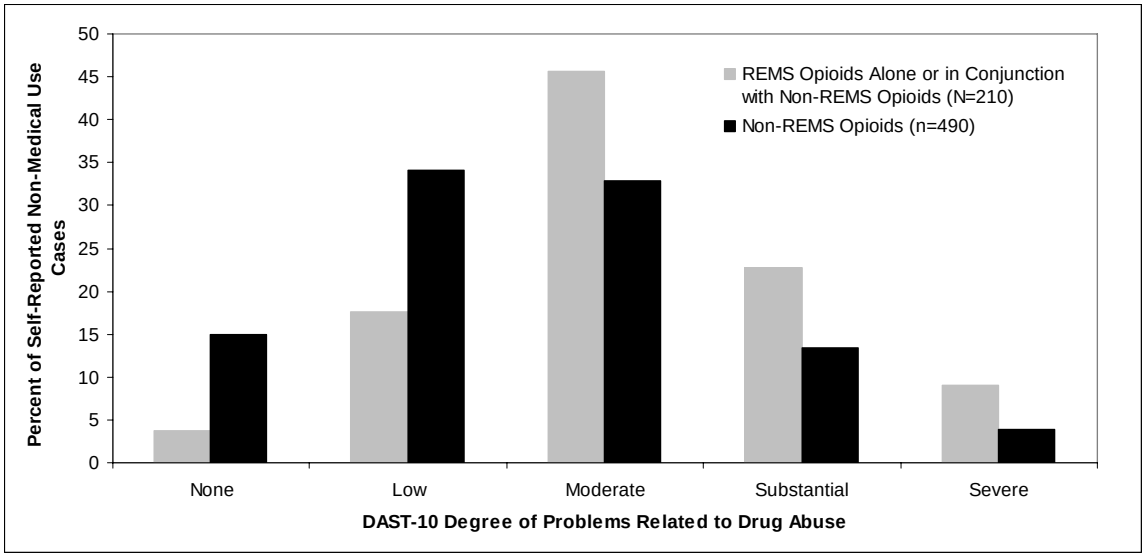
The data presented in this figure represent unintentional general exposures (defined as an unintentional exposure resulting from an unforeseen or unplanned event) which occurred in children less than six years old.

Figure 5. RADARS® System College Survey Program Non-Medical Use, DAST-10 Scores: 2009



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The Drug Abuse Screening Test (DAST) – 10 was designed to be a brief, standardized instrument for assessing the degree of problems related to drug abuse. DAST-10 scores range from zero (no degree of problem related to drug abuse) to 10 (severe degree of problem related to drug abuse)[7].

[7] Skinner, H.A. (1982). The Drug Abuse Screening Test. Addictive Behaviors, 7, 363-371.

Figure 6. RADARS System Drug Diversion Program Rate per 100,000 Population: 2006 – 2009

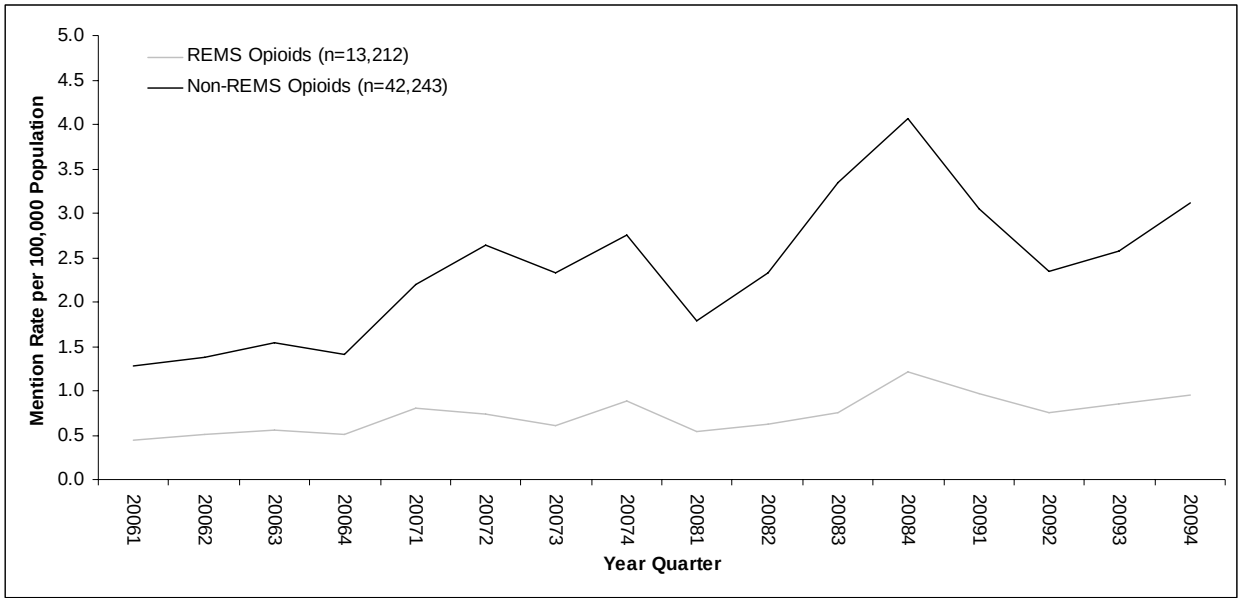

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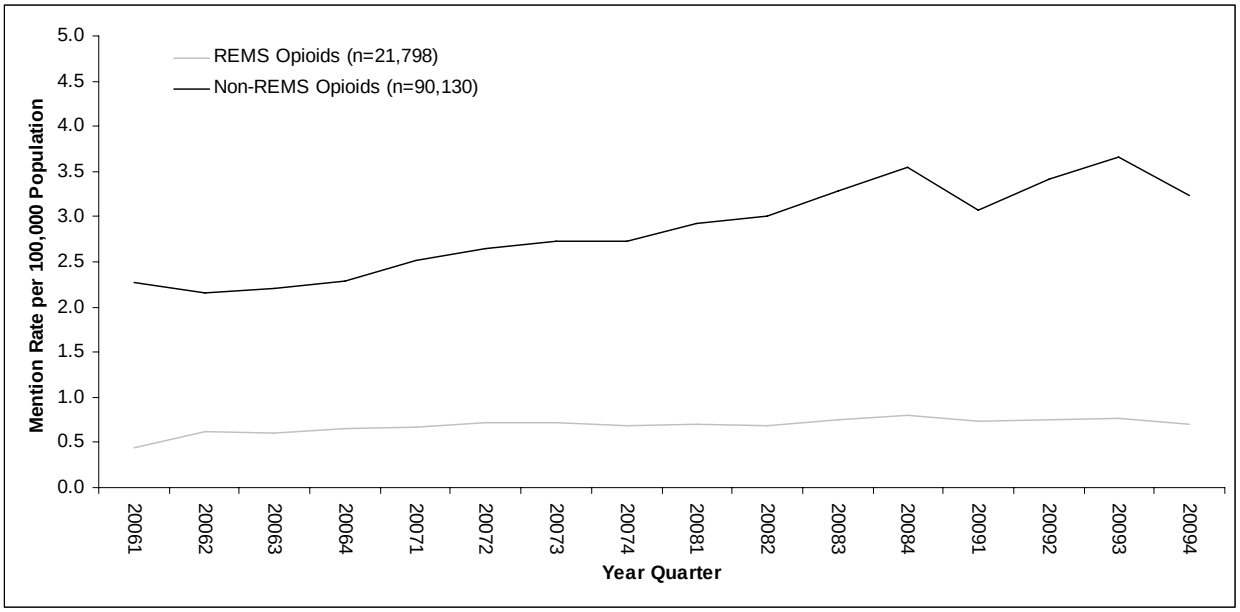
Figure 7. RADARS System Poison Center Program Intentional Exposure Rate per 100,000 Population: 2006 – 2009



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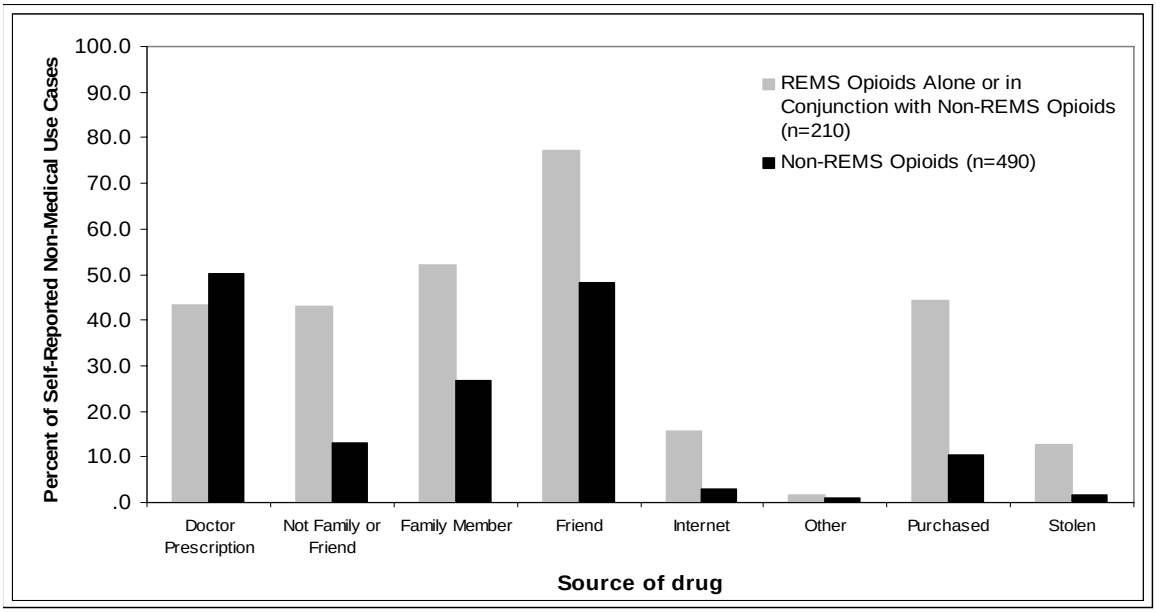
Non-REMS Opioids: Buprenorphine, hydrocodone, tramadol, immediate-release hydromorphone, immediate-release morphine, immediate-release oxycodone, immediate-release oxymorphone, transbuccal fentanyl, fentanyl injectable products.

Quarterly rates for surveillance purposes are calculated by using case counts from the Poison Center program as the numerator, and dividing them by the US 2000 Census Population for each year quarter.

The Poison Center Program collects data on all exposures reported to participating poison centers (48 of 60 US poison centers). Spontaneous calls from the public and healthcare professionals are recorded by poison centers using a standardized, electronic data collection system. Participating poison centers send the coordinating center cases for the RADARS System drugs of interest on a weekly basis. Each case undergoes a rigorous quality control process. Abuse and misuse cases are defined as any intentional exposure (intentional abuse, intentional misuse, suspected suicidal, intentional unknown, and withdrawal) managed by participating poison centers for the products of interest. Cases are assigned to the reported 3-digit ZIP code of the exposed individual's residence.

Figure 8. RADARS® System College Survey Program, Reported Drug Sources: 2009



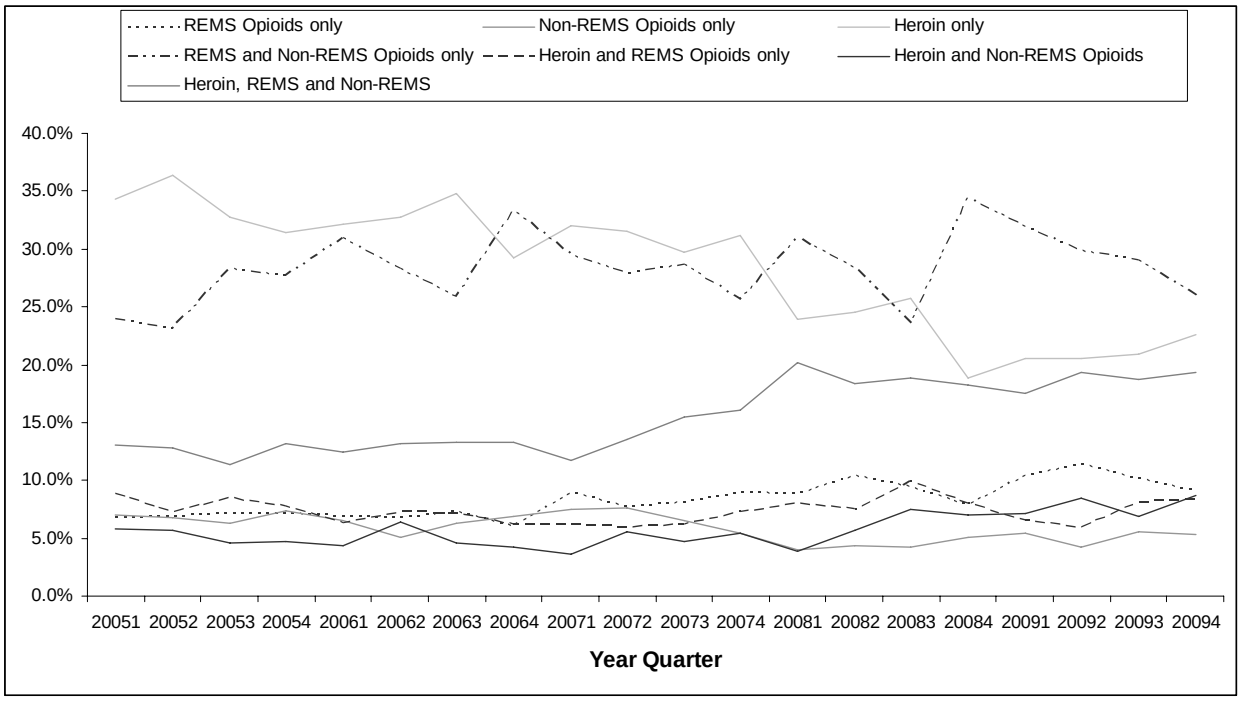
REMS Opioids: Methadone, extended release hydromorphone once launched, extended release morphine, extended-release oxycodone, extended-release oxymorphone, transdermal fentanyl.

Non-REMS Opioids: Buprenorphine, hydrocodone, tramadol, immediate-release hydromorphone, immediate-release morphine, immediate-release oxycodone, immediate-release oxymorphone, transbuccal fentanyl, fentanyl injectable products.

The College Survey Program is an online questionnaire collecting data from self-identified students attending a two- or four-year college, university or technical school at least part-time during the specified sampling period (three times a year corresponding with the end of Fall and Spring semesters and summer break). Each sample is equally distributed across the four geographic regions of the United States and is composed of self-identified students who have agreed to be contacted to complete online surveys. Approximately 2,000 respondents participate in each College Survey launch and are asked to report recreational drug use and non-medical use of prescription opioids, stimulants and muscle relaxants in the previous three months. Cases are assigned to the reported 3-digit ZIP code of the college student's residence during the sampling period.

Data represented above were collected in response to the following survey question: "You indicated that you used X prescription opioid drug during the last three months. From the list below, please select **all** answers that apply to the method in which you obtained the prescription stimulant drug. If you obtained it from more than one source, please **select all answers that apply**." Percentages shown may sum to greater than 100 percent as responses are not limited to one per participant.

Figure 9. RADARS® System Opioid Treatment Program, Proportions of Cases Involving REMS Opioids, Non-REMS Opioids and Heroin, alone and in combination: 2005 – 2009

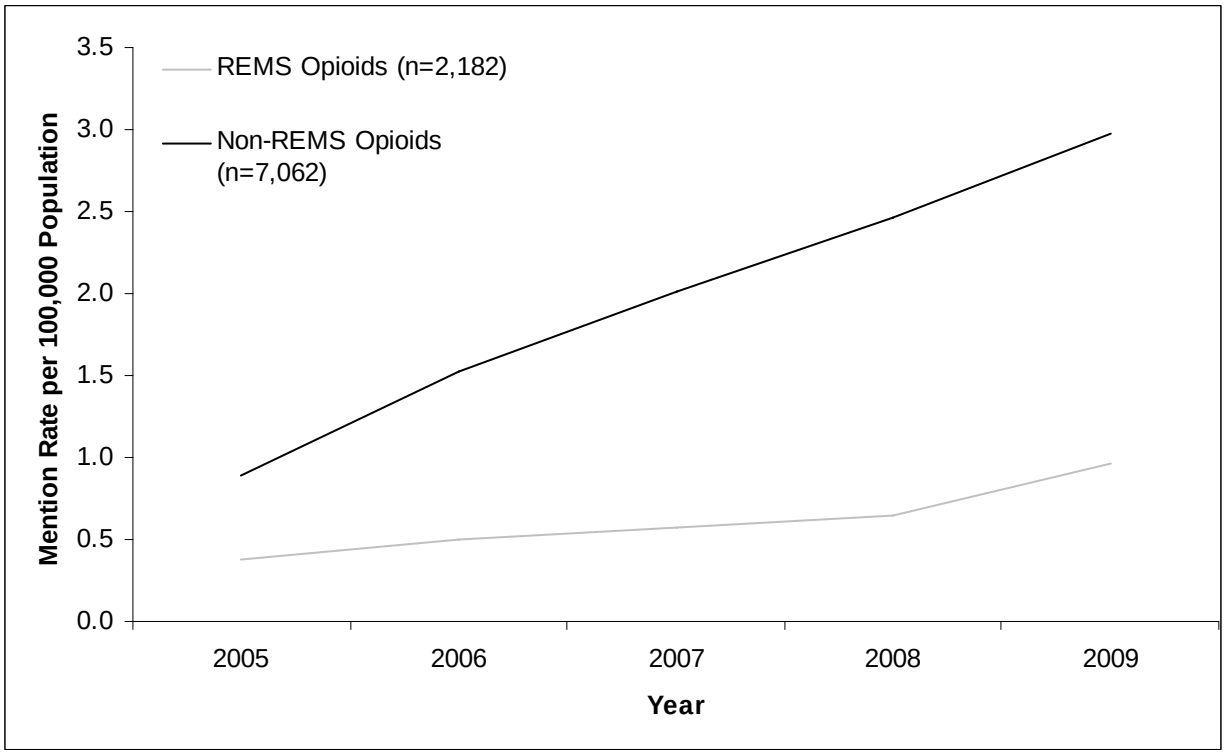


REMS Opioids: Methadone, extended release hydromorphone once launched, extended release morphine, extended-release oxycodone, extended-release oxymorphone, transdermal fentanyl.

Non-REMS Opioids: Buprenorphine, hydrocodone, tramadol, immediate-release hydromorphone, immediate-release morphine, immediate-release oxycodone, immediate-release oxymorphone, transbuccal fentanyl, fentanyl injectable products.

The Opioid Treatment Program is composed of 75 participating methadone treatment programs (also known as opioid treatment programs). Patients who are enrolling at these treatment centers are asked to complete an anonymous questionnaire, which includes questions concerning the patient's drugs of choice, drug use in the past month, lifetime drug abuse, age at first use, and the primary source of the abused drugs. The survey also includes questions about demographics, pain, withdrawal and craving. Cases are defined as self-reported use of a prescription or illicit opioid to get high in the past 30 days. Cases are assigned to the reported 3-digit ZIP code of the patient's residence.

Figure 10. Therapeutic Medication Errors in Adults (≥55 years): RADARS® System Poison Center: 2005 – 2009



REMS Opioids: Methadone, extended release hydromorphone once launched, extended release morphine, extended-release oxycodone, extended-release oxymorphone, transdermal fentanyl.

Non-REMS Opioids: Buprenorphine, hydrocodone, tramadol, immediate-release hydromorphone, immediate-release morphine, immediate-release oxycodone, immediate-release oxymorphone, transbuccal fentanyl, fentanyl injectable products.

Quarterly rates for surveillance purposes are calculated by using case counts from the Poison Center program as the numerator, and dividing them by the US Census Population for each year quarter. Rates were calculated using US Census Population estimates for each year.

The Poison Center Program collects data on all exposures reported to participating poison centers (48 of 60 US poison centers). Spontaneous calls from the public and healthcare professionals are recorded by poison centers using a standardized, electronic data collection system. Participating poison centers send the coordinating center cases for the RADARS System drugs of interest on a weekly basis. Each case undergoes a rigorous quality control process. Abuse and misuse cases are defined as any intentional exposure (intentional abuse, intentional misuse, suspected suicidal, intentional unknown, and withdrawal) managed by participating poison centers for the products of interest. Cases are assigned to the reported 3-digit ZIP code of the exposed individual's residence.