

**DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE
ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE
BRIEFING BOOK
FOR
THE EXTENDED-RELEASE AND LONG-ACTING (ER/LA) OPIOID ANALGESIC
RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

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LIST OF ABBREVIATIONS

ACCME®	Accreditation Council for Continuing Medical Education
ASI-MV	Addiction Severity Index- Multimedia Version
CCCE	Conjoint Committee for Continuing Education
CE	Continuing Education
CHAT	Comprehensive Health Assessment for Teens
CI	Confidence Interval
CME	Accredited Continuing Medical Education
CO*RE	Collaborative for REMS Education
DEA	Drug Enforcement Administration
DO	Doctor of Osteopathic Medicine
ED	Emergency Department
ER	Extended-Release
ETASU	Elements to Assure Safe Use
FAQs	Frequently Asked Questions
FDA	Food and Drug Administration
FDCA	Food, Drug and Cosmetic Act
FPI	Full Prescribing Information
HCP	Healthcare Professional
HIRD	HealthCore Integrated Research Database SM
ICD	International Classification of Diseases
IR	Immediate-Release
IVRS	Interactive Voice Response System
KAS	Knowledge Assessment Score
LA	Long-Acting
LRx	Longitudinal Prescription
MD	Doctor of Medicine
MEMS	Medical Education and Metrics Standards
NAVIPPRO®	National Addictions Vigilance Intervention and Prevention Program
NDA/ANDA	New Drug Application/Abbreviated New Drug Application
NIDA	National Institute on Drug Abuse
NP	Nurse Practitioner
NPA™	National Prescription Audit™
NSAID	Non-steroidal Anti-inflammatory Drug
ONDCP	Office of National Drug Control Policy
PA	Physician's Assistant
PARS	Program and Activity Reporting System
PCP	Primary Care Provider
PIE	Provider Information Exchange
PPA	Patient Prescriber Agreement
RADARS®	Researched Abuse, Diversion and Addiction-Related Surveillance
REMS	Risk Evaluation and Mitigation Strategy
RPC	REMS Program Companies
SAMHSA	Substance Abuse and Mental Health Services Administration
SD	Standard Deviation
US	United States
USPS	United States Postal Service

1. EXECUTIVE SUMMARY

The Sponsors of all Extended-Release and Long-Acting (ER/LA) opioid analgesic drug products (both New Drug Application [NDA] and Abbreviated New Drug Application [ANDA] holders), referred to collectively as the RPC (REMS Program Companies) have worked together with the FDA and the Continuing Education (CE) community to develop and implement a Risk Evaluation and Mitigation Strategy (REMS). The RPC implemented a novel REMS program focused on educating healthcare professionals (HCPs) through accredited Continuing Medical Education/Continuing Education (referred to as CE) to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics. The REMS also includes sending Dear Healthcare Provider letters to all prescribers who are registered with the Drug Enforcement Agency (DEA) to prescribe Schedule II or III narcotics. Letters were sent when the REMS was approved, when the first CE course became available, and annually thereafter to newly DEA-registered prescribers.

Since REMS approval on July 9, 2012, the RPC has collaborated with CE Providers and Accreditors to foster the development of accredited REMS-compliant CE activities, and the first accredited REMS-compliant CE activities were launched on February 28, 2013. As of February 28, 2015, there have been 524 accredited REMS-compliant CE activities launched and 37,512 ER/LA opioid analgesic prescribers and 44,619 non-prescribers have completed an accredited REMS-compliant CE activity. An additional, 28,707 prescribers completed an accredited REMS-compliant CE activity as of February 29, 2016 and 315 accredited REMS-compliant CE activities launched, for a total of 66,219 prescriber completers and 839 accredited REMS-compliant CE activities. The RPC is committed to improving the REMS to help reduce inappropriate prescribing, misuse, and abuse of prescription opioids, while preserving access to these medicines for people with pain severe enough to require long term opioid treatment, and for which alternative treatment options are inadequate.

FDA developed core messages to be communicated to prescribers in the Blueprint for Prescriber Education (FDA Blueprint) which outlines the areas of knowledge that are important in minimizing the risks associated with ER/LA opioid analgesics. The content of an accredited REMS-compliant CE activity must be based on the FDA Blueprint. The Blueprint includes 6 content areas:

- Assessing Patients for Treatment with ER/LA Opioid Analgesic Therapy
- Initiating Therapy, Modifying Dosing, and Discontinuing Use of ER/LA Opioid Analgesics
- Managing Therapy with ER/LA Opioid Analgesics
- Counseling Patients and Caregivers about the Safe Use of ER/LA Opioid Analgesics
- General Drug Information for ER/LA Opioid Analgesic Products
- Specific Drug Information for ER/LA Opioid Analgesic Products

Each CE Provider independently creates customized educational activities using the FDA Blueprint as a roadmap. In addition to accredited REMS-compliant CE activities, there are many other opioid CE courses available to HCPs.

The ER/LA Opioid Analgesics REMS includes an assessment plan that addresses the FDA's requested assessment elements. This plan includes components to assess the extent to which the elements to assure safe use (ETASU) are meeting the goals of the REMS. All assessment components were completed and reported in the most recent ER/LA Opioid Analgesics REMS Assessment Report. These data are summarized in this Briefing Book to illustrate the results of these assessments. For the most recent reporting period, the RPC completed its assessment plan commitments by collecting metrics for the following 8 key areas:

- Prescribers who have successfully completed an accredited REMS-compliant CE activity

- Independent audits of CE activities
- Patients' understanding of the serious risks of ER/LA opioid analgesics (Patient Survey)
- Prescribers' understanding of the serious risks of ER/LA opioid analgesics (Prescriber Survey)
- Prescribers' knowledge of the serious risks of ER/LA opioid analgesics within 6 to 12 months after completing an accredited REMS-compliant CE activity (Long-term Evaluation Survey)
- Evaluation of Drug Utilization Patterns, Prescribing Behaviors and Changes to ER/LA Opioid Access (IMS Data)
- Surveillance monitoring for misuse, abuse, overdose, addiction, and death associated with ER/LA opioid analgesics, as well as resulting interventions (Emergency Department Visits for Opioid Overdose and Poisoning events, Intentional Exposures Among Adolescents and Adults, Unintentional Exposures Among Infants and Children, Rates of People in Substance Abuse Treatment Programs Abusing ER/LA opioid analgesics, Mortality Rates Resulting from Drug Poisoning)

In interpreting the data from the assessments, particularly those associated with outcome surveillance, there are multiple factors along with the REMS that may be contributing to the decrease of ER/LA opioid analgesic abuse, misuse, unintentional overdose, and death, including:

- Changes in healthcare systems that have shifted access and influenced which specialties are likely to treat people with pain
- Requirement for chronic pain patients to be seen by pain specialists instead of Primary Care Providers (PCPs) in some areas
- Requirements from some states and/or health systems for prescriber opioid training outside of the REMS
- Prescribing and prescription monitoring standards that may influence prescriber behavior and impact REMS effectiveness
- Changing societal patterns in drug abuse
- Increasing use of Prescription Drug Monitoring Programs
- Approval of naloxone for use of the emergency treatment of known or suspected opioid overdose
- FDA issuance of a final abuse-deterrent formulation guidance to opioid drug developers
- FDA and DEA education of public on the safe disposal of opioids

These potentially contributing factors, along with other local, state, and federal initiatives aimed at decreasing opioid abuse that were implemented within the same time period, make assessing the impact of the REMS very complex. However, the education delivered as part of the REMS has contributed, along with other efforts, to changes in various metrics associated with opioid safe prescribing knowledge, utilization, and measures of misuse and abuse.

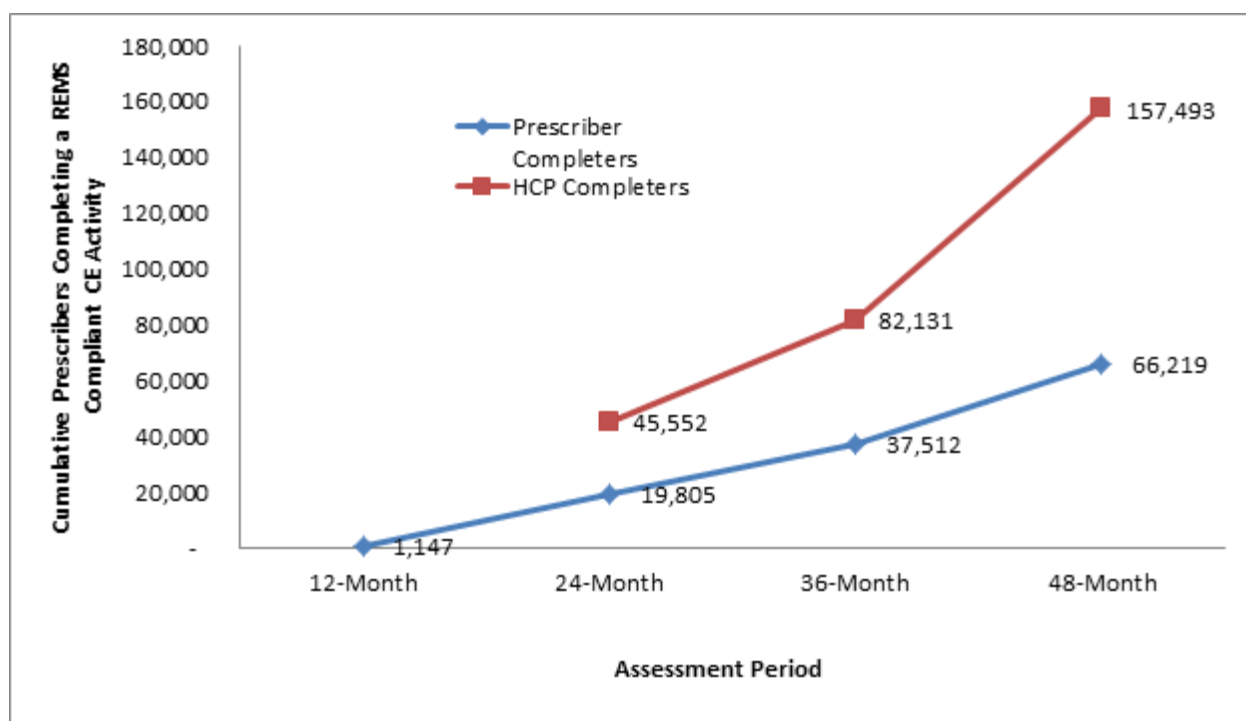
A summary of each of these assessment items evaluated as part of the ER/LA Opioid Analgesics REMS is presented below.

Prescribers who have Successfully Completed an Accredited REMS-Compliant CE Activity

A total of 37,512 ER/LA opioid analgesic prescribers completed an accredited REMS-compliant CE course funded by RPC and met the FDA's "completers" criteria by February 28, 2015.

The REMS requires that accredited REMS-compliant CE training be available to healthcare providers who prescribe ER/LA opioid analgesics, with a goal of training 80,000 opioid analgesic prescribers within 2 years from the time of the first accredited REMS-compliant training became available. The number of prescriber completers has increased steadily over the time period since the REMS CE training introduction in February 2013. The FDA defined criteria to be considered a completer: taking an accredited REMS-compliant training, completing the post-training test, and attesting to having prescribed an ER/LA opioid analgesic in the past year and registered to prescribe a Schedule II and/or III controlled substance. Although this goal was not met, more recent data for March 1, 2015 through February 29, 2016 show a substantial increase of 28,707 prescriber completers for a total of 66,219 completers (Figure 1). A total of 524 accredited REMS-compliant activities had been launched through February 28, 2015, with an additional 315 launched as of February 29, 2016.

FIGURE 1: CUMULATIVE NUMBERS OF ACCREDITED REMS-COMPLIANT CE ACTIVITY COMPLETERS OVER TIME



In addition to the CE completers who met the completer criteria established by FDA, as of February 29, 2016, an additional 91,274¹ individuals completed an RPC-funded accredited REMS-compliant training course and took a post-test evaluation, but did not meet the FDA criterion of having prescribed at least one ER/LA opioid analgesic in the previous year, indicating that training was received by a significant number of additional healthcare professionals who had not attested to have prescribed an ER/LA opioid

¹ Total collected from quarterly reports provided by CE Providers through February 29, 2016

analgesic within the past year. CE Providers have indicated the following reasons that these additional HCPs cannot be counted toward the completer goal:

- they may not have written a prescription for an ER/LA opioid analgesic within the last 12 months;
- they may have been an HCP who uses an institutional DEA number or prescribes under a collaborating physician's DEA number;
- they may be non-prescribing HCPs who took the training because they impact the care of patients treated with ER/LA opioid analgesics, such as nurses or pharmacists who work in healthcare settings where opioids are prescribed or dispensed; or
- they may have taken the CE activity in preparation for beginning to prescribe ER/LA opioid analgesics.

Another 280,968 individuals took some part of an RPC-funded accredited REMS-compliant training course by February 29, 2016, but did not complete a post-training evaluation. Furthermore, HCPs who complete other CE activities related to opioid education (such as state-mandated and National Institute on Drug Abuse (NIDA)-sponsored CE courses) are not counted toward the strict definition of the completer goal since the activities either do not cover the entire content in the FDA Blueprint or were not verified as REMS-compliant. For example, there is a NIDA-sponsored prescriber training on safe prescribing for pain provided by an accredited CE Provider. The course reached 208,310 participants and 106,861 healthcare professionals² completed the training, but since it could not be verified as REMS-compliant, these completers are not eligible to be counted in the REMS-compliant CE completers above. RPC evaluated the NIDA course to assess whether it covers the content stipulated in the FDA Blueprint and the independent evaluation identified that 39% of the FDA Blueprint content was covered, in full or in part. Many other courses, including those by SAMHSA and state medical boards, are also working to educate healthcare providers on safe opioid prescribing, but may or may not meet all of the criteria of the ER/LA Opioid Analgesics REMS-compliant CE.

There have been many challenges to achieving the goal for prescriber completers, as defined in the ER/LA Opioid Analgesics REMS Program. Key challenges identified through conversations with CE Providers and other stakeholders (such as the Conjoint Committee for Continuing Education (CCCE)) include:

- (1) lack of HCP awareness of the REMS
- (2) lack of understanding of the importance of completing ER/LA Opioid Analgesics accredited REMS-compliant CE in contrast to non-REMS-compliant CE;
- (3) the courses are longer and more complex than typical CE leading participants to abandon before completion;
- (4) availability of non-RPC-supported opioid education programs (including opioid trainings supported by NIDA and state-mandated pain or opioid training programs for opioid prescribers) that compete with accredited REMS-compliant CE activities; and,

² Data provided on March 7, 2016 by Medscape/NIDA for two activities: *Safe Prescribing For Pain* and *Managing Pain Patients Who Abuse RX Drugs* (<https://www.drugabuse.gov/opioid-pain-management-cmesces>). This course launched in October 2012 and has since expired.

- (5) varying standards for pain management CE among states, insurers, and professional societies that may encourage providers to take non-REMS-compliant courses.

These challenges have informed some of the RPC's lessons learned and suggestions for improvements to the REMS, as discussed later in this Executive Summary and in Section 6.

Independent Audits of CE Activities

A sample of more than 10% of accredited REMS-Compliant CE activities have been audited with no issues related to content observed.

In order to confirm that the CE activities reflect the FDA Blueprint content and the accrediting bodies' standards for commercial support, independent audits of the education materials used by the CE providers for accredited REMS-compliant CE activities are performed. The REMS requires that a random sample of at least 10% of the RPC-supported, accredited REMS-compliant CE activities are audited annually.

Since the launch of the first RPC-supported accredited REMS-compliant CE activity on February 28, 2013, 524 CE activities have been launched and 56 audits have been conducted, with additional audit reports pending for the reporting period that spans March 1, 2015 – February 29, 2016. Of these, 100% met all criteria for accredited REMS-compliant CE as defined in the REMS Supporting Document and the FDA Blueprint. The Accreditation Council for Continuing Medical Education (ACCME) noted observations for 14 of the audit reports as they did not fully meet expectations with respect to the ACCME® Standards for Commercial Support around obtaining and prominently displaying financial relationships of faculty and/or staff involved in the activity. No observations pertained to content. The RPC has followed up with each provider where observations are noted, and have ensured that all audit findings were remediated.

Patients' Understanding of the Serious Risks of ER/LA Opioid Analgesics

The majority of respondents correctly answered most questions concerning the serious risks of ER/LA opioid analgesic use, what to do in the case of overdose, proper storage, the importance of not sharing medication, and safe use.

A survey was developed to assess how well patients understand the serious risks of ER/LA opioid analgesics. The survey, which could be completed by phone or online, contained questions based on the important messages related to safe use of ER/LA opioid analgesics included in the Patient Counseling Document and the Medication Guide. The survey specifically assessed:

- 1) patients' understanding of the serious risks of ER/LA opioid analgesics,
- 2) receipt and comprehension of the Medication Guide and Patient Counseling Document,
- 3) perceived access to and satisfaction with access to ER/LA opioid analgesics, and
- 4) patient-reported frequency of appropriate prescriber behaviors, including screening and counseling about ER/LA opioid analgesics.

A random sample of adults who had filled at least one prescription for ER/LA opioid analgesics between September 1, 2013, and August 31, 2014, was identified from claims in a large commercial health plan claims database and invited to participate in the survey. Of the 2,441 patients who were contacted, 272 (11%) failed to meet the survey screening criteria, 1,746 (72%) refused to participate, and 423 (17%) completed the survey. Recruitment was stopped after the target number of patients was reached, thus an accurate response rate cannot be computed. The survey included a total of 80 questions, of which 22 assessed respondent knowledge of key elements of safe use of ER/LA opioids as described in the Medication Guide and Patient Counseling Document.

A comparison of the survey respondents to the overall eligible population showed comparability for most demographic and clinical characteristics. The majority of respondents correctly answered most questions

concerning the serious risks of ER/LA opioid analgesic use, what to do in the case of overdose, proper disposal, the importance of not sharing medication, and safe use. The Knowledge Assessment Score (KAS) (i.e., percentage of knowledge questions that a respondent answered correctly) had a mean of 85.6% (Standard Deviation (SD) 10.08) and scores ranged from 40% to 100%. There were 115 (27%) respondents with a KAS below 80%, defining poor knowledge. Questions answered correctly by fewer than 80% of patients concerned storing ER/LA opioid analgesics away from other household medications, the need to read the Medication Guide every time a prescription was filled, never splitting or crushing pills (oral product users only), informing a healthcare provider of fever (patch product users only), and avoid use of hot tubs or saunas (patch product users only).

Patient survey results showed that approximately 80% of respondents reported satisfaction with their access to ER/LA opioid analgesic prescriptions, their ability to obtain medication from a pharmacy, and their general ER/LA opioid analgesic access. It is important to note, however, that these are commercially-insured patients who filled prescriptions for ER/LA opioids, therefore their perceptions of access may differ from those of the population as a whole.

Prescribers' Understanding of the Serious Risks of ER/LA Opioid Analgesics

The majority of the safe use questions/items were answered correctly by more than 80% of participants.

There are two REMS assessment metrics that are evaluated using prescriber surveys. The first, described here, is to assess prescribers' understanding and knowledge of the safe use and appropriate prescribing of ER/LA opioid analgesics as described in the ER/LA Opioid Analgesics REMS educational materials, FDA Blueprint, and Full Prescribing Information (FPI) of each product. The second survey, to evaluate prescribers' knowledge of the serious risks of ER/LA opioid analgesics within 6 to 12 months after completing an accredited REMS-compliant CE activity, is described in the next section and is termed the Long-term Evaluation Survey.

The first prescriber survey was developed based on the aforementioned educational materials. A sample size of 600 was proposed for the survey with 300 selected from a stratified random sample of ER/LA opioid analgesic prescribers known to have prescribed at least one ER/LA opioid analgesic product in the past year (as identified from IMS data) and 300 prescribers selected from a list of those who had completed an accredited REMS-compliant CE activity. This sample size was expected to allow estimation of the comprehension rate for each risk message with a moderately high degree of precision.

A total of 612 prescribers completed the Prescriber Survey via internet or paper. As specified in the protocol, the survey is scored by individual key risk messages, in keeping with FDA's request to understand which messages are well understood. The majority (49/68, 72.1%) of the 68 safe use questions/items were answered correctly by more than 80% of participants. Specifically, results showed that prescribers understood the assessment, management, and counseling requirements for patients who are being considered for treatment with ER/LA opioid analgesics. Fewer than 80% of prescribers answered 19 of the 68 safe use questions correctly, demonstrating a low level of knowledge for these items. The areas where prescribers were less knowledgeable were related to initiation, modification, and discontinuation of ER/LA opioid analgesic therapy, and to product-specific information about ER/LA opioid analgesics.

Per the protocol, the survey analyses included evaluations of prescriber subgroups based on: 1) completing a CE activity and 2) ER/LA opioid analgesic prescribing level (classified as prescribing ER/LA opioid analgesics more than 10 times in the past month). Prescribers who were recruited through CE Providers and prescribers who prescribed a high volume of ER/LA opioid analgesics were significantly more likely to understand the risks and safety information relating to ER/LA opioid analgesics treatment.

Prescriber survey results showed that over half of the 612 prescribers felt the current level of access for their patients who are indicated to take ER/LA opioid analgesics is about right (321/612, 52.5%) while 155 (155/612, 25.3%) felt access is too difficult and 91 (91/612, 14.9%) felt access is too easy.

Prescribers' Knowledge of the Serious Risks of ER/LA Opioid Analgesics Within 6 to 12 Months After Completing an Accredited REMS-compliant CE Activity (Long-term Evaluation Survey)

The majority of the knowledge questions/items were answered correctly by more than 80% of participants.

A second survey of prescribers focused on their retention of REMS messages and knowledge of the FDA Blueprint over the long-term.

A sample of respondents who had completed an accredited REMS-compliant CE activity 6-12 months prior to survey implementation was identified. The target sample size was 600 prescribers. Data on the number of invitations sent was not available from all CE Providers and therefore the response rate cannot be calculated. Of the 546 individuals who responded to the invitation, 485 agreed to participate in the survey and 328 completed the survey, resulting in a 60.1% completion rate. One-third (185/546, 33.9%) of respondents met an exclusion criterion or did not complete all eligibility questions and 6.0% (33/546) eligible respondents did not complete the entire survey. A total of 328 prescribers completed the Long-term Evaluation Survey via a website or paper.

As specified in the protocol, the survey is scored by individual key risk messages, in keeping with FDA's request to understand which messages are well understood. The majority of the 65 knowledge questions/items (45/65, 69.2%) were answered correctly by more than 80% of participants. Twenty (20) items (20/65, 30.8%) were answered correctly by fewer than 80% of participants. Of the 20 items, 6 questions/items were related to how and when to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics; 5 questions/items concerned characteristics of specific ER/LA opioid analgesic products; and 4 questions/items were about how to assess patients for treatment with ER/LA opioid analgesics.

The survey and its results have been shared with the CE Providers. The CE Providers are reviewing these results to determine whether changes to the CE curriculum are warranted. Survey results may suggest that prescribers' knowledge is limited to only the products they prescribe. This phenomenon was not explored in detail in the survey but is being further assessed by the RPC.

In addition to knowledge surveys, other studies were also used to assess changes in outcomes of interest. These included a study of ER/LA opioid utilization as well as multiple surveillance studies to evaluate changes over time in abuse, misuse, and other safety outcomes.

Evaluation of Drug Utilization Patterns, Prescribing Behaviors and Changes to ER/LA Opioid Access

Overall, a significant decrease was observed in total ER/LA opioid analgesic prescription volume from pre-implementation to the active period based on IMS data.

The proportion of non-tolerant patients who were inappropriately prescribed ER/LA opioid analgesics decreased between the pre-implementation and the active periods.

ER/LA opioid analgesics prescription volume decreased significantly for medical specialists with less compelling reasons to prescribe ER/LA opioid analgesics.

Trends in drug utilization, prescribing behaviors, and changes to ER/LA opioid access were evaluated for ER/LA opioid analgesics and comparator products were evaluated using national prescription database systems (IMS Health, National Prescription Audit™ (NPA™) and IMS Health, LifeLink™). The data period used for this analysis spanned from July 1, 2010 through December 31, 2014. The 54-month period was divided into three periods:

- Pre-Implementation: This included the 24-month period (July 2010 – June 2012) before the implementation of the REMS.
- Implementation/Transition: This included the initial 12-month transition implementation period (July 2012 – June 2013) of the REMS in which a number of the REMS functional and operational components were initiated.
- Active Period: This included the subsequent 18-month period (July 2013 – December 2014) following Implementation.

A significant decrease was observed in total ER/LA opioid analgesic prescription volume from pre-implementation to the active period based on IMS data. The average prescription volume per quarter for all ER/LA opioid analgesics decreased from 5.58 million in the pre-implementation period to 5.34 million in the period when the REMS was in place (active period), a decrease of 4.3% ($p < 0.001$).

The proportion of ER/LA products or doses that should not be prescribed to non-tolerant patients was evaluated. Patients were classified as opioid tolerant if they had received a daily morphine equivalent dose ≥ 60 mg for one week or longer prior to the ER/LA opioid analgesic of interest; otherwise, they were classified as opioid non-tolerant. A decrease in the proportion of non-tolerant patients that should not be prescribed specific products or doses was observed for all products studied, although the difference was only statistically significant for ER hydromorphone. The proportion of non-tolerant patients dispensed ER hydromorphone decreased 8.8% from 48.9% in pre-implementation to 44.6% during the active period ($p < 0.001$). Early refills also showed a downward trend for most products included in the REMS.

A comparison of prescribers in medical specialties that often care for patients with acute pain, where ER/LA opioid analgesics are not the first line of treatment, to those specialties more likely to treat patients with chronic pain (such as oncologists and hospice providers) was performed. Benzodiazepines, celecoxib, and IR opioids were evaluated as comparators.

The average monthly prescription volume for the total ER/LA opioid analgesics prescribed by pain specialists and physical medicine and rehabilitation specialists did not change significantly over the study period; however, there was a significant decrease for hospice and palliative medicine specialists (5.9% decrease) and an increase for anesthesiologists (2.8% increase) from pre-implementation to active period. ER/LA opioid analgesic prescriptions written by dentists showed a decrease of 48.5% from the pre-implementation to the active period. Similarly, prescriptions written by emergency room specialists decreased 25.2% from the pre-implementation period to the active period. A significant increase in prescribing of 33.7% among nurse practitioners and 31.2% among physician assistants was seen from the pre-implementation period to the active period. This may reflect increased utilization of these healthcare providers due to changing healthcare systems practices. For most medical specialties, the pattern seen for prescription of ER/LA opioid analgesics is similar to the pattern seen for benzodiazepines and celecoxib.

For the IR opioids, the volume prescribed for a third of the specialists remained the same from pre-implementation to implementation. The volume prescribed from pre-implementation to active period decreased for most prescriber specialists: surgical specialists, emergency medicine specialists, neurologists, hospital and palliative medicine specialists and pediatricians. Prescribing increased among nurse practitioners and physician assistants, a pattern noted for ER/LA opioid analgesics, benzodiazepines, and celecoxib).

Surveillance Monitoring for Misuse, Abuse, Overdose, Addiction, and Death Associated with ER/LA Opioid Analgesics, as well as Resulting Interventions

An important set of REMS assessment metrics included evaluation of misuse, abuse, overdose, addiction, and death associated with ER/LA opioid analgesics. Multiple data sources shown below were used to compare pre-implementation phase to the active period for:

- emergency department visits for opioid overdose and poisoning events (HealthCore Integrated Research DatabaseSM (HIRD) and Medicaid data from one state)

- intentional exposures among adolescents and adults (Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS[®]) System)
- unintentional exposures among infants and children (RADARS[®] System)
- rates of people in substance abuse treatment programs abusing ER/LA opioid analgesics (RADARS[®] System and National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO[®]))
- mortality rates resulting from drug poisoning (RADARS[®] System)

The RPC recognizes that multiple factors along with the REMS may be contributing to the decreases in ER/LA opioid analgesic abuse, misuse, intentional overdose, and death observed in the results discussed below.

Emergency Department Visits and Hospitalizations for Opioid Overdose and Poisoning Events

The incidence of opioid overdose or poisoning decreased slightly between the pre-implementation period and the active period after adjustment for demographic and clinical characteristics.

A retrospective cohort study assessed the incidence of emergency department (ED) visits and hospitalizations due to opioid overdose and poisoning using HIRD (commercially-insured patients) and Medicaid data. In the commercially insured patients, 80,209 ER/LA opioid analgesic recipients were identified in the pre-implementation period (July 1, 2010 - June 30, 2012) and 43,730 in the active period (July 1, 2013 - December 31, 2014). In the Medicaid population for one state 3,488 ER/LA opioid analgesic recipients were identified in the pre-implementation period compared to 3,625 in the active period. Medicaid-insured patients had a much higher incidence of opioid overdose and poisoning events than commercially-insured patients. In the commercially-insured patients the incidence of these events during the pre-implementation period was 84.6 per 10,000 person years versus 244.6 per 10,000 person-years in the Medicaid population. This pattern was also seen in the active period between commercially-insured patients and the Medicaid-insured patients (86.8 and 261.9 per 10,000 person years, respectively). A comparison of the incidence of opioid overdose and poisoning among all ER/LA opioid analgesic users in the commercially-insured patient database, adjusted for possible confounders such as comorbidities and other medications showed an incidence rate ratio of 0.83 (95% Confidence Interval (CI) 0.70-0.99) for the active period compared to pre-implementation. The same pattern of a slight decrease between the active period and pre-implementation in the incidence of opioid overdose or poisoning was seen in the Medicaid population, with an incidence rate ratio of 0.81 (95% CI 0.59-1.18).

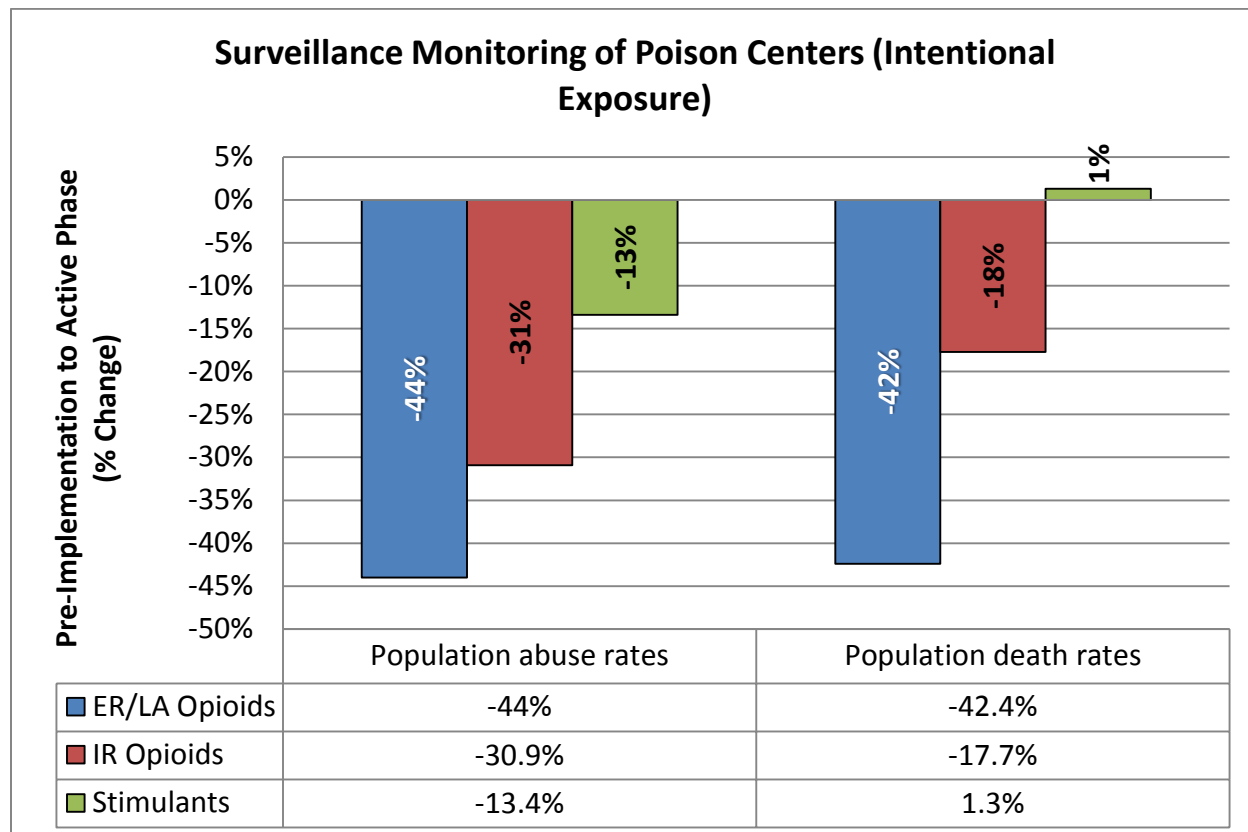
Poison Center Programs

There was a consistent decline in cases of abuse reported to poison centers from the pre-implementation to the active periods.

Poison Center data were used to evaluate trends in abuse and pediatric exposure for ER/LA opioid analgesics, from pre-implementation to the active period. As shown in [Figure 2](#), results from the RADARS[®] System Poison Center Program show a consistent statistically significant decline in abuse between the 2 periods using population-adjusted rates per 100,000 persons (pre-implementation period mean rate of 0.123 and active period mean rate of 0.069, associated with a decrease of 44.0%). Abuse of comparator groups including IR opioids and prescription stimulants also decreased during the same time periods, but less substantially (decreases of 30.9% and 13.4%, respectively). Further, death rates showed a statistically significant decrease from the pre-implementation to the active period for ER/LA opioid analgesics based on both population-adjusted rates (pre-implementation period mean rate of 0.004 and active period mean rate of 0.002, associated with a decrease of 42.4%). While death rates in the IR opioid comparator group also fell during this time period, the decrease was smaller than that of ER/LA opioid analgesics (pre-implementation period mean rate of 0.012 and active period mean rate of 0.010 associated with a decrease of 17.7%). In comparison, the rate of deaths in the prescription stimulant group increased

slightly based on population-adjusted data (pre-implementation period mean rate of 0.002 and active period rate of 0.002 associated with an increased 1.3%).

FIGURE 2: POISON CENTER PROGRAM SUMMARY



Evaluation of unintentional exposures among infants and children was also conducted. A significant decline in unintentional exposure for ER/LA opioid analgesics was seen in population rates from pre-implementation to the active period (pre-implementation period mean rate of 0.530 and active period mean rate of 0.420 associated with a decrease of 20.8%). The comparator groups of IR opioids and prescription stimulants also decreased during the same time periods (decreases of 15.9% and 1.1%, respectively), but the decrease was smaller than that of ER/LA opioid analgesics.

Treatment Center Programs

A decrease in abuse rates for ER/LA opioid analgesics was observed in substance abuse treatment center programs between the pre-implementation and active periods.

Two sources were used to examine abuse in substance abuse treatment center programs.

RADARS® data showed a significant decrease of 47.0% in abuse rates from the pre-implementation to the active period for ER/LA opioid analgesics based on population-adjusted rates. The IR opioid comparator group also fell during this time period (decrease of 12.0% for population-adjusted rates).

Two programs within NAVIPPRO® were also used for this analysis. The Addiction Severity Index-Multimedia Version (ASI-MV), which collects data through a computerized interview on substances used and abused by individuals in treatment for substance use disorders and the Comprehensive Health Assessment for Teens (CHAT), which is a computerized behavioral health assessment targeted to adolescents age 18 and younger entering treatment for drug or alcohol abuse. Data obtained from NAVIPPRO® also showed a decrease in reports of ER/LA opioid analgesic abuse within the ASI-MV and

CHAT programs between the pre-implementation to the active period (decrease of 6.6% and 25.6%, respectively).

Washington State Mortality Rates

Mortality rates due to drug poisoning declined 19.8% from the pre-implementation to the active period.

An evaluation of mortality rates resulting from drug poisoning associated with active pharmaceutical ingredients included in the ER/LA Opioid Analgesics REMS was conducted using a state medical examiner database in Washington. Of the states contacted, only Washington State was able to provide death data within the timeframe required to evaluate and analyze the data for the 36-month FDA Assessment Report. Furthermore, data from Washington State include information on the molecule involved allowing distinction between heroin and prescription opioid products. Future assessment reports will include a broader geographic representation.

Population-based rates of mortality due to drug poisoning in the state of Washington fell 29.8% from pre-implementation to the active period. Rates for benzodiazepines and hydrocodone were evaluated as comparators. Mortality rates associated with benzodiazepines also fell 18.9% and hydrocodone fell 28.1% during the same period. Only the mean decrease over time for all ER/LA opioid analgesics excluding hydrocodone was statistically significant ($p < 0.001$).

Overall Assessment of the Impact of the ER/LA Opioid Analgesics REMS, Lessons Learned and Recommendations

The ER/LA Opioid Analgesics REMS is an education-based program with the goal of reducing serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications.

Rates of understanding of safe use messages were high for both patients and prescribers. RPC is exploring options for increasing knowledge of low-scoring dimensions. Results from the Long-term Evaluation Survey were shared with CE Providers to inform them about gaps in prescriber knowledge and practice so that they can modify their future courses to better address these gaps.

Because the REMS was implemented during a similar timeframe as other public health interventions aimed at safe opioid prescribing and curbing abuse, misuse, and their consequences, it is not possible to causally link the REMS to impacts on utilization or surveillance metrics. However education, such as that delivered by the REMS, is one part of the solution to the problem of opioid misuse and abuse, and positive trends in outcomes have been seen. Prescribing ER/LA opioid analgesics has decreased among medical specialties that are treating patients for acute pain where ER/LA opioid analgesics are not the first line of treatment. Decreases in abuse, misuse, unintentional overdose, and death have been observed since REMS launch. Based on data from surveys, there is indication that the REMS has not had a negative impact on access for patients needing ER/LA opioid analgesics, though the sample is not representative of all patients and other interventions could have impacts on access that are not detectable through surveys focused on REMS education.

The implementation of this complex, CE-focused ER/LA Opioid Analgesics REMS by a consortium of 23 companies, has led to a variety of lessons learned. These lessons can be leveraged to improve upon the existing REMS and to inform the design of other class-wide REMS programs in the future (See [Table 1](#)).

TABLE 1: ER/LA OPIOID ANALGESICS REMS LESSONS LEARNED

LESSON LEARNED	BACKGROUND
Importance of Collaboration	The 23 companies of the RPC, FDA, and the CE community have worked to ensure that nearly 839 accredited REMS-compliant continuing education courses have been offered. This has required engaging with accreditors, data providers for assessments, program managers, medical writers, and others in the course of design, implementation, and assessment of the program.
Importance of Project Management for Class-wide Initiatives	The scope of this REMS is unique, given the CE emphasis, number of participating companies, and varied assessments. Dedicated project management is essential to ensure forward motion, quality assurance, and that reporting requirements are fulfilled.
Importance of the Communication Plan	Awareness of the REMS was low. Identifying which elements had satisfactory or better reach and which were not effective is important to meet goals of the REMS. Alternative communication strategies should be explored.
Importance of Reviewing Data Collected Through Assessments in Order to Identify Areas for Improvement	<p>Each assessment had identified weaknesses that are targets for improvement.</p> <p>Surveys:</p> <ul style="list-style-type: none"> • Pre-specifying demographic data to collect on CE completers • Direct comparisons of knowledge for CE completers vs. non-completers • Enhanced recruitment efforts to ensure sample sizes are met and are representative • Survey questions answered correctly by a smaller proportion of participants should be shared with CE Providers to be considered for their next curriculum updates. <p>Surveillance Studies:</p> <ul style="list-style-type: none"> • Expanding studies to include <ul style="list-style-type: none"> ○ Data on deaths ○ Different patient risk profiles • Evaluation of surveillance findings in the context of the external environment <ul style="list-style-type: none"> ○ Impacts of changes in the healthcare system ○ Changes in drug abuse patterns and their impacts on observed trends in abuse, misuse, death, and other key outcomes.

Create Short, Simple Materials Directed at

Among the educational tools created for the REMS were

LESSON LEARNED	BACKGROUND
Patients	a single-sheet medication guide for patients to be distributed with each prescription, and a 1-page Patient Counseling Document. Reports of receipt and use of these documents were high.
Leverage Adult Education Best Practices	Healthcare provider associations report that the accredited REMS-compliant education is important, but lacks creativity to engage learners and is longer than other programs. For participation in the CE to increase and be effective, innovative training programs and using more case-based interactive learning techniques, linked to individual prescribers and practice needs, addressing knowledge gaps more specifically, should be considered.

With these lessons learned in mind, and given the context of the data from the various REMS assessments, the RPC recommends six changes to enhance the REMS content and implementation and to better deliver education on safe ER/LA opioid prescribing to healthcare providers.

RPC Recommendations for REMS Enhancements:

1. Enhance REMS communication activities

To engage more HCPs in accredited REMS-compliant CE activities, it will be important to enhance communication about the REMS. One improvement will be to improve the accessibility of the ER/LA Opioid Analgesics REMS website, so that interested healthcare providers can more easily access accredited REMS-compliant CE activity content. In addition, the RPC plans to launch an awareness campaign featuring a general-audience website and additional materials later in 2016; these will be shown at conferences and in journals targeted to specialties and provider groups who may not have been well-reached in the past.

2. Expand the REMS to include the extended healthcare team

The current goal of CE for this REMS involves a focus on educating ER/LA opioid analgesic prescribers. Education of all team members involved in patient care is critical for implementation of REMS learnings. This will include increasing awareness of the accredited REMS-compliant CE activities among non-prescribers and ensuring that all accredited REMS-compliant CE activities are accepted for CE credit by accrediting bodies for nurses, pharmacists and others.

3. Revise the FDA Blueprint for Prescriber Education to reflect stakeholder input and feedback

- The RPC suggests revising the FDA Blueprint for Prescriber Education to reflect evolving stakeholder input and feedback and to take into consideration the needs of adult learners. Suggested revisions include condensing the FDA Blueprint, emphasizing case studies, utilizing adaptive approaches to ensure prescribers have necessary knowledge (such as a demonstration of knowledge to opt out of specific sections of the training), emphasizing general principles of safe ER/LA opioid analgesic prescribing rather than details of specific drugs, addressing other topics in pain management (such as how to deal with patients suspected of abuse, misuse, or diversion or use of naloxone for overdose), and establishing standard assessments across accredited REMS-compliant CE activities.

4. The majority of RPC supports tying Schedule II and Schedule III Narcotics DEA registration and re-registration to either completion of prescription opioid education or other attestation of prior knowledge such as board certification in pain medicine

This type of targeted education is an approach to ensuring all prescribers have received appropriate training in pain management with opioids so their patients can continue to access

treatment options. The RPC understands that this would require cross-agency communication and congressional approval to implement.

5. Encourage federal agencies to collaborate in developing an education solution, utilizing the principles of this REMS

The New England Journal of Medicine article by Califf, Woodcock and Ostroff (2016)³ makes several references to the importance of other federal agencies, including NIDA and SAMHSA, working together with FDA to align goals in order to impact improper use of prescription opioids. Currently, there are multiple safe opioid prescribing CE courses offered by various federal agencies, each with a different approach and emphasis. The RPC supports the development of a shared or common education that includes the REMS, as a part of an overall opioid strategy. In addition, consideration of more innovative approaches that use more case-based interactive learning techniques, linked to individual prescribers and practice needs and more specifically addressing knowledge gaps.

6. Evaluate the pros and cons of including IR opioids in the ER/LA Opioid Analgesics REMS

The FDA announced in February 2016³ that one item to be considered by the Advisory Committee in May will be to add IR opioids to this REMS program. The RPC supports careful consideration of the pros and cons and the feasibility of this change in the REMS.

The ER/LA Opioid Analgesics REMS is the first REMS to utilize accredited CE as a medium to deliver REMS education. It is also the first REMS to include such a large group of participating companies, including those of varying sizes, and with both brand and generic products. The RPC continues to work closely with the CE community and other stakeholders to enhance efforts to reach and train ER/LA opioid analgesic prescribers and other healthcare professionals responsible for patient treatment, as well as distributing the Medication Guide and Patient Counseling Document. In addition to tracking the accredited REMS-compliant CE activity completion, the RPC employs comprehensive assessments of a wide array of outcomes to evaluate whether the REMS is meeting the established goals. The RPC will continue to implement the REMS and measure its impact as one part of a national response to the opioid abuse problem, with the aim of reducing the serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of ER/LA opioid analgesics.

The RPC believes expanding the REMS in evidence-driven ways, based on lessons learned during REMS implementation, will help to educate providers on safe use of opioids and, as part of a larger public health strategy, further reduce inappropriate prescribing, misuse and abuse of these medications.

³ Califf RM, Woodcock J, Ostroff S. A proactive response to prescription opioid abuse. N Engl J Med. 2016. doi:10.1056/NEJMs1601307.

2. BACKGROUND

On April 19, 2011, in accordance with section 505-1 of the Federal Food Drug and Cosmetic Act (FDCA), the FDA determined a REMS was necessary for all ER/LA opioid analgesic drug products to ensure that their benefits outweigh their risks, especially with regard to specific adverse outcomes. The goal of the ER/LA Opioid Analgesics REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of particular interest include addiction, unintentional overdose, and death (see [Appendix 1](#) for the ER/LA Opioid Analgesics REMS). In the interest of public health, and to minimize the burden on the healthcare delivery system of having multiple unique REMS programs, the FDA determined that a single shared system should be used to implement this REMS.

The NDA/ANDA holders of the following branded and generic drug products are required to participate in the ER/LA Opioid Analgesics REMS: extended-release and long-acting, oral-dosage formulations containing hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, and tapentadol; transdermal and buccal delivery systems containing fentanyl or buprenorphine; and methadone formulations that are indicated for use as analgesics (see [Appendix 2](#) for a full list of ER/LA opioid analgesics). The REMS was approved by FDA on July 9, 2012. Currently, 23 companies participate in the ER/LA opioid class REMS.

The elements of the REMS include Medication Guides, Elements to Assure Safe Use (ETASU) and a Timetable for Submission of Assessments. Under the REMS ETASU, the NDA/ANDA holders must do the following:

- Ensure that training is available to prescribers who prescribe the ER/LA opioid analgesics
- Provide prescribers information that can be used to educate patients about the risks of ER/LA opioid analgesics and their safe use, storage, and disposal
- Inform prescribers of the existence of the ER/LA Opioid Analgesics REMS and the need to successfully complete the necessary training

2.1. Blueprint Elements

The FDA Blueprint for Prescriber Education for ER/LA opioid analgesics (“FDA Blueprint”) includes 6 key elements. These include:

- Patients should be assessed for treatment with ER/LA opioid analgesic therapy.
- Prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics.
- Management of ongoing therapy with ER/LA opioid analgesics is important.
- It is important to counsel patients and caregivers about the safe use of ER/LA opioid analgesics.
- Prescribers must be familiar with general information concerning ER/LA opioid analgesics.
- Prescribers must be familiar with product-specific drug information concerning ER/LA opioid analgesics.

The full FDA Blueprint is included in [Appendix 3](#).

2.2. Medication Guide

A Medication Guide will be dispensed with each ER/LA opioid analgesic prescription in accordance with 21 CFR § 208.24.

The Medication Guides for ER/LA opioid analgesics are part of the ER/LA Opioid Analgesics REMS program and will be available through the ER/LA Opioid Analgesics REMS website (<http://www.er-la-opioidrems.com/IwgUI/rems/products.action>). Screenshots of the ER/LA Opioid Analgesics REMS website are included in [Appendix 4](#).

2.3. Elements to Assure Safe Use

Training is available to prescribers who prescribe the ER/LA opioid analgesics in the form of accredited Continuing Education. The ER/LA Opioid Analgesics REMS represents the first time that accredited CE has been used to fulfill a REMS training requirement. Training will be considered “REMS-compliant training” under this REMS if:

- Training provided by (CE) Providers is offered by an accredited Provider to licensed prescribers,
- It includes all elements of the FDA Blueprint,
- It includes a post-course knowledge assessment of all of the sections of the FDA Blueprint, and
- It is subject to independent audit to confirm that conditions of the REMS training have been met.

The FDA established completion targets for each year of the REMS implementation. The following CE-related performance goals were established:

- Not later than March 1, 2013, the first REMS-compliant training would be made available.
- Within 2 years from the time the first REMS-compliant training becomes available, 80,000 prescribers (based on 25% of the 320,000 active prescribers in 2011) would have been trained.
- Within 3 years from the time the first REMS-compliant training becomes available, 160,000 prescribers (based on 50% of the 320,000 active prescribers in 2011) will have been trained.
- Within 4 years from the time the first REMS-compliant training becomes available, 192,000 prescribers (based on 60% of the 320,000 active prescribers in 2011) will have been trained.

The FDA defined criteria to be considered a completer: taking a REMS-compliant training, completing the post-training test, and attesting to having prescribed an ER/LA opioid analgesic in the past year and registered to prescribe a Schedule II and/or III controlled substance.

To ensure that offered REMS-compliant training meets all of these criteria, the NDA/ANDA holders are required to conduct independent audits of the educational materials. These audits must:

1. Be conducted by an auditor independent of the NDA/ANDA holders. (Accreditation bodies of CE providers would be considered independent of the NDA/ANDA holders and would be eligible to conduct the audits.)
2. Evaluate:
 - a. whether the content of the training covers all components of the FDA Blueprint approved as part of the REMS;
 - b. whether the knowledge assessment measures knowledge of all sections of the FDA Blueprint; and
 - c. for training conducted by CE providers, whether the training was conducted in accordance with the standards for CE of the ACCME®), or of another CE accrediting body appropriate to the prescribers’ medical specialty or healthcare profession.
3. Be conducted on a random sample of 1) at least 10% of the training funded by the NDA/ANDA holders, and 2) REMS-compliant training not funded by the NDA/ANDA holders but that will be counted towards meeting the performance goals

To facilitate prescriber awareness of the availability of the REMS and REMS-compliant training, within 30 calendar days of the approval of the REMS, the NDA/ANDA holders would make available, and then maintain, a web site that will contain information about the REMS specified below (www.er-la-opioidrems.com):

- a. A current list of the REMS-compliant training that is supported by educational grants from the NDA/ANDA holders, when this information becomes available.
- b. A copy of the Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics.
- c. A copy of the Prescriber Letters 1, 2, and 3 (when mailed and for at least one year thereafter)

The REMS includes a plan to inform prescribers and potential prescribers who are registered with the Drug Enforcement Administration (DEA) to prescribe Schedule II and III narcotics using the DEA database of registered prescribers about the REMS and the need to complete the necessary training. The primary communication methods to disseminate this information include Dear DEA-Registered Prescriber Letters and Dear Professional Organization/Licensing Board Letters. Performance goals established for these communications are:

- Dear DEA-Registered Prescriber Letter 1 would be sent not later than 60 days after the initial approval of this REMS
- Dear DEA-Registered Prescriber Letter 2 would be sent not later than 30 days before the first prescriber REMS-compliant training required by the REMS was offered by Providers
- At least annually from the date of initial approval of the REMS, the DEA Registration Database will be reviewed and Dear DEA-Registered Prescriber Letter 3 will be sent to all newly DEA-registered prescribers who are registered to prescribe Schedule II and III narcotics
- Dear Professional Organization/Licensing Board Letter 1 would be sent not later than 60 days after REMS approval
- Dear Professional Organization/Licensing Board Letter 2 would be sent not later than 30 days before the first prescriber REMS-compliant training is available

The Dear DEA-Registered Prescriber Letter 3 is included in [Appendix 5](#).

Educational materials were developed for prescribers to use in educating their patients. The REMS includes the Patient Counseling Document (see [Appendix 6](#)) on ER/LA opioid analgesics and Medication Guides. These materials must be accessible to prescribers; the RPC maintains an ER/LA Opioid Analgesics REMS website that includes these downloadable forms. Prescribers can also order Patient Counseling Document pads through the website.

On an annual basis, surveillance monitoring activities are conducted to evaluate abuse, misuse, abuse, overdose and death to assess the impact of the REMS. Additionally, prescription data are used to describe trends in the number of prescriptions for ER/LA opioid analgesics and comparators, as well as, to evaluate changes in prescribing behavior of prescribers.

2.4. Timetable for Submission of Assessments

REMS assessments are to be submitted to the FDA at 6 months and 12 months after the REMS is initially approved from the date of approval of the REMS, and annually thereafter.

To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment. The NDA/ANDA holders will submit each assessment so

that it will be received by the FDA on or before the due date based on the initial approval date of the REMS.

2.5. Current State of Opioid Abuse in the US

The adverse impact of opioid abuse and misuse takes many forms, chief among them are overdose and addiction. According to Centers for Disease Control and Prevention (CDC), rates of opioid overdose deaths jumped significantly, from 7.9 per 100,000 in 2013 to 9.0 per 100,000 in 2014, a 14% increase.⁴

An important component of this problem is that opioid abuse encompasses both prescribed and non-prescribed IR and ER/LA opioid analgesics, as well as heroin and illicitly-manufactured fentanyl. As the REMS applies only to ER/LA opioid analgesics, the data presented within this Briefing Book will focus on data related to ER/LA opioid analgesics, not IR opioids or heroin. The RPC recognizes that opioid abuse is a complex problem requiring a comprehensive solution, as reflected in the President's 2014 national drug control plan. Because multiple interventions to address opioid abuse were undertaken in a similar timeframe, it is difficult to separate the impact of the REMS from other interventions, though overall trends impacted by public health interventions, including REMS education, can be evaluated.

In addition to mortality, other types of adverse health events tied to prescription opioid abuse have increased over the last decade. Rates of emergency department (ED) visits associated with pharmaceutical misuse or abuse increased 114 percent between 2004 and 2011.⁵ In 2011, more than 1.4 million ED visits annually were due to the misuse or abuse of pharmaceuticals, with 420,000 involving prescription opioids and 425,000 involving benzodiazepines. In addition, the admission rate for substance abuse treatment for prescription opioid abuse in 2009 was almost 6 times the rate in 1999.⁶

The RPC supports many aspects of the position on opioid abuse as presented in the recent New England Journal of Medicine article by Califf, Woodcock and Ostroff (2016).⁷ A societal approach is needed to address gaps in our efforts to curtail abuse and misuse, while ensuring access to opioid medication for patients who suffer from chronic pain severe enough to warrant its use.

⁴ CDC. Increases in Drug and Opioid Overdose Deaths — United States, 2000–2014. CDC. Available at <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm64e1218a1.htm>. December 18, 2015; Accessed: December 24, 2015.

⁵ Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. The DAWN Report: Highlights of the 2011 Drug Abuse Warning Network (DAWN) Findings on Drug-Related Emergency Department Visits. Retrieved from : <http://www.samhsa.gov/data/sites/default/files/DAWN127/DAWN127/sr127-DAWN-highlights.htm>

⁶ Paulozzi L, Jones C, Mack K, Rudd R; Centers for Disease Control and Prevention (CDC). Vital signs: overdoses of prescription opioid analgesics—United States, 1999–2008. MMWR Morb Mortal Wkly Rep. 2011;60(43):1487–1492.

⁷ Califf RM, Woodcock J, Ostroff S. A proactive response to prescription opioid abuse. N Engl J Med. 2016. doi:10.1056/NEJMSr1601307.

3. REMS ASSESSMENT

A critical aspect of the REMS is assessment of the effectiveness of the program in meeting its goals. The FDA has indicated 8 key areas for assessment as well as evaluation of the functional components of the REMS implementation. These elements are shown in the table below.

TABLE 2: FDA-REQUIRED REMS ASSESSMENTS

FDA REQUIREMENTS
1: Assessment of how many prescribers of ER/LA opioid analgesics have successfully completed the training. Specify performance goals for number of prescribers trained by time.
2: Independent audit of the quality of the content of the educational materials used by the CE Providers to provide the education. The audit should evaluate the quality of the content against the content approved by the FDA as part of the REMS, as well as against the ACCME [®] 's and other accrediting bodies' standards for commercial support.
3a: Prescriber survey Evaluation of HCP awareness and understanding of the serious risks associated with these products (e.g., through surveys of HCPs) and specification of measures that would be taken to increase awareness if surveys of HCPs indicate that HCP awareness is not adequate.
3b: Long-term evaluation
4: Patient survey Evaluation of patients' understanding of the serious risks of these products.
5: Surveillance monitoring for misuse, abuse, overdose, addiction, death and any intervention to be taken resulting from signals of these metrics, including information for different risk groups (e.g., teens, chronic abusers) and different settings (e.g., emergency rooms, addiction treatment centers, poison control call centers). As much as possible, the information should be drug-specific.
6: Evaluation of drug utilization patterns (IMS data)
7: Evaluation of changes in prescribing behavior of prescribers, e.g., prescriptions to non-opioid tolerant patients, excessive prescriptions for early refills.
8: Monitoring patterns of prescribing to identify changes in access to ER/LA opioid analgesics
Evaluation of Functional Components <ul style="list-style-type: none"> REMS Website Dear DEA-Registered Prescriber Letter Dear Professional Organization/Licensing Board Letter Call Center (Modified March 19, 2014 to Interactive Voice Response System)

In regard to the surveillance monitoring requirement, [Table 3](#) includes the assessment source related to each risk type addressed in the REMS.

TABLE 3: ASSESSMENT SOURCE FOR EACH REMS-RELATED RISK

RISKS ADDRESSED IN THE REMS	ASSESSMENT SOURCE
Abuse	Poison Center Data, Drug Treatment Center Data, College Survey Program
Misuse	Poison Center Data
Unintentional Overdose	Surveillance of Emergency Department Visits and Hospitalizations
Death	Poison Center Data, Mortality Rates Resulting From Drug Poisoning

4. 36-MONTH FDA ASSESSMENT RESULTS

Section 4.1 through Section 4.6 provides a summary of the assessment results included in the most recent FDA Assessment Report that was submitted in July 2015.

4.1. Prescribers Who Have Successfully Completed Training

The ER/LA Opioid Analgesics REMS represents the first time that certified CE has been used to fulfill a REMS training requirement. For purposes of this Briefing Book CE is used as an overarching term covering CE and CME. In early 2012, the RPC initiated discussions with national accrediting bodies to identify approaches to CE data collection/aggregation and independent audits, which could be conducted in a manner accordant with the Accreditors' standards for commercially supported CE. A working group consisting of representatives from the National CE Accrediting Bodies, National CE Provider Organizations, Professional Societies/other invited experts, RPC, and the agency worked together to revise the Medical Education Metrics Specifications (MEMS) to provide a data structure that allows for collection and analysis of CE data in order to fully meet the Agency requirements for the ER/LA Opioid Analgesics REMS.

Evaluating the extent to which the training is effective in meeting the performance goals of the ER/LA Opioid Analgesics REMS is a key component of the overall REMS evaluation. This assessment began with the implementation of accredited REMS-compliant CE activities on February 28, 2013. To assess the engagement of prescribers in the REMS CE, each independent CE Provider transmits required information associated with their RPC-supported, accredited REMS-compliant CE activities to the appropriate National Accrediting Bodies. These Accrediting Bodies then compile their data. The CE Data Aggregation Vendor collects this ER/LA opioid analgesic prescriber completer data from the Accrediting Bodies to report on the number of ER/LA opioid analgesic prescribers who successfully completed accredited REMS-compliant CE activities through the end of the CE data collection period.

As of February 28, 2015, a total of 524 accredited REMS-compliant activities have launched and a total of 37,512 prescribers have completed accredited REMS-compliant CE activity. All activities were accredited by at least 1 of 6 National Accrediting Bodies.

Based on an FDA request for the most current data, the RPC obtained a preliminary count of the number of completers through February 29, 2016, obtained outside of the formal data aggregation process. An additional 28,707 prescribers completed an accredited REMS-compliant CE activity between March 1, 2015 and February 29, 2016, for a cumulative total of 66,219. A breakdown of prescriber completers by year and cumulatively through February 29, 2016 is presented in [Table 4](#).

TABLE 4: PRESCRIBERS COMPLETING AN ACCREDITED REMS COMPLIANT CE ACTIVITY

	ACCREDITED REMS- COMPLIANT CE ACTIVITIES LAUNCHED ¹	PRESCRIBERS COMPLETING ACCREDITED REMS-COMPLIANT TRAINING	CUMULATIVE PRESCRIBERS COMPLETING ACCREDITED REMS- COMPLIANT TRAINING
6-Month Assessment	N/A	N/A	N/A
12-Month Assessment February 28, 2013-May 10, 2013	9	1,147	1,147
24-Month Assessment May 11, 2013-February 28, 2014	262	18,658	19,805
36-Month Assessment March 1, 2014-February 28, 2015	253	17,707	37,512
48-Month Assessment March 1, 2015-February 29, 2016	315	28,707	66,219

¹ An accredited REMS-compliant CE activity may be launched in one reporting period but be active in subsequent reporting periods.

“Prescriber” completers are defined as “clinicians who are registered with the DEA to prescribe Schedule II and/or III controlled substances and have written at least one ER/LA opioid analgesic prescription in the past year.” Completion of an activity is defined as “Prescribers that have completed all components of an educational activity and met the education provider's criteria for passing. Components of an educational activity include instruction, assessment of learning, and potentially evaluation.”

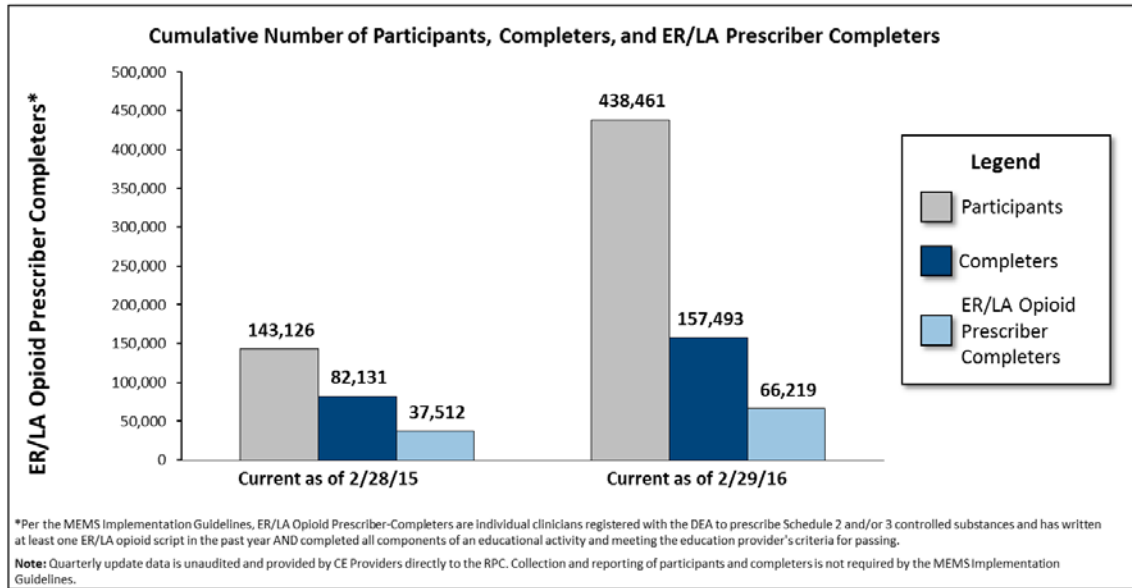
The RPC recognizes that this number of ER/LA opioid analgesic prescriber completers does not meet the REMS goal of 80,000 within 2 years following availability of the first accredited REMS-compliant training (February 28, 2015). CE Providers have found that approximately 54% of HCPs (44,619/82,131) completing an accredited REMS-compliant CE have indicated that they had not written a prescription for an ER/LA opioid analgesic in the past year. As such, well over half of all clinicians who “successfully complete” accredited REMS-compliant CE cannot be counted toward the REMS completer goal.

As of February 28, 2015, 37,512 ER/LA opioid analgesic prescribers had completed the RPC-supported accredited REMS-compliant training. As shown in [Figure 3](#), this represented 45.7%⁸ of the total healthcare professionals that have completed an accredited REMS-compliant CE activity (37,512/82,131). As of February 29, 2016 a total of 66,219 ER/LA opioid analgesic prescribers had completed the RPC-supported accredited REMS-compliant training, which accounts for 42.0%⁹ of all completers (66,219/157,493).

⁸ Based on the total gathered from quarterly reports provided by CE Providers through February 28, 2015

⁹ Based on the total gathered from quarterly reports provided by CE Providers through February 29, 2016

FIGURE 3: ACCREDITED REMS-COMPLIANT PARTICIPANTS, COMPLETERS AND ER/LA PRESCRIBERS (FEBRUARY 28, 2013-FEBRUARY 29, 2016)



4.1.1. Characteristics of ER/LA Opioid Analgesic Prescribers Completing Training

A break-down of training by profession of the 37,512 ER/LA opioid analgesic prescribers as of February 28, 2015 is provided below. The majority of prescribers who completed the CE training were physicians (25,713/37,512, 68.5%). The remaining prescribers were primarily advanced practice nurses (8,144/37,512, 21.7%) or physician assistants (2,299/37,512, 6.1%).

FIGURE 4: RPC-SUPPORTED, ACCREDITED REMS-COMPLIANT ER/LA OPIOID ANALGESIC PRESCRIBERS COMPLETING TRAINING BY PROFESSION (FEBRUARY 28, 2013- FEBRUARY 28, 2015)

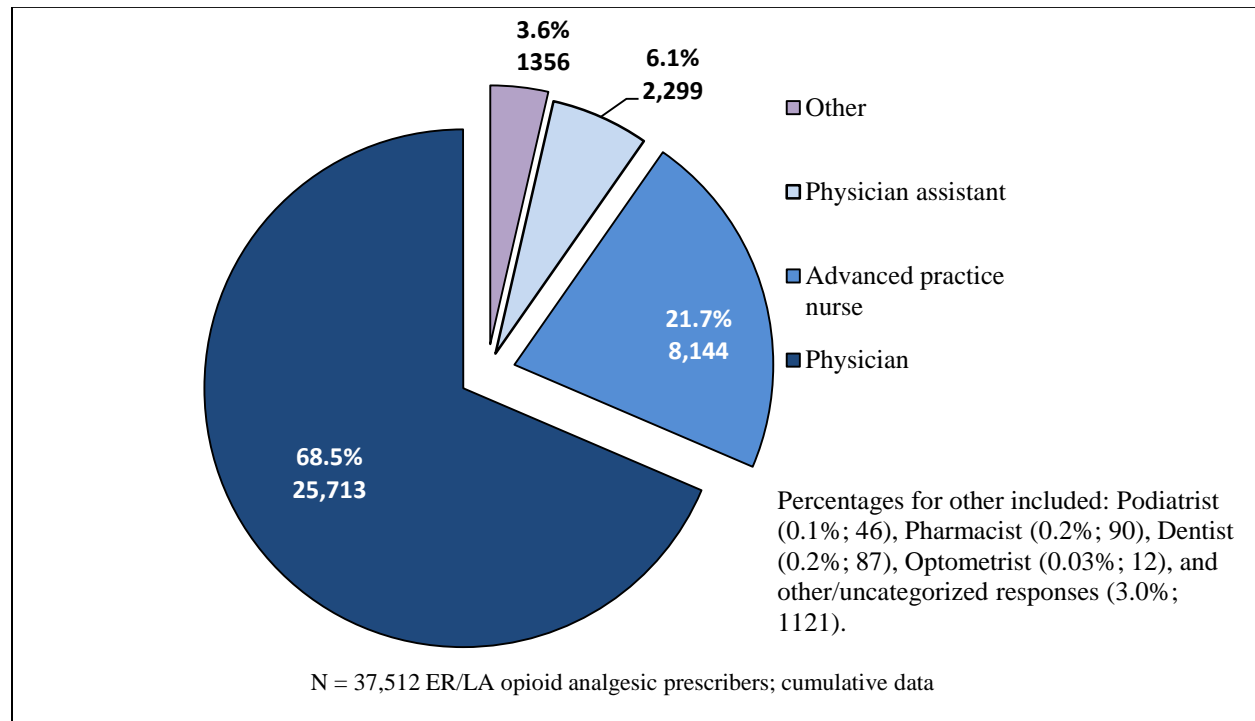
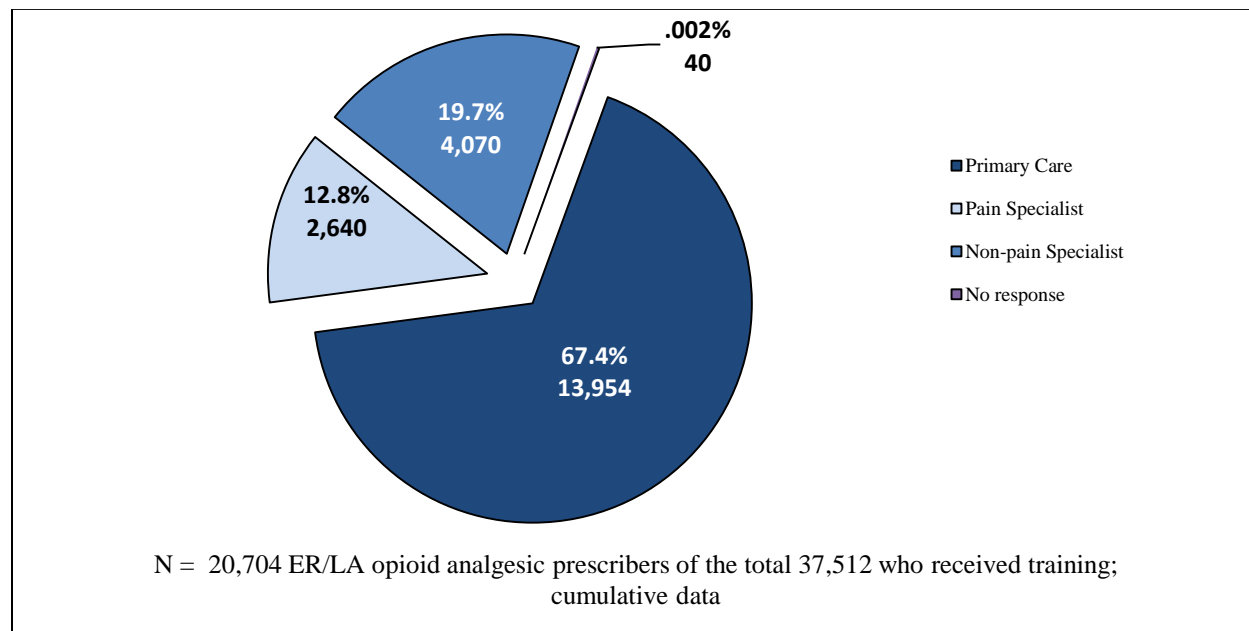


Figure 5 provides data according to the practice type, or the clinical practice focus of the ER/LA opioid analgesic prescriber. Practice type was an optional MedBiquitous (REMS CE data collection standards vendor) metric category captured by some CE Providers for those ER/LA opioid analgesic prescribers completing accredited REMS-compliant training. These data were collected on 20,704 ER/LA opioid analgesic prescribers. For those prescribers for whom a practice area was reported, 67.4% were primary care physicians (13,954/20,704).

FIGURE 5: ER/LA OPIOID ANALGESIC PRESCRIBERS COMPLETING RPC-SUPPORTED, ACCREDITED REMS-COMPLIANT TRAINING BY PRACTICE TYPE (FEBRUARY 28, 2013- FEBRUARY 28, 2015)



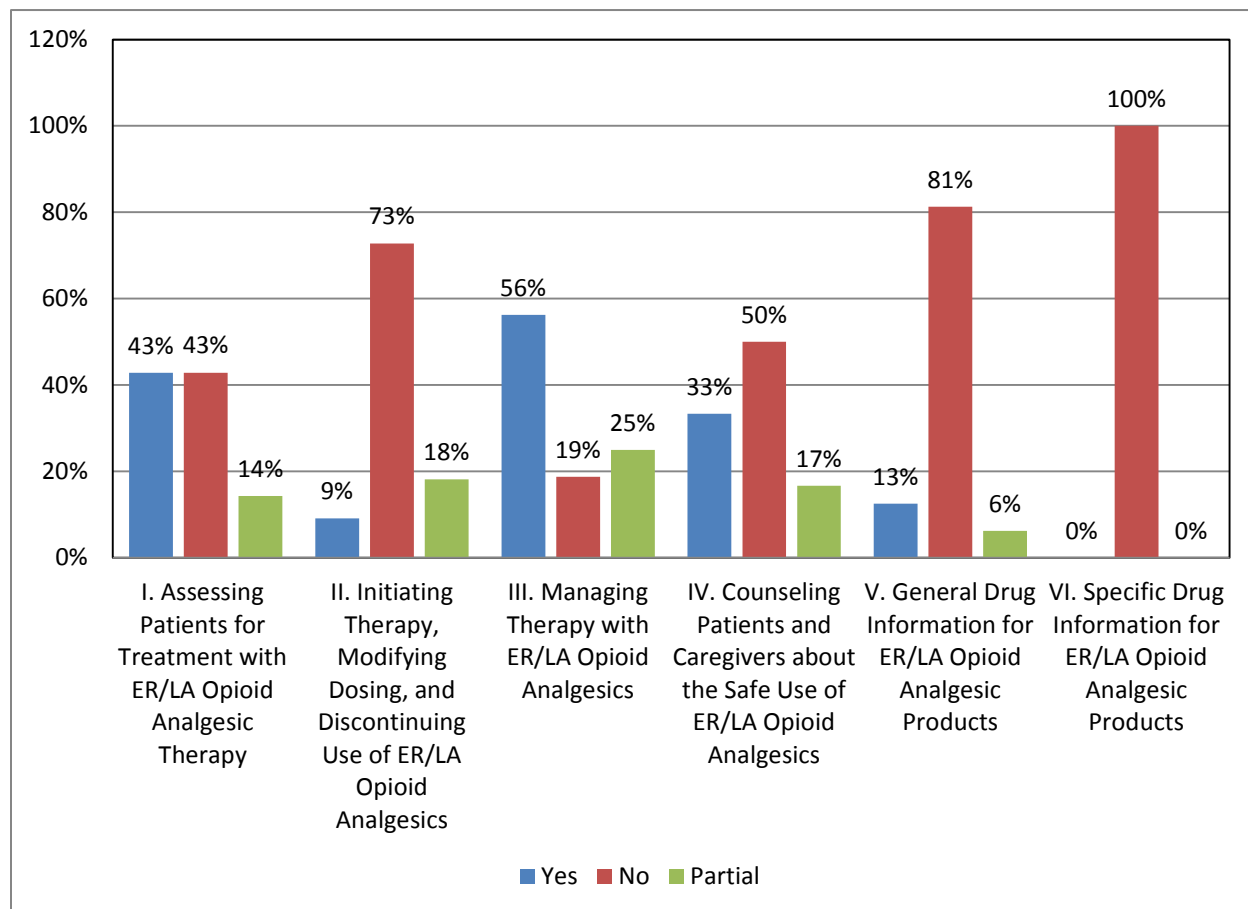
4.1.2. ER/LA Opioid Analgesic Prescribers Completing Non-RPC-Supported REMS-Compliant Training

There have been 18 non-RPC supported CE Activities reported to ACCME (or other accreditors if applicable), with 1,747 prescriber completers. These 18 activities were “self-identified” as REMS-compliant by the CE Provider in ACCME’s Program and Activity Reporting System (PARS) database. Due to the Accreditors’ need to maintain confidentiality of data related to non-RPC-supported activities, RPC itself cannot directly verify that non-RPC supported Activities are REMS-compliant. Instead, RPC is made aware of information on non-RPC-supported activities which have been attested to as being REMS-compliant through communications issued by the Accrediting Bodies which govern the accredited CE Providers. These prescribers are not included in the total number of prescriber completers reported.

The RPC continues to actively explore ways to identify completers of non-RPC-supported CE that aligns with the FDA Blueprint and conforms fully to the REMS requirements. To determine potential options to count non-RPC supported CE as REMS-compliant, RPC worked with a third-party to evaluate one identified non-RPC supported CE based on the concepts of the FDA Blueprint. *Safe Prescribing for Pain*, a NIDA course, was mapped to the educational items contained within the FDA Blueprint which showed that approximately 31% of the FDA Blueprint educational content was covered in full by the CE activity and another 8% included in part. See [Figure 6](#) for a breakdown of topics covered in the curriculum.

A total of 208,310 participants and 106,861 healthcare professionals¹⁰ completed *Safe Prescribing for Pain or Managing Patients Who Abuse Prescription Drugs*, offered by NIDA, from October 2012 until the expiration of the programs (<http://pcssmat.org/announcement-from-the-national-institute-on-drug-abuse-new-cmece-course-adds-to-physician-toolbox-for-addressing-substance-use-in-patients/>).

FIGURE 6: FDA BLUEPRINT MESSAGES COVERED IN A NON-RPC-SUPPORTED CE ACTIVITY ADMINISTERED BY NIDA



4.1.3. Challenges of ER/LA Opioid Analgesics REMS CE

The RPC has identified 3 predominant challenges in getting prescribers to complete accredited REMS-compliant CE activities.

Challenge #1: Lack of awareness of the REMS and the importance of completing ER/LA Opioid Analgesics Accredited REMS-compliant CE

¹⁰ Data provided on March 7, 2016 by Medscape/NIDA for two activities: *Safe Prescribing For Pain* and *Managing Pain Patients Who Abuse RX Drugs* (<https://www.drugabuse.gov/opioid-pain-management-cmesces>). This course launched in October 2012 and has since expired.

While prescribers are generally aware of the overall public health/patient safety issues associated with the use of opioid analgesics, feedback from CE Providers and members of the CCCE indicate that this generalized “opioid awareness” may not translate into prescriber predisposition to completing accredited REMS-compliant CE.

The RPC, CCCE and CE Providers are pursuing further insights into lack of awareness. A survey done by Collaborative for REMS Education (CO*RE)¹¹ in November and December 2013 (8 months after the launch of the first accredited REMS-compliant CE activity) demonstrated that 41% of the 2,629 respondents were unaware of the FDA ER/LA Opioid Analgesics REMS. Additionally, a survey was done by Boston University.¹² Results shows that the ER/LA opioid REMS training SCOPE of Pain improved clinician-level safe opioid prescribing outcomes, however, its impact on mitigating opioid misuse risk and harm while maintaining access to opioids for those that are or would benefit remains an unanswered question. While education cannot be the only strategy to combat this national crisis, it can help improve clinician behaviors and be a major part of the solution.

Feedback and information received to date suggests 3 contributing factors to lack of awareness of the REMS and the importance of completing ER/LA Opioid Analgesics accredited REMS-compliant CE:

1. The term “REMS” itself is not explicitly meaningful to prescribers
2. There is considerable ambiguity associated with the term “REMS” given the variability in clinician-related requirements from one REMS to another
3. Many available opioid educational activities are not REMS-compliant; prescribers may find it difficult to distinguish between those that are and are not REMS-compliant
 - a. Prescribers who complete non-REMS compliant CE, particularly activities endorsed by NIDA/Office of National Drug Control Policy (ONDCP)/Substance Abuse and Mental Health Services Administration (SAMHSA) or those required for state licensure, are unlikely to complete accredited REMS-compliant CE since prescribers may consider it redundant.
 - b. Further, prescribers may not complete an accredited REMS-compliant CE activity due to an assumption of knowledge. For example, a pain specialist may choose to complete a different CE activity than accredited REMS-compliant CE as they may think they already know the material.

Challenge #2: Education is not tailored to the adult professional learner

Another factor that negatively impacts prescriber completion of accredited REMS-compliant CE activities is the overall format of accredited REMS-compliant CE activities. Specifically, the length of activities and the associated time commitment for completion, coupled with no accommodation for demonstration of prior knowledge or competency impacts prescriber willingness to complete accredited REMS-compliant CE activities.

¹¹ Collaborative for REMS Education Partners. 2011 needs assessment and educational design report; Long-acting and extended-release analgesic opioids REMS. CO*RE website. <https://issuu.com/cafamilydocs/docs/core.needs-summit.report.august9-2011>. Accessed March 28, 2016.

¹² Alford DP, Zisblatt L, Ng P, Hayes SM, Peloquin S, Hardesty I, White JL. SCOPE of pain: An evaluation of an opioid risk evaluation and mitigation strategy continuing education program. *Pain Med.* 2015. doi: 10.1111/pme.12878.

The REMS dictates that the CE activities must include the full content of the FDA Blueprint, as well as an assessment covering all sections of the FDA Blueprint, in order to be considered REMS-compliant. Based on the amount of content encompassed by the FDA Blueprint, the challenge of CE activity length and structure cannot be easily addressed without creating options to customize learning activities based on a prescriber's demonstration of prior learning and competence. Additionally, many other non-REMS CE activities (including other opioid-related CE) do not require a mandatory assessment, which presents an added hurdle to prescribers completing an already lengthy educational activity.

Finally, feedback from REMS CE Providers, Accrediting Bodies, the CCCE, and from learners themselves emphasizes that the prescriptive nature of the FDA Blueprint is not conducive to the type of education that is engaging to adult professional learners. While CE Providers strive to develop innovative approaches and formats for presenting the FDA Blueprint, including interactive case studies, they report that the rigidity and extent of content makes it difficult to tailor educational activities to meet the specific knowledge/competence/performance gaps of the diverse groups of learners who comprise the REMS target audiences.

Challenge #3: Available opioid education that competes with Accredited REMS-Compliant CE activities

A substantial factor impacting the number of ER/LA opioid analgesic prescribers who engage in and complete accredited REMS-compliant CE is the fact that there are innumerable non-REMS-compliant CE activities (hereafter in this section referred to as non-RPC funded CE activities) related to opioids available to clinicians, both online and in live peer-to-peer settings. Feedback received from both CE Providers and the CCCE has informed the RPC that non-RPC funded CE activities potentially dilute the audience of ER/LA prescribers who may complete the accredited REMS-compliant CE activities. Prescribers may choose to complete these non-RPC funded CE activities versus accredited REMS-compliant CE activities since completion of these non-RPC funded CE activities may fulfill state-mandated licensure requirements, are offered or endorsed by prominent, non-industry-related organizations (such as NIDA, ONDCP, or SAMHSA), or appeal to prescribers since they cover opioid risk management within the broader context of appropriate pain management, rather than having a singular focus on ER/LA opioid analgesics.

As a result of the feedback received from CE Providers and the CCCE, the RPC has conducted an analysis to understand the extent of competing accredited CE activities related to opioid analgesics. The investigation included a keyword search to determine the number of non-RPC funded CE activities that may be identified if a prescriber attempted to search for CE activities related to opioids, controlled substances, pain management or another similar search term. After the extent of search results was determined, a further examination and categorization was completed to understand the type of non-RPC funded CE activities returned.

A total of 150 non-RPC-funded accredited CE activities related to opioid analgesics were reviewed and categorized. These 150 activities included in the analysis were identified in the keyword search as having high relevance and prominence. Key findings from the analysis of these non-RPC-funded accredited CE activities related to opioid analgesics included:

- ~87% of the activities would most accurately be described as “Non-REMS Opioid-Related CE”
 - ~34% of the “Non-REMS Opioid Related CE” activities were endorsed, developed, or funded by federal agencies such as NIDA, ONDCP, SAMHSA, and NINDS
- 8% of the activities were identified by the CE Provider as “FDA Blueprint-Compliant”
- A significant percentage of activities provide the additional benefit to prescribers of meeting state-mandated CE requirements for license renewal. These include:

- 100% (12 out of 12) of those non-RPC funded CE activities identified by the CE Provider as “FDA Blueprint-Compliant”
- ~38% of the “Non-REMS Opioid-Related CE activities”

Based on discussions with different stakeholders that provide education around the topic of ER/LA opioid analgesics, RPC continues to encourage stakeholder participation and explore options for increasing prescriber completer counts.

The RPC CE Subteam continues to work closely with RPC-supported CE Providers, as well as the CCCE to identify means of addressing the challenge of non-RPC funded CE activities competing with accredited REMS-compliant CE activities. To date, the RPC has taken the following steps to enhance and formalize communication channels with RPC-supported CE Providers:

- Hosted biannual Provider Information Exchange (PIE) teleconferences to facilitate discussion and enable Accredited CE Providers to share general experiences and challenges in providing accredited REMS-compliant CE as well as best practices for conducting CE Activities and optimizing the number of successful completers,
- Developed and implemented a plan for regular milestone-related and ad hoc calls with grantees and CE team members designated as “Point of Contact” to discuss progress toward goals, challenges, and necessary modifications to increase reach and completion rates.
- Discussed and presented on the topic during the July 22, 2015 CCCE/FDA REMS meeting held at the FDA White Oak Campus.
- Contracted with an external agency to begin development of a REMS Awareness Campaign, to include a CE-specific website to house all information regarding RPC accredited REMS-compliant CE, including content and references, and an ER/LA Opioid Analgesics REMS logo/tagline to allow prescribers to easily identify each activity that is part of the ER/LA Opioid Analgesic REMS.
- Funded grants with unique and innovative formats to provide accredited REMS-compliant CE activities in formats more conducive to the adult learner
- Continued to work in collaboration with the CCCE towards the opportunity to include demonstration of prior knowledge as a method of conducting accredited REMS-compliant CE
- ER/LA Opioid Analgesics REMS Plenary Session at the annual national meeting for CE Providers (Alliance for Continuing Education in the Health Professions) to familiarize all CE Providers with the requirements for REMS-compliance, and to encourage CE Providers who offer opioid-related CE to assure it is REMS-compliant. The first session was conducted on January 15, 2016.

Next steps currently being explored include:

- ER/LA Opioid Analgesics REMS information at the annual national meeting for CE Providers to help inform non-RPC funded CE Providers about the requirements for REMS-compliant CE activities, and to convey the importance of opioid CE being REMS-compliant

4.2. Independent Audit of Continuing Education Activities

In order to assure that the overall content and quality of the accredited certified educational activities complies with the FDA Blueprint, the RPC has audits conducted by parties that are independent of industry and acceptable to both the FDA and various CE Accrediting Bodies. This allows the educational offerings to be assessed for compliance to the Blueprint in an independent manner. Based on the Blueprint auditor criteria, the audits are conducted by an auditor independent of the NDA/ANDA holders.

(Accreditation bodies of CE Providers would be considered independent of the NDA/ANDA holders and would be eligible to conduct the audits.) Specifically the audits evaluate:

- whether the content is factually correct
- whether the content of the training covers all sections of the FDA Blueprint;
- whether the post-course knowledge assessment measures knowledge of all sections of the FDA Blueprint; and
- whether the training was conducted in accordance with the standards for CE of the ACCME® or other accrediting bodies (including Standards for Commercial Support) and is independent of the pharmaceutical industry's influence and the content is free from promotional material. (Specific medication information will be included in CE activities as dictated in the FDA Blueprint. However, the information presented will be free of promotional messaging.)

The CE activity audits are based on a random sample of at least 10% of the RPC-supported, accredited REMS-compliant CE activities and REMS-compliant training not funded by the RPC but that will be counted towards meeting the REMS performance goals. These audits occur at least once for each activity, preferably prior to finalization of the CE content, and are repeated if substantial changes to content are made. Currently, there are 5 nationally recognized Accrediting Bodies that have submitted independent audit reports.

Since the launch of the first RPC-supported, accredited REMS-compliant CE activity on February 28, 2013, 524 CE activities have been launched and 56 audits have been conducted, with additional audit reports pending for the additional 315 activities in the reporting period that spans March 1, 2015 – February 29, 2016. Of these, 100% met all criteria for REMS-compliant CE as defined in the REMS Supporting Document and the FDA Blueprint. ACCME noted observations for 14 of the audit reports as they did not fully meet expectations with respect to the ACCME® Standards for Commercial Support around obtaining and prominently displaying financial relationships of faculty and/or staff involved in the activity. No observations pertained to content. The RPC has followed up with each provider where observations are noted, and have ensured that all audit findings were remediated.

4.3. Patient Survey

To assess patient knowledge of the safe use of ER/LA opioid analgesic products following implementation of the REMS, a cross-sectional survey of commercially insured patients was conducted. The survey included questions assessing the respondents' knowledge about the safe use of ER/LA opioid analgesics, the receipt and comprehension of the Medication Guide and Patient Counseling Document, and perceived access and satisfaction with access to pain medication. The patient survey also identified patient-reported prescriber behaviors, including appropriate screening and counseling.

The primary objectives of the patient survey were:

1. To determine whether patients received the Medication Guide and/or Patient Counseling Document and from whom;
2. To determine whether patients read the Medication Guide and/or the Patient Counseling Document;
3. To assess whether the patient understood the serious risks associated with the use of their ER/LA opioid analgesic;
4. To assess whether the patient knows what to do if they take too much drug;
5. To assess whether the patient understands the need to store the drug in a safe place;
6. To assess whether the patient knows they should not share the drug with anyone;

7. To assess whether the patient understands how to use the drug safely; and
8. To assess the impact of the ER/LA Opioid Analgesics REMS on access to treatment.
 - compared to before the implementation of the REMS, do patients perceive a change following REMS in physicians' prescribing of pain medication;
 - compared to before the REMS, do patients perceive a change following REMS in access to medications to treat pain; and
 - compared to before the REMS, do patients perceive a change following REMS in satisfaction with access to pain treatment.

4.3.1. Methods

The survey population was identified from medical and pharmacy claims in the HIRD based on the following inclusion criteria:

- at least one pharmacy claim for an ER/LA opioid analgesic in the most recent 12-months of claims data
- currently active, commercially-insured, survey eligible members with medical and pharmacy benefits
- at least 18 years of age as of the date of the most recent ER/LA opioid analgesic dispensing (the index date)
- a non-missing telephone number and/or address
- does not appear on the HealthCore "Do-not-call" list
- no history of substance abuse identified in the claims data

Eligible patients were invited to participate in a survey by a pre-notification letter. Patients who did not respond to the invitation letter were then contacted by telephone and invited to participate. Consenting patients were excluded if they failed to validate their name and date of birth, stated that they had not filled a prescription for an ER/LA opioid analgesic in the 12 months prior to the survey date, were employed as a licensed physician, were unsure of their ER/LA opioid analgesic, or were employed or had immediate family members that were current or former employees of vendor companies who developed and/or implemented the survey; the FDA; or members of the RPC. The survey averaged approximately 20 minutes. Patients who completed the survey received a \$20 check for their time.

Questions in the survey asked patients whether they:

- received the Medication Guide (described by interviewer or shown on the Internet) and/or Patient Counseling Document during the past 12 months;
- read the Medication Guide and/or had a provider that referenced the Patient Counseling Document;
- understood the Medication Guide and/or Patient Counseling Document;
- understood the serious risks associated with the use of the most recent ER/LA opioid analgesic which was dispensed to them, as described in the respective core section of the Medication Guide or Patient Counseling Document;
- understood how to use the drug safely;
- understood what to do if they take too much drug;
- understood the need to store the drug in a safe place; and

- understood not to share the drug with anyone.

In addition to these main outcomes of interest, patient demographic characteristics and information on use of ER/LA opioid analgesics were collected.

Comparability between patients who completed the survey and all those with ER/LA opioid analgesic prescriptions in the HIRD was determined using the following covariates:

- age
- gender
- US region (Northeast, South, Midwest and West)
- duration of continuous health plan eligibility prior to the most recent dispensing of an ER/LA opioid analgesic (months)
- status as a new user of ER/LA opioid analgesics (i.e., whether the patient had continuous health plan eligibility for at least six months prior to the first recorded dispensing of an ER/LA opioid analgesic)
- duration of ER/LA opioid analgesic therapy during continuous health plan enrollment
- specific ER/LA opioid analgesic(s) used most recently before the survey
- number of previous dispensings of ER/LA opioid analgesics prior to the index date
- number of distinct drugs dispensed during the past six months prior to the index date
- medical condition(s) for which ER/LA opioid analgesics are indicated

4.3.2. Statistical Methods

The statistical analyses performed in this study were descriptive. Prior to assessing descriptive statistics on the survey data, an analysis was done that compared the demographic characteristics of patients who completed the survey (respondents) with the demographic characteristics of those patients who did not complete the survey (all non-respondents) including those who, could not be contacted, who were excluded because they no longer met study inclusion criteria, or who refused to participate in the study.

A knowledge assessment score (KAS) for each patient was calculated from their self-reported responses to the knowledge questions. The KAS was defined as the proportion of knowledge questions that the patient answered correctly. A mean knowledge score was reported overall and by drug group (e.g., methadone, transdermal delivery systems, and oral products that are not methadone). The percentage of patients above and below a threshold KAS of 80% was also calculated.

We described the level of knowledge, as defined by the KAS, of the risks and safe use of ER/LA opioid analgesics among patients who:

- Did and did not receive the Medication Guide and/or Patient Counseling Document;
- Did and did not read/reference the Medication Guide and/or Patient Counseling Document; and
- Did and did not understand the Medication Guide and/or Patient Counseling Document

4.3.3. Survey Administration

Of 11,500 patients who met the claims-based inclusion/exclusion criteria between September 1, 2013 and August 31, 2014, 2,441 patients were contacted of which 272 (11%) failed to meet the survey screening criteria, 1,746 (72%) refused to participate, and 423 (17%) completed the survey

As shown in Table 5, the 423 survey respondents were more often female and slightly older than patients in the sampling frame, but were comparable in terms of region and clinical characteristics at baseline. Further, Table 6 provides a comparison of survey respondents to all ER/LA opioid users in the HIRD since 2012. Survey respondents were more often female and slightly older than patients receiving ER/LA opioids in the HIRD overall since 2012. More had received opioids from a pain specialist, however this is difficult to interpret as a larger proportion of the overall sample had an unknown specialist type prescribing opioids.

TABLE 5: COMPARISON OF PATIENT SURVEY RESPONDENTS TO THE SAMPLING FRAME

	SURVEY RESPONDENTS		SAMPLING FRAME	
	<i>N</i>	(%)	<i>N</i>	(%)
Total	423	(4)	11,077	(96)
Age in years				
18 to 34	49	(12)	1,226	(11)
35 to 49	116	(27)	3,421	(31)
50 to 64	238	(56)	6,007	(54)
65+	20	(5)	423	(4)
Gender				
Female	253	(60)	5,632	(51)
Male	170	(40)	5,445	(49)
US Census region of residence				
Northeast	54	(13)	1,415	(13)
South	110	(26)	3,156	(28)
Midwest	141	(33)	2,886	(26)
West	114	(27)	3,529	(32)
Unknown	<5	(<1)	111	(1)
Specific ER/LA opioid analgesic(s) used most recently before the survey				
<u>Oral drugs that are not methadone only</u>	<u>265</u>	<u>(65)</u>	<u>7,488</u>	<u>(68)</u>
<u>Patch and no methadone</u>	<u>114</u>	<u>(27)</u>	<u>2,431</u>	<u>(22)</u>
<i>Patch only</i>	113	(27)	2,398	(22)
<i>Patch and oral drug(s) that are not methadone</i>	< 5	(< 1)	33	(< 1)
<u>Methadone</u>	<u>44</u>	<u>(10)</u>	<u>1,158</u>	<u>(10)</u>
<i>Methadone only</i>	44	(10)	1,121	(10)
<i>Methadone and oral drug(s) that are not methadone</i>	0	(0)	23	(< 1)
<i>Methadone and patch</i>	0	(0)	14	(< 1)
<i>Methadone, oral drug(s) that are not methadone, and patch</i>	0	(0)	0	(0)
Duration of continuous health plan eligibility prior to the most recent dispensing of an ER/LA opioid analgesic, mean (STD)	11.9 (5.8)		12.0 (5.5)	
Duration of ER/LA opioid analgesic(s) used most recently	5.95 (6.5)		5.9 (6.6)	

	SURVEY RESPONDENTS		SAMPLING FRAME	
before the survey, months, <i>mean (STD)</i>				
Number of previous dispensings of ER/LA opioid analgesics prior to the index date, <i>mean (STD)</i>	6.5 (7.2)		6.9 (8.3)	
Number of distinct drugs dispensed during the past six months prior to the index date, <i>mean (STD)</i>	9.2 (6.0)		8.0 (5.2)	
Medical condition(s) for which ER/LA opioid analgesics are indicated ⁷				
Amputation in the lower limbs or extremities	< 5	(< 1)	30	(< 1)
Arthritis, arthropathies, osteoarthritis, and musculoskeletal pain	362	(86)	9,472	(86)
Chronic pain	166	(39)	3,799	(34)
Fibromyalgia	92	(22)	2,213	(20)
Malignancy	64	(15)	1,606	(15)
Multiple sclerosis	8	(2)	115	(1)
Neuropathic pain	104	(25)	2,311	(21)
Peripheral vascular disease with claudication, ischemic extremity pain and/or skin ulcers	7	(2)	280	(3)
Stroke	17	(4)	414	(4)
Other	24	(6)	593	(5)
Unspecified abdominal pain	97	(23)	2,425	(22)
None of the above	27	(6)	753	(7)

TABLE 6: COMPARISON OF RESPONDENTS TO ALL ER/LA OPIOID USERS IN THE HIRD SINCE 2012

	SURVEY RESPONDENTS		ALL ER/LA OPIOID USERS	
	<i>N</i>	(%)	<i>N</i>	(%)
Total	423	(100)	43,730	(100)
Age in years				
Under 18	0	(0)	235	(1)
18 to 34	45	(11)	3,466	(8)
35 to 49	108	(26)	9,526	(22)
50 to 64	245	(58)	18,943	(43)
65+	25	(6)	11,560	(26)
Gender				
Female	253	(60)	24,395	(56)
Male	170	(40)	19,335	(44)
US Census region of residence				
Midwest	141	(33)	13,147	(30)

	SURVEY RESPONDENTS		ALL ER/LA OPIOID USERS	
Northeast	54	(13)	6,087	(14)
South	110	(26)	11,323	(26)
West	114	(27)	12,475	(29)
Unknown	< 5	(< 1)	698	(2)
Type of healthcare provider that first prescribed the survey index ER/LA opioid analgesic drug				
Pain specialist	179	(42)	11,220	(26)
Primary care physician, general practitioner, internal medicine specialist, or family practice physician	107	(25)	9,257	(21)
Other or unknown type of specialist	137	(32)	23,253	(53)

4.3.4. Survey Results

See [Appendix 7](#) for the distribution of questions/items ranked by Patient Survey score.

Medication Guide and Patient Counseling Document

As shown in [Table 7](#), most respondents reported receiving a Medication Guide and having read at least some of the Medication Guide. Of those who read or received, most reported they understood at least half.

TABLE 7: MEDICATION GUIDE AND PATIENT COUNSELING DOCUMENT RECEIPT AND UNDERSTANDING

	PATIENT SURVEY PARTICIPANTS N = 423		
	RECEIVED (%)	READ/PRESCRIBER REFERENCED (%)	UNDERSTAND (%)
Medication Guide ¹	409 (96.7)	410 (96.9)	414 (97.9)
Patient Counseling Document ²	182 (43.0)	109 (25.8)	254 (60.0)

¹ Based on Questions MG4, MG7, and MG12

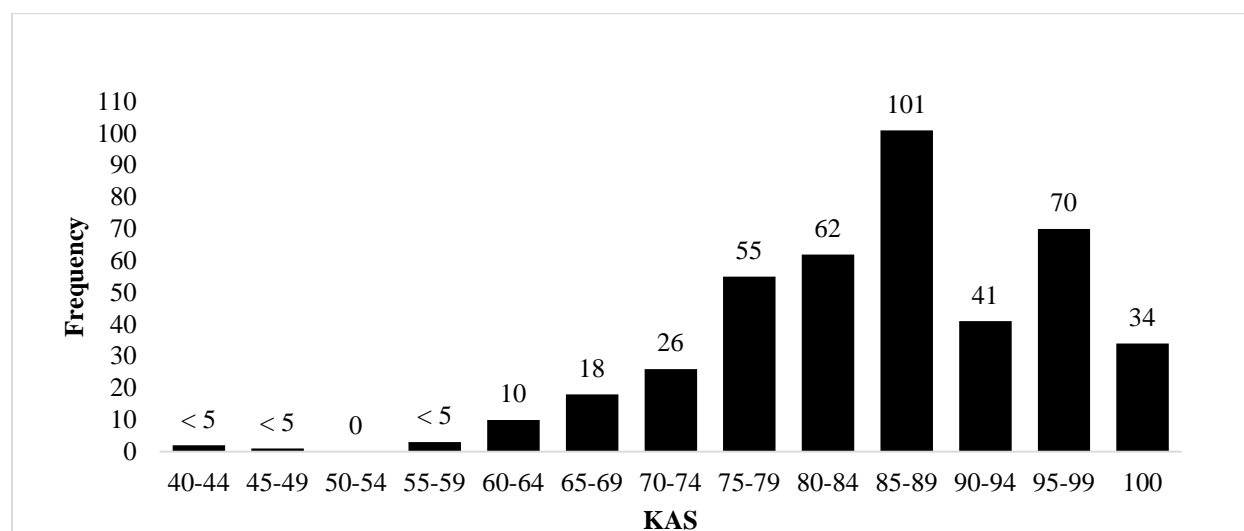
² Based on Questions PC3b, PC3c, and PC3d

All respondents either received, read/had a prescriber who referenced or understood the Medication Guide or Patient Counseling Document.

Knowledge Assessment

The majority of respondents correctly answered most questions concerning the serious risks of ER/LA opioid analgesic use, what to do in the case of overdose, proper storage, the importance of not sharing medication, and safe use. The KAS (i.e., proportion of knowledge questions that a respondent answered correctly) had a mean of 85.6% (Standard Deviation (SD) 10.08) and scores ranged from 40% to 100%. There were 34 (34/423, 8.0%) respondents with a KAS below 70% and 115 (115/423, 27.2%) with a KAS below 80% (inclusive of those with a response below 70%) (Figure 7).

FIGURE 7: DISTRIBUTION OF PATIENT KAS SCORES



Results by key risk message were as follows:

- *Patient understanding of the serious risks associated with the use of their ER/LA opioid analgesic*
 - Overall, 93% (394/423) of respondents correctly identified that overdoses may cause life-threatening breathing problems, respiratory depression, or abnormally slow breathing that can lead to death and 81% (342/423) knew that ER/LA opioid analgesics can make you dizzy, lightheaded, or sleepy.

- *The patient knows what to do if they take too much drug*
 - 97% (412/423) of respondents were aware of the need to seek emergency medical care for respiratory, chest, or facial swelling side effects, and 88% (374/423) knew to seek emergency medical care for an overdose even if the patient felt fine.
- *The patient understands the need to store the drug in a safe place*
 - The risk of death in children using the respondent's ER/LA opioid analgesic was recognized by 93% (393/423) of the respondents and 93% (393/423) recognized that ER/LA opioid analgesics should not be thrown away in the trash.
 - Fewer respondents (300/423, 71%) were aware that ER/LA opioid analgesics should not be stored in a medicine cabinet next to other household medications.
- *The patient knows they should not share the drug with anyone*
 - Respondents recognized that ER/LA opioid analgesics should not be given to others with the same condition (415/423, 98%) and that selling or giving away these medications is against the law (413/423, 98%).
- *The patient understands how to use the drug safely*
 - A high proportion of respondents were aware of the necessity of informing their healthcare providers about all other medications being used (394/423, 93%), over-the-counter medications (369/423, 87%), any history of substance or prescription drug abuse, alcohol addiction, or mental health problems (382/423, 90%), and whether to take more medication if the current dose was not controlling their pain (405/423, 96%); 84% identified the need to talk to a healthcare provider prior to stopping ER/LA opioid analgesics (357/423).
 - The need to abstain from alcohol was recognized by 93% of respondents (394/423).
 - Only 55% of respondents correctly identified the need to read the attached Medication Guide at each dispensing (232/423).
 - A small number of questions were asked only to respondents using a particular ER/LA opioid analgesic type:
 - Among respondents using oral products, 76% recognized that pills should not be split or crushed (204/268), and 93% recognized that more medication should not be taken in case of a missed dose (248/268).
 - Among respondents using transdermal products, 70% knew to inform their healthcare provider of any fever (71/101), 77% knew not to use a hot tub or sauna while using their ER/LA opioid analgesics (78/101) and 90% knew that the patch should not be cut in half in attempt to use less medicine (91/101).

The mean KAS was comparable across ER/LA opioid analgesic types (non-methadone oral products: 85.8, SD 9.89 versus patch products: 85.5, SD 10.07 and methadone users: 85.1, SD 11.12). Scores were generally similar across each key risk message. A higher proportion of patch users knew to seek emergency medical help for an overdose even if the respondent feels fine (95% of patch users (96/101), 89% of methadone users (48/54) and 86% of other oral product users (230/268)). A lower proportion of methadone users correctly identified the need to read the Medication Guide at each dispensing (48% of methadone users (26/54), 54% of oral product users (146/268) and 59% of methadone users (60/101)).

Respondents stating that they did not read the Medication Guide (13/423) had a slightly lower overall KAS (mean 72.0, SD 14.6 versus mean 86.0, SD 9.6 among respondents who stated that they read the

Medication Guide). These respondents more often answered questions about serious risks, safe storage and safe use incorrectly. In contrast, respondents who received the Patient Counseling Document or had a healthcare provider who referenced or understood the Patient Counseling Document had similar KAS values compared with those who did not (mean 85.5, SD 9.5 for those who received the Patient Counseling Document versus mean 85.6, SD 10.5 for those who did not). However, respondents whose providers did not give or reference the Patient Counseling Document less often understood benefits and risks, safe discontinuation, and what to do in the event of a missed dose based on their self-reported comprehension. Respondents with only one ER/LA opioid analgesic dispensing had slightly lower KAS scores than those with multiple dispenses (mean 82.5, SD 10.2 versus mean 86.7, SD 9.8).

The 115 respondents with a KAS < 80% showed knowledge deficits in most of the key risk message areas, but were aware that they should not share the drug with others with the same condition (110/115, 96%).

Provider Screening and Counseling

Over 90% of respondents reported that their HCPs discussed medical history and how much medication to use when their ER/LA opioid analgesic was first prescribed (392/423 and 391/423, respectively). In the 12 months prior to the survey, 55% of respondents reported that they were instructed on the proper disposal of unused medication (234/423) and 58% on safe discontinuation (246/423). Discussions with HCPs about how to keep ER/LA opioid analgesics safe and away from children were reported by 66% (279/423), not sharing medication by 70% (297/423), risks of overdose by 74% (312/423), and common side effects by 75% (317/423). Only 43% (183/423) of the respondents reported that their prescribing HCPs always, regularly, or sometimes used a Patient Counseling Document when discussing ER/LA opioid analgesics.

Compared with patch or methadone users, oral product users less often reported provider use of the Patient Counseling Document (39% of oral product users (105/268), 50% of patch users (50/101) and 52% of methadone users (28/54)), discussing keeping ER/LA opioid analgesics away from children (61% of oral product users (164/268), 72% of patch users (73/101) and 78% of methadone users (42/54)), and instruction not to share ER/LA opioid analgesics with others (68% of oral product users (182/268), 78% of patch users (79/101) and 80% of methadone users (43/54)). Respondents who received the Medication Guide and those who reported that they understood the Patient Counseling Document more often reported that their healthcare providers had discussed each of the applicable key points. A lower proportion of one time prescription users and individuals with a KAS <80% reported that their healthcare provider had discussed these key points.

4.3.4.1. Evaluation of Changes in Access based on Patient Survey Results

Among 423 patient survey respondents, 302 (302/423, 71%) stated that they were able to obtain a prescription for ER/LA opioid analgesics from their healthcare providers when needed for pain, which varied across medication types with fewer patch users (68/101, 67%) and more methadone users (40/54, 74%) reporting satisfaction. Respondents who did not understand the Medication Guide or Patient Counseling Document, or had only one recorded ER/LA opioid analgesic dispensing less often confirmed their access to obtain a prescription. Only 60% of single dispensing users (67/112) and 65% of respondents with a KAS <80% stated that they were satisfied with their ability to get a prescription when needed for ER/LA opioid analgesics from a healthcare provider when needed for pain (75/115). Satisfaction with their ability to get a prescription was reported by 83% of respondents (349/423), and was slightly higher for methadone users (47/54, 87%).

There were 329 (329/423, 78%) respondents who reported general satisfaction with access to ER/LA opioid analgesic treatment, and 337 (337/423, 80%) who were satisfied with their ability to get ER/LA opioid analgesics from a pharmacy. Nearly half of respondents (196/423, 46%) felt that they needed to

see their healthcare provider too often when more ER/LA opioid analgesics were needed. Respondents reported overall satisfaction with access to ER/LA opioid analgesics (329/423, 78%).

Among 383 non-neutral respondents (i.e., excluding the 40 respondents (9%) who indicated that they were neither satisfied nor dissatisfied with access to ER/LA opioid analgesics), 54 (54/383, 14%) were dissatisfied and 329 (329/383, 86%) respondents were satisfied with their access to ER/LA opioid analgesics. Satisfied respondents were more often female (60% (197/329) versus 54% (29/54)), from the Midwest (37% (121/329) versus 20% (11/54)) and married (71% (235/329) versus 54% (29/54)). A lower proportion of satisfied respondents (47% (155/329) versus 63% (34/54)) had completed at least a 2-year college degree. It is important to note that these respondents were drawn from a sample of patients who had commercial insurance and had received at least one prescription for ER/LA opioids; their experience may not be representative of the uninsured or those with other types of insurance, or of those who have never received an ER/LA opioid prescription.

4.3.5. Limitations of the Patient Survey

The patient survey utilized an administrative claims database to identify patients who were eligible to complete the survey and was subject to the limitations inherent in the use of such data. The database is representative of the commercially-insured population in the US; however it is not representative of individuals without medical insurance or those with government-sponsored insurance such as Medicaid. Since the study population is limited to adults with commercial insurance, representation of patients 65 years of age and older was limited to those patients that receive medical and pharmacy benefits through continued coverage by an employer. Additionally, parents or caregivers of children under the age of 18 using an ER/LA opioid analgesic or those individuals that did not have current health plan benefits at the time the patient list is generated were unable to be surveyed.

Although all patients were required to have a pharmacy benefit, patients were identified on the basis of submitted pharmacy claims; patients who chose not to use their pharmacy benefit were not identified as being eligible for the survey unless there were submitted pharmacy claims.

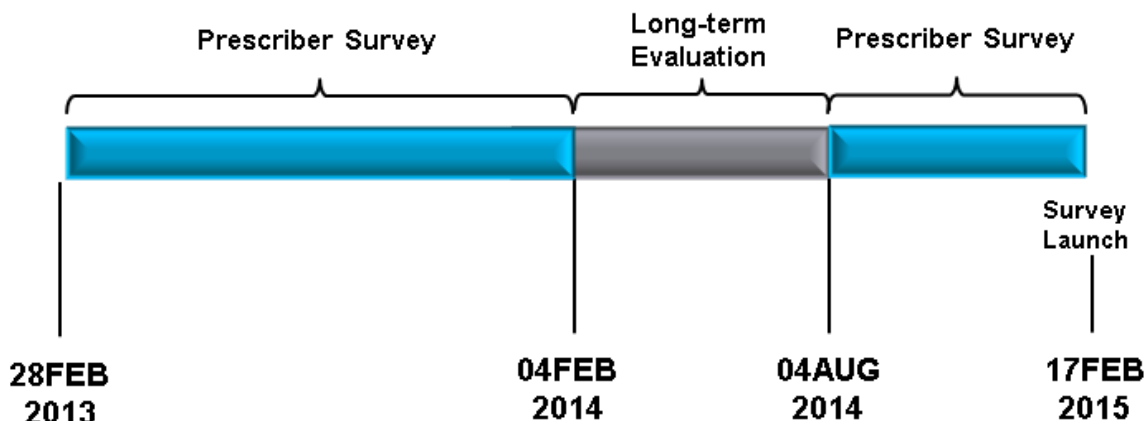
The large size of the HIRD was a study strength in that there were a sufficient number of patients who met eligibility criteria for the survey to achieve the targeted sample size of 400 completed surveys for the main patient survey. Utilization of the HIRD provides data necessary to merge patients' survey data with their administrative claims data to study the health care research utilization or incorporating data from patients' administrative claims records with their survey data.

4.4. Prescriber Surveys

Two prescriber surveys are used to evaluate the REMS. The Prescriber Survey is designed to collect information on HCP awareness and understanding of the serious risks associated with the ER/LA opioid analgesics. The Long-term Evaluation Survey has a similar goal, but is targeted to prescribers that have completed accredited REMS-compliant CE activity within 6 to 12 months prior to the survey. Both surveys are designed to align with the messages contained within the FDA Blueprint.

The figure below illustrates the timeframes covered by each of the two surveys.

**FIGURE 8: PRESCRIBER SURVEY AND LONG-TERM EVALUATIONS
SURVEY TIMEFRAMES**



4.4.1. Analysis of Prescriber Surveys

The analysis of a key risk message for Prescriber Survey and the Long-term Evaluation Survey evaluated the percentage of prescribers who chose the correct response(s) to each individual question/item defined as a key risk message. The questions were grouped according to 6 key risk messages based on the FDA Blueprint:

- 1: Patients should be assessed for treatment with ER/LA opioid analgesic therapy.
- 2: Prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics.
- 3: Management of ongoing therapy with ER/LA opioid analgesics is important.
- 4: It is important to counsel patients and caregivers about the safe use of ER/LA opioid analgesics.
- 5: Prescribers must be familiar with general information concerning ER/LA opioid analgesics.
- 6: Prescribers must be familiar with product-specific drug information concerning ER/LA opioid analgesics.

4.4.2. Prescriber Survey

Healthcare providers' awareness and understanding of the serious risks associated with the ER/LA opioid analgesics is evaluated through a survey of HCPs. The Prescriber Survey was conducted in 2015, approximately 2 years post-launch of the accredited REMS-compliant CE. There was a targeted effort to include prescribers who were known to have completed an accredited REMS-compliant CE activity so that they could be compared with those who did not. Prescribers were identified for an invitation to complete the Prescriber Survey through IMS data as well as through CE completer data. Prescriber eligibility was determined based on the responses to questions regarding agreement to participate, lack of association with the RPC companies, FDA, and the Prescriber Survey Vendor; as well as having prescribed ER/LA opioid analgesics at least once in the past 12 months.

The specific objectives for the prescriber survey are:

- To assess the understanding of ER/LA opioid prescribers of the serious risks associated with the use of the ER/LA opioids and how to prescribe ER/LA opioids appropriately, including the six domains of the FDA Blueprint
- To assess ER/LA opioid prescribers' opioid prescribing behavior and practice, including questions from the six domains of the FDA Blueprint, where applicable and feasible
- To assess awareness of the availability of the accredited REMS-compliant training
- To compare the survey results between prescribers who have and have not completed a CE activity

4.4.2.1. Methods

A sample size of 600 completed surveys was proposed for the survey with 300 selected from a stratified random sample of ER/LA opioid analgesic prescribers known to have prescribed at least one ER/LA opioid analgesic product in the past year as identified from IMS data plus 300 prescribers who had completed an accredited REMS-compliant CE activity as identified by CE Providers who were able to support recruitment. Prescribers were excluded from completing the survey if they:

- did not agree to participate in the survey
- had worked for or had family members who worked for one of the sponsor companies, vendor company, or FDA
- did not self-report that they had prescribed an ER/LA opioid at least once in the last 12 months

The prescriber characteristics collected for each survey completer included:

- average number of times in the past month he/she prescribed ER/LA opioid analgesics
- ER/LA opioid analgesics prescribed in the last 12 months
- average number of times per month in the past 3 months he/she considered prescribing an ER/LA opioid analgesic but decided not to
- reasons he/she decided not to prescribe an ER/LA opioid analgesic
- gender
- medical degree
- number of years practicing medicine since completing post-graduate education
- general practitioner or specialist
- medical specialty
- state or US territory of practice

Demographic characteristics of survey completers sampled from IMS data were compared with the characteristics of all ER/LA opioid analgesic prescribers identified in the IMS database based on the characteristics presented below. A similar comparison could not be done for the sample provided from CE Providers as general demographic characteristics are not available.

TABLE 8: PRESCRIBER SURVEY: COLLECTED PRESCRIBER CHARACTERISTICS

Average number of times in the past month he/she prescribed ER/LA opioid analgesics	General practitioner or specialist
State or US territory of practice	Medical specialty
Medical Degree	

4.4.2.2. Statistical Methods

Primary analyses were performed for all questions comprising each of the six key risk messages. The primary analysis for a key risk message evaluates the rate for each correct response to each individual question/item defined by the key risk message. Exact binomial two-sided 95% CIs were calculated according to the method of Clopper-Pearson for the proportion of respondents who give the correct responses (Clopper and Pearson, 1934). In addition to the analyses of each individual key risk message, an overall Knowledge Score was computed for each respondent. The Knowledge Score is defined as the number of correct responses to all items of all key risk messages.

A target comprehension rate of at least 80% was desired for each key risk message. The number and percentages of prescribers who answered at least 80% of the items in the key risk message correctly were summarized.

4.4.2.3. Prescriber Survey Administration

The Prescriber Survey was launched on February 18, 2015. A total of 612 prescribers completed the survey. A total of 301 respondents that completed a survey were invited through CE Providers by email and had completed an accredited REMS-compliant CE course. Data on the number of invitations sent were not available from all CE Providers and therefore a response rate cannot be computed for this segment of the sample. Of the 11,284 prescribers invited by mail using information obtained from IMS, 311 respondents completed a survey and were considered as not completing an accredited REMS-compliant CE course, though 54% (132/246) noted on the survey that they had taken an accredited REMS-compliant CE activity. Based on the number of invitations sent, the response rate for recruitment through IMS data was 2.8%; however, the response rate cannot be calculated because once the target number of surveys was achieved after 8 weeks of survey fielding the survey was closed. The due diligence process included at least two mail reminders.

Respondents had the option to self-administer through a secure website or calling the call center to obtain a paper survey. The survey averaged approximately 25 minutes. Prescribers who completed the survey received a \$125 MasterCard® gift card for their time.

4.4.2.4. Prescriber Survey Results

As shown in [Table 9](#), survey respondents from the IMS segment of the sample were significantly different than all ER/LA opioid prescribers identified in the IMS database. The survey respondents tended to more often have prescribed an ER/LA opioid analgesic in the past month prior to the survey, included more NPs and PAs, and a smaller proportion of MDs and were more likely to be a General Practitioner or a Pain Management Specialist.

TABLE 9: DESCRIPTION OF ELIGIBLE PRESCRIBERS AND ALL SURVEY RESPONDENTS INVITED FROM IMS DATA FOR THE PRESCRIBER FOLLOW-UP SURVEY

QUESTION	COMPLETED PRESCRIBERS RECRUITED FROM IMS N=311		ALL PRESCRIBERS INVITED WHO HAVE PRESCRIBED AN ER/LA MEDICINE N=11,881 ^[1]		ALL PRESCRIBERS WHO HAVE PRESCRIBED AN ER/LA MEDICINE N=420,154 ^[1]		p-value
	N	%	N	%	N	%	
Question 58: On average, how many times in the past month have you prescribed ER/LA opioid analgesics?							
0 times ^[2]	8	2.6	4,310	36.3	256,345	61.0	
Fewer than 5 times	72	23.2	2,405	20.2	80,244	19.1	
6-10 times	60	19.3	825	6.9	30,278	7.2	
11-20 times	47	15.1	963	8.1	24,377	5.8	
21-30 times	30	9.6	851	7.2	9,694	2.3	
31-40 times	16	5.1	517	4.4	4,821	1.1	
41-50 times	19	6.1	309	2.6	2,863	0.7	
51 or more times	56	18.0	1,701	14.3	11,532	2.7	<.0001
I don't remember	3	1.0	0	0.0	0	0.0	
Geographic Distribution (based on Question 67) ^[3]							
Northeast	22	7.1	1,242	10.5	40,886	9.7	
East	65	20.9	1,939	16.3	65,598	15.6	
Central	85	27.3	3,307	27.8	120,877	28.8	
South	60	19.3	2,275	19.1	90,656	21.6	
West	79	25.4	3,092	26.0	98,993	23.6	
US Territories	0	0.0	25	0.2	3,114	0.7	<.0001

QUESTION	COMPLETED PRESCRIBERS RECRUITED FROM IMS N=311		ALL PRESCRIBERS INVITED WHO HAVE PRESCRIBED AN ER/LA MEDICINE N=11,881 ^[1]		ALL PRESCRIBERS WHO HAVE PRESCRIBED AN ER/LA MEDICINE N=420,154 ^[1]		p-value
	N	%	N	%	N	%	
Missing	0	0.0	1	0.0	30	0.0	
Question 63: What is your medical degree?							
Doctor of Medicine (MD)	137	44.1	7,271	61.2	295,866	70.4	
Doctor of Osteopathic Medicine (DO)	8	2.6	612	5.2	34,827	8.3	
Nurse Practitioner (NP)/Advanced Practice Nurse (APN)	79	25.4	2,106	17.7	42,380	10.1	
Physician Assistant (PA)	87	28.0	1,834	15.4	33,471	8.0	
Dentist ^[4]	0	0.0	36	0.3	4,394	1.0	
Optometrist ^[4]	0	0.0	4	0.0	334	0.1	
Podiatrist ^[4]	0	0.0	13	0.1	3,015	0.7	
Veterinarian ^[4]	0	0.0	4	0.0	5,235	1.2	<.0001
Missing	0	0.0	1	0.0	632	0.2	
Question 65/66: Are you a general practitioner or specialist / What is your primary medical specialty? Please select one response only ^[5]							
General Practitioner ^[6]	54	37.2	2,033	25.8	85,518	25.8	
Oncology	7	4.8	425	5.4	10,307	3.1	
Neurology	3	2.1	230	2.9	6,645	2.0	
Anesthesiology	3	2.1	508	6.4	6,940	2.1	
Rheumatology	3	2.1	146	1.9	3,283	1.0	
Orthopedics	4	2.8	283	3.6	16,365	4.9	

QUESTION	COMPLETED PRESCRIBERS RECRUITED FROM IMS N=311		ALL PRESCRIBERS INVITED WHO HAVE PRESCRIBED AN ER/LA MEDICINE N=11,881 ^[1]		ALL PRESCRIBERS WHO HAVE PRESCRIBED AN ER/LA MEDICINE N=420,154 ^[1]		p-value
	N	%	N	%	N	%	
Pain Management	28	19.3	244	3.1	2,638	0.8	
Hospice/Palliative Care	1	0.7	10	0.1	148	0.0	
Internal Medicine	13	9.0	1,921	24.4	83,641	25.3	
Other	29	20.0	2,812	35.7	142,645	43.1	<.0001
<p>^[1] These data are coming from IMS database extracted December 2014.</p> <p>^[2] IMS data includes any prescriber who has prescribed an ER/LA medicine in the last 12 months. Therefore, the percentage for prescribing '0 times' for all prescribers invited and all prescribers who have prescribed is based on prescribers that have prescribed in the past 12 months, but who have not prescribed in the past month.</p> <p>^[3] Northeast includes: CT, DC, MA, ME, MD, NH, RI and VT. East includes: DE, NJ NY, and PA. Central includes: AR, IA, IN, IL, KS, KY, MI, MN, MO, ND, NE, OH, OK, SD, TN, WI and WV. South includes: AL, FL, GA, LA, MS, NC, SC, TX and VA. West includes: AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA and WY. US Territories includes: American Samoa, Guam, Northern Mariana Islands, Puerto Rico, and US Virgin Islands.</p> <p>^[4] Not a category in the Survey.</p> <p>^[5] Only specialties for Medical Doctor (MD) and Doctor of Osteopathic Medicine (DO) are summarized.</p> <p>^[6] General Practitioner includes General Practice and Family Medicine</p> <p>Note: p-values are from chi-square tests for the comparison of the completed prescribers from IMS and all prescribers who have prescribed ER/LA medicine.</p>							

The majority of respondents were male (333/612, 54.4%), and 53.6% (328/612) of the respondents held Doctor of Medicine (MD) or Doctor of Osteopathic Medicine (DO) degrees. Nearly half of these physicians participating reported practicing medicine for 6 or more years (286/612, 46.7%). The largest categories of respondents by specialty were either General Practitioners (253/612, 41.3%) or in Pain Management (132/612, 21.6%). The largest number of participants were from the West region of the United States (US) (193/612, 31.5%) and had prescribed ER/LA opioid analgesics fewer than 5 times in the past month (171/612, 27.9%).

[Table 10](#) describes the demographic and clinical characteristics of the prescribers that participated in the Prescriber Survey broken down by recruitment source. It should be noted that approximately 53.7% of prescribers recruited through IMS data reported completing a REMS-compliant CE activity.

TABLE 10: PRESCRIBER SURVEY: COMPARISON OF HCPS INVITED FROM THE IMS DATA AND HCPS RECRUITED BY CE PROVIDERS - COMPLETED SURVEYS

QUESTION	RECRUITMENT SOURCE		
	IMS Data (N=311) n (%)	CE Provider (N=301) n (%)	p-value
Question 3: Have you completed a REMS-compliant Continuing Education (CE) activity?			
Yes	132 (53.7)	235 (87.7)	
No	114 (46.3)	33 (12.3)	<.0001
I don't remember	65	33	
Question 58: On average, how many times in the past month have you prescribed ER/LA opioid analgesics?			
0 times	8 (2.6)	22 (7.4)	
Fewer than 5 times	72 (23.4)	99 (33.2)	
6-10 times	60 (19.5)	66 (22.1)	
11-20 times	47 (15.3)	29 (9.7)	
21-30 times	30 (9.7)	22 (7.4)	
31-40 times	16 (5.2)	15 (5.0)	
41-50 times	19 (6.2)	11 (3.7)	
51 or more times	56 (18.2)	34 (11.4)	0.0012
I don't remember	3	3	
Question 60: In the last 3 months, how many times per month on average have you considered prescribing ER/LA opioid analgesics but decided not to?			
0-1 time	95 (33.8)	111 (40.2)	
2-3 times	84 (29.9)	93 (33.7)	
4-5 times	44 (15.7)	33 (12.0)	
6-7 times	16 (5.7)	13 (4.7)	
8-9 times	10 (3.6)	5 (1.8)	
10 or more times	32 (11.4)	21 (7.6)	0.1868
I don't remember	30	25	
Question 61: What were the reasons you decided not to prescribe an ER/LA opioid analgesic (select all that apply)			
I am selecting my patients differently based on assessment	135 (43.4)	117 (38.9)	
I have fear about prescribing ER/LA opioids	43 (13.8)	42 (14.0)	
I am prescribing ER/LA opioids for a shorter period of time	35 (11.3)	36 (12.0)	
I changed to prescribing more immediate-release opioids	68 (21.9)	71 (23.6)	
I changed to prescribing more non-opioid medications	113 (36.3)	123 (40.9)	
Other	62 (19.9)	61 (20.3)	
Question 62: What is your gender?			
Male	174 (56.3)	159 (53.4)	
Female	135 (43.7)	139 (46.6)	0.4646
Prefer not to answer	2	3	
Question 63: What is your medical degree?			
Doctor of Medicine (MD)	137 (44.1)	155 (51.5)	
Doctor of Osteopathic Medicine (DO)	8 (2.6)	28 (9.3)	

QUESTION	RECRUITMENT SOURCE		
	IMS Data (N=311) n (%)	CE Provider (N=301) n (%)	p-value
Nurse Practitioner (NP)	63 (20.3)	64 (21.3)	
Advanced Practice Nurse (APN)	16 (5.1)	7 (2.3)	
Physician Assistant (PA)	87 (28.0)	47 (15.6)	<.0001
Question 64: In total, how many years have you been practicing medicine, since completing your post-graduate education? (MDs and DOs only)			
Less than 3 years	5 (3.5)	10 (5.6)	
3-5 years	1 (0.7)	22 (12.2)	
6-10 years	15 (10.4)	30 (16.7)	
11-15 years	14 (9.7)	18 (10.0)	
More than 15 years	109 (75.7)	100 (55.6)	0.0001
Prefer not to answer	1	3	
Geographic Distribution (based on Question 67)^[1]			
Northeast	22 (7.1)	40 (13.4)	
East	65 (20.9)	46 (15.4)	
Central	85 (27.3)	42 (14.0)	
South	60 (19.3)	57 (19.1)	
West	79 (25.4)	114 (38.1)	<.0001
Prefer not to answer	0	2	
Question 65/66: Are you a general practitioner or specialist / What is your primary medical specialty? Please select one response only.			
General Practitioner	120 (38.6)	133 (44.2)	
Oncology	22 (7.1)	13 (4.3)	
Neurology	4 (1.3)	6 (2.0)	
Anesthesiology	3 (1.0)	15 (5.0)	
Rheumatology	4 (1.3)	0	
Orthopedics	20 (6.4)	8 (2.7)	
Pain Management	77 (24.8)	55 (18.3)	
Hospice/Palliative Care	4 (1.3)	12 (4.0)	
Internal Medicine	14 (4.5)	11 (3.7)	
Other	43 (13.8)	48 (15.9)	0.0007

[1] Northeast includes: CT, DC, MA, ME, MD, NH, RI and VT. East includes: DE, NJ NY, and PA. Central includes: AR, IA, IN, IL, KS, KY, MI, MN, MO, ND, NE, OH, OK, SD, TN, WI and WV. South includes: AL, FL, GA, LA, MS, NC, SC, TX and VA. West includes: AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA and WY. US Territories includes: American Samoa, Guam, Northern Mariana Islands, Puerto Rico, and US Virgin Islands.

Note: Question numbers are referring to the Prescriber Survey. P-values are based on a chi-square test excluding non-informative categories (e.g., categories like 'I don't remember', 'Prefer not to answer')

4.4.2.4.1. Key Risk Messages

Survey respondents were asked to complete 68 questions about the safe use of the ER/LA opioid analgesics. The majority of questions/items (49/68, 72.1%) were answered correctly by more than 80% of participants, indicating a reasonably high level of knowledge. However, 19 (19/68, 27.9%) of questions were answered correctly by fewer than 80% of participants, suggesting areas that need further consideration, either in terms of presentation of REMS message or of question design. Of these lower scoring questions, 26% were regarding tolerance (5/19) and 26% were regarding formulations/conversion

(5/19). The remaining items were spread across the 6 key risk messages. See [Appendix 8](#) for the distribution of questions/items ranked by Prescriber Survey score.

4.4.2.4.2. Awareness and Use of REMS Educational Materials

Prescribers were asked about their awareness, receipt, and review of educational materials associated with the ER/LA Opioid Analgesics REMS, specifically, the Medication Guide(s), Dear DEA-Registered Prescriber Letter, Patient Counseling Document and ER/LA Opioid Analgesics REMS website (www.er-la-opioidrems.com).

A comparison of prescriber reported awareness of the REMS materials and whether they read the material between respondent recruitment sources is included in [Table 11](#).

TABLE 11: PRESCRIBER AWARENESS AND READING OF REMS MATERIALS

REMS MATERIAL	PRESCRIBER SURVEY	
	% OF PRESCRIBERS AWARE OF THE MATERIAL N=612	% OF PRESCRIBERS THAT READ THE MATERIAL ¹
Medication Guide(s) for the ER/LA opioid analgesics they prescribe	60.3%	90.1%
Dear DEA-Registered Prescriber Letter	37.1%	88.8%
Patient Counseling Document	43.3%	94.8%
ER/LA Opioid Analgesics Website	39.7%	82.5%

¹ Percentages are based on the total number of prescribers who indicated they were aware and had access to the specific REMS material.

In the Prescriber Survey, respondents were also asked about their awareness of REMS-compliant CE and whether they knew how to access the activities. A total of 335 prescribers reported being aware of the availability of REMS-compliant CE activities (335/612, 54.7%), with 314 (314/612, 51.3%) prescribers knowing how to access REMS-compliant CE activities. The majority of prescribers invited through IMS were not aware of REMS-compliant CE activities (180/311, 57.9%) and did not know how to access REMS-compliant CE activities (200/311, 64.3%). Prescribers who had been invited through CE Providers reported being aware of CE activities (214/301, 71.1%), but only 55.1% (166/301) knew how to access REMS-compliant CE activities.

4.4.2.4.3. Prescriber Behaviors

Respondents were asked questions that allowed analysis of prescribing activities and behaviors and opinions regarding any barriers that may prevent appropriate patients from accessing ER/LA opioid analgesics.

Most respondents reported counseling patients on safe administration of ER/LA opioid analgesics including correctly tapering when discontinuing treatment (514/612, 84.0% of all respondents), what to do if a dose is missed (523/612, 85.5% of all respondents), and to take their medication in the form it was provided (566/612, 92.5% of all respondents). Fewer (391/612, 63.9% of all respondents) reported using the Patient Counseling Document as provided in the REMS to guide these discussions; 70.1% of those invited by a CE Provider reported using it (211/301). In contrast, 57.9% (180/311) of those invited by IMS reported using the Patient Counseling Document. The topics most often discussed by respondents are

the potential side effects, including overdose and respiratory depression, and the need to keep ER/LA opioid analgesics away from children.

About two-thirds (402/612, 65.7%) of all respondents regularly or always use structured interview or screening tools when assessing patients' risk of abuse or misuse of an ER/LA opioid analgesic and 76.3% (467/612) at least regularly complete a Patient Prescriber Agreement (PPA) at the time of first prescription. Very few prescribers (7/612, 1.1%) reported rarely reassessing the need for ER/LA opioid analgesics and only one reported never doing so.

4.4.2.4.4. Prescribers Perception of Patients' Ability to Access ER/LA Opioid Analgesics

Most prescribers perceive access to ER/LA opioid analgesics moderately easy to easy (383/612 or 62.6% of respondents chose 5 to 8 on a scale of 1 to 10) and indicate insurance issues and affordability as the greatest obstacles to patient access. Both prescribers who had taken CE and those who had not taken CE thought that ease of access was "about right" for patients for whom ER/LA opioid analgesics are indicated (52.5% (158/301) and 52.4% (163/311), respectively). Prescribing choices made by about half of all respondents have not changed since the implementation of the ER/LA Opioid Analgesics REMS, however 38.1% (233/612) of respondents feel that the REMS adds difficulty to patient access of opioid analgesics. Sub-populations differences were observed in those that have changed their prescribing habits; however, as more prescribers who were invited by a CE Provider reported prescribing more IR opioids (34/301, 11.3%) than those who were invited by IMS (20/311, 6.4%). Similarly, when stratifying results based on recruitment method, prescribers who were invited by a CE Provider reported prescribing more non-opioid medications (81/301, 26.9%) than those who were invited by IMS (57/311, 18.3%).

4.4.2.5. Limitations of Prescriber Survey

The respondent sample from IMS differed in demographic characteristics from the overall list of ER/LA opioid analgesic prescribers, limiting the generalizability of the results. Further this type of comparison was unable to be conducted for the CE Provider sample.

Responses to the question of whether the respondent had completed a REMS-compliant CE activity showed that a small percent of respondents (33/268, 12.3%) who were known REMS-compliant CE activity completers indicated they had not done so, and approximately half of the respondents from the IMS sample indicated that they had completed a REMS-compliant CE activity. Therefore, comparisons between the two segments may underestimate knowledge gain through REMS-compliant CE activities.

4.4.3. Long-term Evaluation

Healthcare providers' awareness and understanding of the serious risks associated with the ER/LA opioid analgesics was evaluated through a survey of HCPs who had completed an accredited REMS-compliant CE activity within 6 to 12 months prior to the survey. The survey was a combination of questions included on the Prescriber Survey and case scenarios requiring that HCPs apply the knowledge they obtained through the accredited REMS-compliant CE activity.

This cross-sectional survey was focused on prescriber knowledge and behavior as outlined in the FDA Blueprint and included a total of 65 key risk message items. HCPs that completed an accredited REMS-compliant CE within the past 6 to 12 months were invited to participate. Eligibility was determined via screening questions at the beginning of the survey.

The specific objectives of the Long-term Evaluation Survey were to evaluate:

- understanding by ER/LA opioid prescribers of the serious risks associated with the use of the ER/LA opioids they prescribe and how to prescribe ER/LA opioids appropriately according to the six domains of the FDA Blueprint
- whether the CE activities impacted prescribers' self-reported opioid prescribing behavior and practice

- whether ER/LA opioid prescribers encountered any barriers to applying knowledge gained in CE activities
- whether ER/LA opioid prescribers found completion of REMS-compliant training to be manageable or experienced obstacles to completion, including the time and/or effort required being overly burdensome.

4.4.3.1. Methods

A sample size of 600 completed surveys was proposed for the survey. Prescribers identified by participating CE providers as having completed an accredited REMS-compliant CE activity within 6 to 12 months prior to survey completion were recruited. Prescribers were excluded from completing the survey if they:

- did not agree to participate in the survey
- had worked for or had family members who worked for one of the sponsor companies, vendor company, or FDA
- did not self-report that they had prescribed an ER/LA opioid at least once in the last 12 months

The following prescriber characteristics were collected for each survey completer.

- average number of times in the past month he/she prescribed ER/LA opioid analgesics
- average number of times per month in the past 3 months he/she considered prescribing an ER/LA opioid analgesic but decided not to
- reasons he/she decided not to prescribe an ER/LA opioid analgesic
- how the types of medications prescribed for him/her has changed since participating in a REMS-compliant CE
- how his/her prescribing behavior changed since participating in REMS-compliant CE
- the ER/LA opioid analgesics prescribed in the last 12 months
- gender
- medical degree
- number of years practicing medicine since completing post-graduate education
- general practitioner or specialist
- medical specialty
- state or US territory of practice

Comparability between prescribers surveyed with all prescribers completing an accredited REMS-compliant CE activities could not be done as standard demographic data are not collected across all CE Providers.

4.4.3.2. Statistical Methods

All statistical analyses were descriptive, i.e., no formal hypothesis was tested. Counts and percentages were calculated for each question/item in the questionnaire.

Primary analyses were performed for all questions comprising each of the six domains in the FDA Blueprint. The primary analysis for a domain evaluated the rate for each correct response to each individual question/item defined by the core blueprint message. Exact binomial two-sided 95% CIs were calculated according to the method of Clopper-Pearson for the proportion of respondents who give the

correct responses (Clopper and Pearson, 1934). A target comprehension rate of at least 80% was desired for each FDA blueprint message.

4.4.3.3. Long-term Evaluation Survey Administration

Of the respondents invited, 328 completed the survey. Data on the number of invitations sent was not available from all CE Providers and therefore the response rate cannot be calculated. Of the 546 individuals who responded to the invitation, 485 agreed to participate in the survey and 328 completed the survey. All prescribers provided consent to participate in the survey. Prescriber eligibility was determined based on a number of questions including lack of associations with the RPC companies, FDA, and the Long-term Evaluation Survey Vendor; as well as having prescribed ER/LA opioid analgesics at least once in the past 12 months.

Respondents had the option to self-administer through a secure website or call the call center to obtain a paper survey. The survey averaged approximately 30 minutes. Prescribers who completed the survey received a \$150 MasterCard® gift card for their time.

4.4.3.4. Long-term Evaluation Survey Results

The population of male respondents was larger than female, 55.5% (182/328) and 41.8% (137/328) respectively (9 or 2.7% preferred not to answer the question), and the majority of the respondents (216/328, 65.9%) hold MD or DO degrees and one Registered Pharmacist (RPh) participated. Over half of the physicians participating (129/216, 59.7%) reported practicing medicine for more than 15 years and almost 40% (130/328) of respondents practice in the West region of the US. For those who identified as a specialist (156/328, 47.6%) the most commonly reported specialty was Pain Management (44/156, 28.2%). About half (172/328, 52.4%) of respondents had prescribed ER/LA opioid analgesics 10 or fewer times in the past month.

4.4.3.4.1. Key Risk Messages

Survey respondents were asked to complete questions about the safe use of the ER/LA opioid analgesics. The majority of key risk message questions/items (45/65, 69.2%) were answered correctly by more than 80% of participants, indicating a reasonably high level of knowledge. However, there were 20 (30.8%) questions/items that were answered correctly by fewer than 80% of respondents. Of these 20 questions/items, 4 (20%) of the low scoring questions/items were related to patients being assessed for treatment with ER/LA opioid analgesic therapy, 6 (30%) were related to prescribers being familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics, 2 (10%) were related to management of ongoing therapy with ER/LA opioid analgesics is important, 1 (5%) was related to the importance of counseling patients and caregivers about the safe use of ER/LA opioid analgesics, 2 (10%) were related to prescribers being familiar with general drug information concerning ER/LA opioid analgesics, and the remaining 5 (25%) were related to prescribers being familiar with product-specific drug information concerning ER/LA opioid analgesics. No question/item related to product specific information was answered correctly by more than 80% of respondents. The questions and correct answers ranked by score are shown in [Appendix 9](#).

4.4.3.4.2. Prescriber Behaviors

The survey included questions related to prescribing behavior. Nearly half of the respondents (155/328, 47.3%) reported that they had considered prescribing ER/LA opioid analgesics between 2-5 times within the last 3 months but decided not to do so. The most common reasons for not prescribing included: prescribers selecting patients differently based on assessment (181/328, 55.2%), changes to prescribe more non-opioid medications (147/328, 44.8%), and fear about prescribing ER/LA opioid analgesics (48/328, 14.6%).

Respondents were also asked questions about any changes that may have occurred in their prescribing activities and behaviors and opinions specifically following participation in a REMS-compliant CE activity for ER/LA opioid analgesics.

Almost all respondents indicated maintaining or increasing the frequency of counseling patients about the most common side effects of ER/LA opioid analgesics, what to do if a dose is missed, the importance of keeping ER/LA opioid analgesics away from children, to not sell, share, or give away ER/LA opioid analgesics, and how to safely taper when discontinuing and dispose of unused products.

Despite these increases in safe use behavior, many respondents reported that they still encounter patient non-compliance with dose reconciliation efforts (188/328, 57.3%) and that they have insufficient time during clinical encounters to address all ER/LA treatment considerations (207/328, 63.1%) as barriers to application of the information they have taken from their CE activity.

Table 12 presents other changes in Prescriber behavior following participation in a REMS-compliant CE activity.

TABLE 12: CHANGES IN PRESCRIBER BEHAVIOR FOLLOWING PARTICIPATION IN REMS-COMPLIANT CE

PRESCRIBER BEHAVIOR REPORTED	% OF ALL PRESCRIBERS THAT INDICATED THE BEHAVIOR (N=328)
Using the Patient Counseling Document as provided in the REMS to guide discussions with patients at least the same amount or more often since completing a CE activity	76.5
Having increased the frequency of discussions with patients about important risks including overdose and respiratory depression	64.9
Gained new insights into ER/LA opioid analgesic prescribing considerations as a result of completing a CE activity	51.8
Increased their use of structured screening tools	49.7
Increased their use of structured screening tools and PPAs when initiating patients on ER/LA opioid analgesics	47.6
Monitor their patients through urine drug screens more often than they did prior to completing a CE activity	49.1
Monitor their patients through state Prescription Monitoring Program databases more often than they did prior to completing a CE activity	63.7

4.4.3.5. Limitations of Long-term Evaluation Survey

CE Providers were asked to recruit all CE participants who had taken a course during the specified time period (6-12 months prior to survey administration). However, data on the number of participants, the number invited, and the demographic characteristics of the invited population could not be obtained prohibiting analysis of the generalizability of the results.

4.5. Evaluation of Drug Utilization Patterns, Prescribing Behaviors, and Changes to ER/LA Opioid Access

To assess the ER/LA Opioid Analgesics REMS an evaluation of drug utilization patterns, changes in prescribing behavior and changes in access to ER/LA opioid analgesics was conducted. These

assessments were based on two IMS Health data sources: IMS Health, National Prescription Audit™ (NPA™) and IMS Health, LifeLink™ patient-level longitudinal prescription (LrX) database.

IMS Health, National Prescription Audit™ (NPA™)

The IMS National Prescription Audit™ is the industry standard for measuring the outflow of prescriptions from retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers. For this study, IMS data reflect the Retail channel, which tracks the volume of pharmaceutical prescriptions dispensed through Chain Store Pharmacies, Independent Store Pharmacies, and Food Store Pharmacies. Data are projected to national estimates. Projected data are representative of the U.S. population with a prescription from a retail pharmacy.

IMS Health, LifeLink™ patient-level longitudinal prescription (LRx) database

The IMS LRx database consists of patient de-identified longitudinal prescription data from a sample of the IMS Health retail and mail order prescription universe (NPA™). Data are collected for the LRx database via direct data feeds from retail (pharmacy chains, food stores, independents and mass merchandisers) and mail service pharmacies included in the IMS Health data supplier panel. All data loaded into the LRx database are encrypted using a proprietary encryption algorithm to de-identify and assign each patient a unique patient ID, which ensures HIPAA compliance. Encrypted patient IDs allow IMS to account for patient travel across data suppliers within the sample without losing visibility to the patient.

The database provides robust coverage of the retail prescription universe, with approximately 65% of all retail prescriptions filled in the U.S. captured within the database. Over 150 million unique de-identified patients are contained within the database along with prescribing information for over one million prescribers. Relationships with LRx data suppliers are broader than the longitudinal prescription data alone as they encompass core IMS prescription services such as NPA™ and Xponent, resulting in a very stable data supply for the database. The database contains IMS prescriber IDs and zip codes for each transaction, allowing for accurate prescriber-level and sub-national reporting of patient-level data metrics.

These analyses included only the retail pharmacy channel; long-term care and mail order/specialty pharmacy channels were not included.

4.5.1. Drug Utilization Patterns

The evaluation of drug utilization patterns was conducted in order to describe trends in the number of prescriptions for ER/LA opioid analgesics and comparator products using a national prescription database system.

The specific objectives of this retrospective cross-sectional study included:

1. To estimate monthly number of prescriptions for a one-year period before, and each month after, the implementation of the REMS.
2. To compare average number of prescriptions per 3-month period in the 2 years before as compared to the same measure during the implementation and active periods
3. To compare the changes in prescribing, both by number of prescriptions and patients, stratified by prescriber specialty. These trends and changes over time were estimated for the following groups of opioids:
 - Total ER/LA opioid analgesics included in the class REMS
 - Each product in the ER/LA opioid analgesic class
 - Comparator products

4. To show switches (absolute and rates of switching) from ER/LA opioid analgesics to comparator analgesics (IR opioids and celecoxib) with introduction of the REMS. Rates of switching were reported in terms of monthly switch rates and aggregated (averaged) monthly switch rates observed during each study phase (pre-implementation and active periods).

4.5.1.1. Methods

To evaluate the above objectives, a retrospective cross-sectional study using data drawn from the IMS Health, National Prescription Audit™ (NPA™) and IMS Health, LifeLink™ patient-level longitudinal prescription (LRx) database was conducted. Comparators were broken into 3 categories:

- IR opioid analgesics. These products included oral forms, and were assessed at the product group level. Specific products included fentanyl, fentanyl citrate, hydrocodone-acetaminophen, hydrocodone-ibuprofen, hydromorphone HCl, morphine sulfate, oxycodone HCl, oxymorphone HCl, and tapentadol HCl.
- Prescription Nonsteroidal Anti-Inflammatory Drug (NSAID), celecoxib, as an “analgesic control” group. Celecoxib was selected as the only NSAID comparator because all celecoxib strengths require prescriptions. This is not the case with many other NSAIDs, which do not require prescriptions or do not require prescriptions for some strengths. As a result, data would not be available in IMS or other claims databases. In addition, just as with the ER/LA opioid analgesics, celecoxib is more likely to be used for longer term pain due to its lower risk of gastrointestinal bleeding as compared to other prescription NSAIDs that are generally more often used for acute pain than chronic pain.
- Benzodiazepines as an “abuse control” group since this class of prescription drugs is subject to abuse. These products were assessed at the product group level. Specific products included alprazolam, chlordiazepoxide HCl, clorazepate dipotassium, diazepam, halazepam, lorazepam and oxazepam.

The initial study sample included all patients who filled a prescription for ER/LA opioid analgesics included in the class REMS or comparator products anytime between July 1, 2010 and December 31, 2014.

Patients meeting *both* of the following inclusion criteria were selected for inclusion in a given reporting month:

- filled at least one prescription of the drug of interest during a given month in the reporting period
- continuous eligibility in the LRx database was required to ensure availability of complete patient history, and to determine the following:
 - consistent supply of data from pharmacies used by patients to the LRx database throughout the study period (Constant Store Panel).
 - activity by patients in the LRx database (for any market) prior to the study period (Patient Start Date).

4.5.1.2. Statistical Methods

All measures described below were aggregated monthly and/or quarterly in the pre-REMS implementation (July 2010 - June 2012), implementation (July 2012 – June 2013), and active periods (July 2013 – December 2014). Monthly and quarterly assessment of prescription volume was based at the product group level for ER/LA opioid analgesics and for comparator products. As a result, monthly and quarterly assessment of patient volume was conducted at the ER/LA opioid analgesics product group level and at the product group level for comparator products.

Mean and 95% CI were calculated for average monthly patient volumes and switch rates for each study period. Changes in prescribing before and after REMS implementation were performed by calculating and comparing the average percent changes in average switch rates between the Pre-Implementation and Active Periods. Differences in the average change in switch rates were assessed for statistical significance using Student's T-test and / or Z-test approximations. P values less than 0.05 were considered significant.

Prescription and patient counts were projected to the national level based on the LRx prescription sample with projection factors derived from the prescriptions in LRx relative to NPA™ total prescription. Projected data are representative of the U.S. population with a prescription from a retail pharmacy.

4.5.1.3. Results

One year prior to REMS implementation (July 2011), the total ER/LA opioid prescription volume was 1.82 million; at the end of the active period (December 2014) it was 1.86 million. Total ER/LA opioid prescriptions fluctuated over the study period, with the lowest volume (1.65 million) during the active period (February 2014). From the year prior to implementation to the end of the active period, the monthly prescription volume for celecoxib remained stable at about 0.63 million. The monthly prescription volumes fluctuated for benzodiazepines (ranging from 6.48 million to 7.39 million) and IR opioids (ranging from 9.10 million to 13.18 million); however, IR opioids showed a trend towards a general decrease.

As shown in [Table 13](#), the average prescription volume per quarter for all ER/LA opioids in the pre-implementation period was estimated at 5.58 million, and volume decreased by 4.3% ($p < 0.001$) from pre-implementation to active period to 5.34 million. The largest decrease (20.7%) was observed in patients between 19 and 40 years of age. A decrease of 7.6% was observed for IR opioids, which were used as a comparator.).

For the comparator products, significant changes were observed across periods for most product groups. The average quarterly volume for benzodiazepines significantly increased by 1.5% ($p = 0.020$) from pre-implementation to active period. A significant decrease was observed for celecoxib from pre-implementation to active period (7.9% decrease, $p = 0.001$). For IR opioids, there was a significant decrease from pre-implementation to active period (7.6% decrease, $p = 0.033$).

TABLE 13: COMPARISON OF THE AVERAGE 3-MONTH PRESCRIPTION ACROSS PRE-IMPLEMENTATION, IMPLEMENTATION, AND ACTIVE PERIOD

	PRESCRIPTION VOLUME				STATISTICAL COMPARISON WITHIN PRODUCT TYPE	PERCENT CHANGE WITHIN PRODUCT TYPE
PRODUCTS	PRE- IMPLEMENTATION		ACTIVE PERIOD		PRE- IMPLEMENTATION VS ACTIVE PERIOD	PRE- IMPLEMENTATION VS ACTIVE PERIOD
	Mean	95% CI	Mean	95% CI	P-Value (T-Test)	% Change
Total ER/LA Opioids	5,575,834	(5,492,547- 5,659,120)	5,336,053	(5,261,224- 5,410,881)	0.000	-4.3%
Comparators						
IR Opioids	37,339,058	(36,775,169- 37,902,947)	34,519,228	(32,011,268- 37,027,188)	0.033	-7.6%
Celecoxib	2,004,906	(1,940,976- 2,068,836)	1,846,409	(1,784,750- 1,908,068)	0.001	-7.9%
Benzodiazepines	20,922,561	(20,746,496- 21,098,626)	21,226,458	(21,006,901- 21,446,014)	0.020	1.5%

Change in the average quarterly prescription volume before and after implementation of the REMS was assessed by prescriber specialty. For ER/LA opioid analgesics, PCPs, pain specialists, anesthesiologists, physical medicine & rehabilitation specialists, nurse practitioners and physician assistants had the largest prescription volume. Total ER/LA opioid analgesics exhibited a decrease in average quarterly prescription volume for most of the specialties from pre-implementation to active period. The exceptions were the pain specialty (no change), hospice and palliative medicine and physical medicine & rehabilitation and all other specialties (significant decreases from pre-implementation to active period), anesthesiologists (significant increase from pre-implementation to active period), and nurse practitioners and physician assistants who saw significant increases across study periods. The largest significant decreases in average prescription volume per quarter were observed for dentists (pre-implementation to active period: 48.5% decrease, $p < 0.001$) and emergency medicine specialists (25.5% decrease, $p < 0.001$). The largest increases were observed for nurse practitioners (pre-implementation to active period: 33.7% increase, $p < 0.001$) and physician assistants (31.2% increase, $p < 0.001$).

Switching from REMS products to the IR opioid group or celecoxib was assessed overall and by prescriber specialty. The proportion of patients who switched from REMS products to the IR opioids was highest for the anesthesiology, pain, and hospice and palliative medicine specialties, where approximately 19.3%, 19.6%, and 31.5% of patients switched to IR opioids, respectively. The switch rate from REMS products to celecoxib was also highest for these same 3 specialties, with switch rates of approximately 21.7%, 23.2% and 55.6%. The monthly switch rate from REMS products to celecoxib notably fluctuated for hospice and palliative care ranging from 5.0% to 55.6%.

From pre-implementation to active period, the largest decreases in the proportion of patients who switched from REMS products to IR opioids were observed for 2 specialties with less compelling reasons to prescribe ER/LA opioid analgesics: dentists (from 0.84% to 0.62%; 26.3% decrease, $p < 0.001$) and emergency medicine specialists (from 1.43% to 1.11%; 22.3% decrease, $p < 0.001$), as well as anesthesiologists (from 18.2% to 15.1%; 17.1% decrease, $p < 0.001$). From pre-implementation to active period, the proportion of patients who switched from REMS products to celecoxib generally increased or remained stable. The largest increases were observed for: pediatricians (from 3.66% to 4.07%; 11.3% increase, $p < 0.001$) and rheumatologists (from 3.69% to 3.91%; 5.9% increase, $p < 0.001$).

4.5.2. Evaluation of Changes in Prescribing Behaviors

The same retrospective cross-sectional study described in the last section was used to evaluate changes in prescribing behavior, including prescriptions to non-opioid tolerant patients, excessive prescriptions, and early refills.

The specific objectives of this study included:

1. For products that are indicated for use in opioid-tolerant patients only (i.e., fentanyl transdermal patches, extended-release hydromorphone tablets and extended-release morphine dosage forms >90 mg), describe trends in the proportion of prescriptions for these products to opioid-non-tolerant patients in the year preceding the availability of REMS-compliant CE courses and compare the proportion of prescriptions to opioid non-tolerant patients in the pre-implementation and active periods
2. For products whose labels indicate that higher dosage strengths should only be used in opioid-tolerant patients, describe trends in the proportion of prescriptions prescribed to opioid non-tolerant patients with a high starting dosage strength; compare the proportion of prescriptions for such products that are prescribed to opioid non-tolerant patients with a high starting dosage strength in the pre-implementation and active periods
3. Describe changes in the volume of ER/LA opioid analgesics prescriptions and compare this prescription volume in the pre-implementation and active periods

4. To compare the proportion of patients with concomitant use of benzodiazepines and ER/LA opioid analgesics in the pre-implementation and active periods

4.5.2.1. Statistical Methods

All measures described below were aggregated monthly in the pre-implementation, implementation and active period. Data on unique patients prescribed ER/LA opioid analgesics are only available by product strength, while data is available on product level for comparator products. As a result, monthly assessment of patient volume was conducted at the individual product strength level for ER/LA opioid analgesics and at the product group level for comparator products.

Mean and 95% CI were calculated for average monthly patient volumes and switch rates for each study period. Changes in prescribing before and after REMS implementation were performed by calculating and comparing the average percent changes in average switch rates between the Pre-Implementation and Active Periods. Differences in the average change in switch rates were assessed for statistical significance using Student's T-test and / or Z-test approximations. P values less than 0.05 were considered significant.

Unless otherwise stated, patient counts were projected to the national level based on the LRx prescription sample with projection factors derived from the prescriptions in LRx relative to NPA™ total prescription.

4.5.2.2. Results

Results of the evaluation of changes in prescribing behaviors showed, relative to the overall number of patients prescribed these drugs, the proportion of non-tolerant patients being prescribed ER/LA opioid analgesics intended for opioid-tolerant patients changed significantly only for ER hydromorphone. As shown in [Table 14](#), the proportion of non-tolerant patients dispensed ER hydromorphone decreased 8.8% from pre-implementation to 44.6% during the active period ($p < 0.001$).

TABLE 14: COMPARISON OF THE AVERAGE MONTHLY PROPORTION OF OPIOID NON-TOLERANT PATIENTS PRESCRIBED PRODUCTS INDICATED FOR OPIOID TOLERANT PATIENTS ONLY ACROSS PRE-IMPLEMENTATION AND ACTIVE PERIOD

ER/LA OPIOID	PATIENT VOLUME				STATISTICAL COMPARISON WITHIN PRODUCT TYPE	PERCENT CHANGE WITHIN PRODUCT TYPE
	PRE-IMPLEMENTATION		ACTIVE PERIOD		PRE-IMPLEMENTATION VS ACTIVE	PRE-IMPLEMENTATION VS ACTIVE
	MEAN	95% CI	MEAN	95% CI	P-VALUE (T-TEST)	% CHANGE
Fentanyl TD						
Total patient volume	312,579	(309,896-315,262)	322,013	(318,086-325,940)	0.000	312,579
% Non-tolerant	50.3%	(49.40%-51.27%)	49.5%	(48.29%-50.62%)	0.221	-1.7%
ER Hydromorphone						
Total patient volume	6,522	(5,332-7,713)	13,500	(12,585-14,415)	0.000	6,522
% Non-tolerant	48.9%	(48.18%-49.65%)	44.6%	(43.23%-45.97%)	0.000	-8.8%
ER Morphine ≥90mg						
Total patient volume	53,368	(52,870-53,866)	45,696	(44,510-46,883)	0.000	53,368
% Non-tolerant	30.3%	(28.97%-31.55%)	29.4%	(27.87%-30.91%)	0.369	-2.9%

Changes in prescribing behavior in terms of high-starting dose opioids prescribed to non-tolerant patients were also analyzed. Such changes described in terms of proportion of non-tolerant patients prescribed high starting dose ER/LA opioid analgesic products differed, depending on products and strengths. For several strengths, the average proportion of non-tolerant patients prescribed high starting dose fentanyl, oxycodone HCl, oxymorphone HCl, and tapentadol HCl decreased significantly from the pre-implementation to the active period. Conversely, for several strengths, there was an increase in the average proportion of non-tolerant patients prescribed high starting dose buprenorphine during the study periods whereas the proportion of non-tolerant patients prescribed hydromorphone HCl and morphine sulfate remained the same throughout the study periods.

When early refill for the REMS products was analyzed, different patterns in change were seen in terms of early refill rates. The rate of early refill decreased during the study periods for all ER/LA opioid analgesics except morphine-naltrexone which decreased slightly during the first 6 months of pre-implementation, and increased thereafter.

In terms of early refill prescription volume, a significant decrease from pre-implementation was observed for almost all products (with the exception of buprenorphine and hydromorphone HCl, for which a significant increase was observed, and for morphine-naltrexone [statistical comparisons could not be conducted]). It is crucial to note that since refill data were not projected to national estimates, changes observed during the study period may have been impacted, at least in part, by sample fluctuations.

Finally, changes across periods among the patients who concomitantly used a benzodiazepine in combination with ER/LA opioid analgesics were assessed. Results revealed a decrease in the proportion of patients with concomitant use of benzodiazepine and all ER/LA opioid analgesics, except morphine-naltrexone, from the pre-implementation to the active period.

4.5.3. Monitoring Patterns of Prescribing to Identify Changes in Access to ER/LA Opioid Analgesics

Patterns of prescribing were monitored for changes in access to ER/LA opioid analgesics. Using the same data sources as described in the last two sections (IMS Health, National Prescription Audit™ (NPA™) and IMS Health, LifeLink™ patient-level longitudinal prescription (LRx) database) to compare changes in number of prescriptions by prescriber types with less (e.g., Dentist) and more (e.g., Oncologist, Hospice Care) compelling reasons to prescribe ER/LA opioid analgesics.

Specific outcomes measured for this retrospective cross-sectional study were to measure:

- monthly volume of prescriptions from specialties assumed to be relatively unaffected by the REMS
- monthly volume of prescriptions from specialties assumed to be more affected by the REMS

4.5.3.1. Statistical Methods

Measurements of changes in prescribing during the pre-implementation, implementation, and active period of the REMS were performed. The average percent changes in average monthly volumes from pre-implementation to the active period, and 95% CI around average volume monthly were calculated. The statistical significance of these changes was estimated by T-test. P values less than 0.05 were considered significant.

4.5.3.2. Results

The average monthly prescription volume for the total ER/LA opioid analgesics prescribed by pain specialists and physical medicine and rehabilitation specialists did not change significantly over the study period. Prescription volume for hospice and palliative medicine specialists significantly decreased (5.9% decrease, $p = 0.006$) and increased for anesthesiologists (2.8% increase, $p = 0.013$) from pre-implementation to active period. Nurse practitioners and physician assistants experienced a significant increase in the volume of total ER/LA opioid analgesics prescribed over the study period, with an increase of 33.7% and 31.2% from the pre-implementation to the active period (both $p < 0.001$), respectively. The other prescriber specialists evaluated had a significant decrease in the prescription volume for total ER/LA opioid analgesics. The largest percent decrease from pre-implementation to active periods was observed for dentists (48.5% decrease) and emergency medicine specialists (25.5% decrease) (all $p < 0.001$).

For the non-REMS products, the volume of benzodiazepines prescribed by PCPs, dentists, neurologists and the all other specialist categories did not significantly change across study periods. Large, significant increases from pre-implementation to active periods were observed for nurse practitioners and physician assistants in the volume of benzodiazepines (34.3% increase and 29.0% increase, respectively; both $p < 0.001$). Pediatricians also increased benzodiazepine prescribing (pre-implementation to active period: 7.8% increase, $p < 0.001$). Prescribed volume for benzodiazepines decreased across periods for the other specialists. Hospice and palliative medicine specialists had a significant and large percent decrease in

volume, with a 43.1% decrease from pre-implementation to active period, while a substantial decrease was also observed for pain specialists (13.2% decrease) as well as anesthesiologists (14.9% decrease) (all $p < 0.001$).

There were significant increases in the volume of celecoxib prescribed by pain specialists and by anesthesiologists from pre-implementation to the active period (5.8% increase, $p < 0.0001$). A significant increase in the volume of celecoxib from pre-implementation to active periods was observed for nurse practitioners (29.2% increase) and physician assistants (31.3% increase) (all $p < 0.001$). All other prescriber specialists had a significant decrease in the volume of celecoxib prescribed. Hospice and palliative medicine specialty had the largest percent decrease, a 50.0% decrease from pre-implementation to active period, while dentists had a decrease of 33.5%, oncologists had a decrease of 26.5%, and neurologists had a decrease of 23.0%, respectively (all $p < 0.001$).

For the IR opioids, the volume prescribed from pre-implementation to active period decreased for most prescriber specialists. Significant and large increases from pre-implementation to the active periods were observed for nurse practitioners (26.5% increase) and physician assistants (21.3% increase) (all $p < 0.001$). Significant and large decreases from pre-implementation to the active periods were observed for surgical specialists (16.0% decrease) and emergency medicine specialists (16.0% decrease) (all $p < 0.001$). Significant and large decreases were observed from pre-implementation to the active period for neurologists (14.6% decrease), hospice and palliative medicine specialists (13.8% decrease) and pediatricians (13.0% decrease) (all $p < 0.001$).

4.6. Surveillance Monitoring

A number of sources were used to collect surveillance data regarding misuse, abuse, overdose, addiction, and death for the 36-Month FDA Assessment Report. These sources include the following, and are summarized in greater detail in [Table 15](#):

- emergency department (ED) visits and hospitalizations for opioid overdose and poisoning events using either a national representative database of ED visits or an analysis of public and/or private insurance claims databases
- intentional exposures among adolescents and adults, including severity and deaths, using nationally-based poison control surveillance data
- unintentional exposures among infants and children, including severity and deaths, using nationally-based poison control surveillance data
- rates of individuals in substance abuse treatment programs abusing ER/LA opioid analgesics, as well as source of acquiring the ER/LA opioid analgesics, as compared to comparator (IR opioids and benzodiazepines) using national surveillance systems for substance abuse treatment seekers
- mortality rates resulting from drug poisoning associated with active pharmaceutical ingredients included in the ER/LA Opioid Analgesics REMS using state medical examiner databases from Washington

TABLE 15: DATA SOURCES USED FOR SAFETY SURVEILLANCE

ASSESSMENT COMPONENT	DATA SOURCE	DESCRIPTION
Component 1- Emergency Department Visits	HealthCore Integrated Research Database SM (HIRD)	The HIRD SM is a broad, clinically rich and geographically diverse spectrum of longitudinal claims data from health plan members in the Northeastern, Mid-Atlantic, Southeastern, Midwest, Central, and Western regions of the US.
	Medicaid Data	Medicaid program for one state for which de-identified data are currently available for research.
Component 2- Intentional Exposures Among Adolescents and Adults	Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS [®]) System	The RADARS [®] System provides post-marketing surveillance of prescription medication abuse, misuse, and diversion to pharmaceutical companies, regulatory agencies and policy-making organizations.
Component 3- Unintentional Exposures Among Infants and Children		
Component 4- Substance Abuse Treatment Programs	National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO [®])	The NAVIPPRO [®] System provides real-time, product-specific surveillance information from a network of several hundred substance abuse treatment centers around the US in order to monitor emerging trends in substance abuse from adults and adolescents, respectively.
Component 5- Mortality Rates	State Medical Examiner Databases (Washington)	Data provided via State Department of Health Vital Statistics Office.

4.6.1. Surveillance of Emergency Department Visits and Hospitalizations for Opioid Overdose and Poisoning Events

The first component of safety surveillance monitoring includes a retrospective cohort study using the HIRD commercially-insured and Medicaid data from one state. The study was designed to assess the incidence of ED visits and hospitalizations due to opioid overdose and poisoning.

The study included the following objectives:

1. Compute the incidence rate of ED visits and hospitalizations for opioid overdose/poisoning and death among patients prescribed ER/LA opioid analgesics;
2. Compare the incidence rate of ED visits and hospitalizations for opioid overdose/poisoning and death across the REMS pre-implementation period (July 2010 through June 2012), REMS implementation period (July 2012 through June 2013) and REMS active period (July 2013 through August 2014), stratified by exposed versus unexposed person-time, separately for new and non-new ER/LA opioid analgesic users;
3. Describe risk factors for ED visits and hospitalizations for opioid overdose/poisoning and death among patients prescribed ER/LA opioid analgesics; and

4. Compute the incidence rate of ED visits and hospitalizations for opioid overdose/poisoning across the REMS pre-implementation, REMS implementation and REMS active periods among all patients with or without ER/LA opioid analgesic treatment.

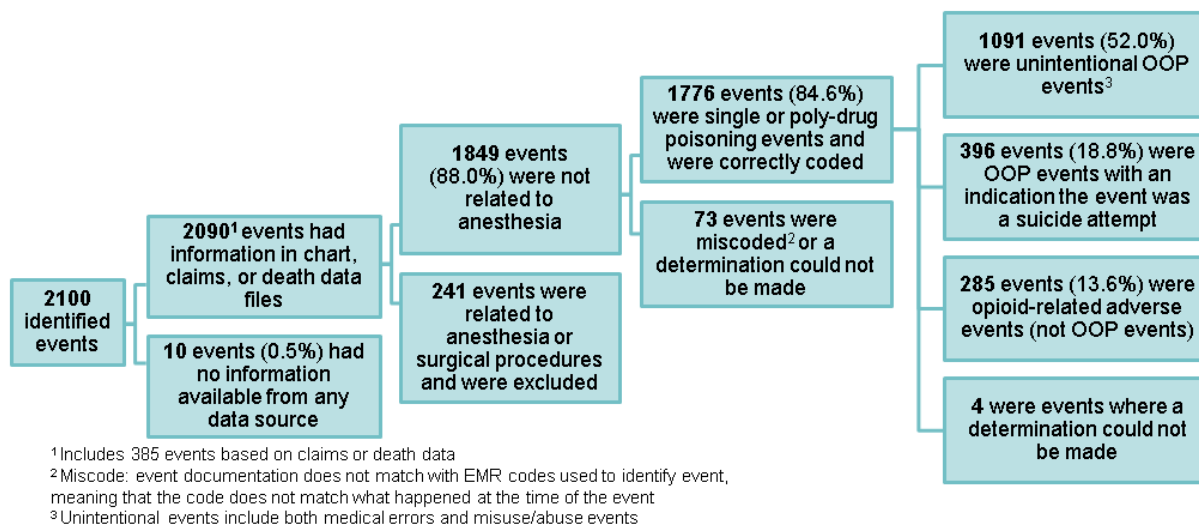
4.6.1.1. Methods

In the main analyses, patients who received at least one dispensing of an ER/LA opioid analgesic during at least one REMS study period and who had at least 6 months of prior continuous health plan eligibility were included. Additional analyses considered patients enrolled in the HIRD or a participating Medicaid plan with or without ER/LA opioid analgesic exposure. Patients were followed from the time of the first ER/LA opioid analgesic dispensing occurring in a REMS period until the end of the REMS period, the end of health plan eligibility or the first instance of a study outcome. Exposed person-time included any time during a treatment episode, unexposed person-time included time after a treatment episode, and all person-time included both exposed and unexposed person-time. The primary analyses included only exposed person-time.

In the HIRD, patients were defined as either new users or non-new users upon the start of their follow-up during each REMS period. New users were individuals for whom there were no prior recorded dispensings of ER/LA opioid analgesics identified in the administrative claims data at any time prior to the start of follow-up. Non-new users were individuals for whom pharmacy dispensings were identified within the REMS period-specific baseline period. Patients were considered as new users only in the specific REMS period during which they first started follow-up. Because of the small available sample size for Medicaid, stratification by new versus non-new user status was not performed for this data source.

A validation study was conducted using data from on Kaiser Permanente Northwest Region (KPNW) and Kaiser Permanente Northern California (KPNC) memberships between August 2008 and October 2012. Two groups of opioid-specific ICD-9 codes were assessed: (1) poisoning codes (965.xx, E850.x, and X42) and (2) AE codes (E935.x and Y45) combined with ICD-9 codes for overdose symptoms (e.g., altered consciousness, respiratory distress, etc.). The validation scheme is shown in [Figure 9](#) below.

FIGURE 9: OPIOID ICD-9 VALIDATION SCHEME



There was a 71% (1487/2100) positive predictive value to detect opioid overdose poisoning events not related to inpatient anesthesia. Therefore the analyses used these ICD codes to identify opioid overdose poisoning events.

4.6.1.2. Statistical Methods

Incidence rate ratios were computed comparing the pre-implementation period to the active period, both unadjusted and adjusted for patient and treatment characteristics. Comparisons were adjusted using stepwise regression to select covariates from a list that included age, gender, geographic region, pain conditions for which ER/LA opioid analgesics are indicated, psychiatric comorbidities (including drug addiction), history of overdose/poisoning, the Deyo-Charlson comorbidity index, opioid use characteristics (including whether the event occurred during the dispensed period for analysis of all person-time only, prior use of ER/LA and/or immediate release opioids, and duration of use), prescriber specialty, number of prescribers or pharmacies used, and use of non-opioid medications of abuse potential. Manual review in which terms that were omitted were entered back into the model did not subsequently affect results.

Analyses were performed separately for Medicaid-insured and commercially-insured individuals. Primary analyses considered the incidence rate during a treatment episode. In commercially-insured patients, we also calculated rates for all users and new users separately. Secondary analyses considered all person-time, including the treatment episode and person-time after the treatment episode. Sensitivity analyses removed patients who received products available with abuse-deterrent properties at any time during the study period.

To explore the effect of abuse deterrent technology on changes in abuse and misuse rates, data were reanalyzed excluding opioids that are recognized by FDA as having abuse deterrent properties (OxyContin[®], Embeda[®]) along with reformulated opioids not recognized by FDA as having abuse deterrent properties (EXALGO[®], Opana[®] ER, OXAYDO[®], Nucynta[®] ER, and Zohydro[®] ER).

4.6.1.3. Results for Commercially-Insured Patients

A total of 80,209 ER/LA opioid analgesic users meeting all study criteria were identified in the pre-implementation period and 43,730 in the active period.

4.6.1.3.1. Commercially-Insured Patient Demographic and Clinical Characteristics

Across periods, mean age was 55 to 56 years, and 56% of patients were female. Back pain was the most common pain diagnosis recorded during the baseline period, followed by arthritis/musculoskeletal pain and abdominal pain. Several patient characteristics changed significantly from the pre-implementation to the active period. Baseline opioid dependence was recorded for 5.8% of the patients during the pre-implementation and 10.6% during the active period. Increases across the REMS periods were also observed for several psychiatric comorbidities, including anxiety disorders (29.7% to 39.5%), depressive disorders (28.2% to 35.8%), and sleep disorders (30.3% to 37.8%). Prior and concomitant use of immediate release opioid analgesics was very common, with over 80% of patients using both ER/LA and immediate release opioids during follow-up across all REMS study periods. Both prior and concomitant use of benzodiazepines and sleep medications were also frequently observed.

4.6.1.3.2. Incidence of Overdose or Poisoning in Commercially-Insured Patients

As shown in [Table 16](#) among all users during a treatment episode, the unadjusted incidence of opioid overdose or poisoning was 84.6 (95% CI 76.5-93.5) per 10,000 person-years in the pre-implementation period and 86.8 (95% CI 75.0-99.9) in the active period.

**TABLE 16: INCIDENCE OF OPIOID OVERDOSE OR POISONING, BY TYPE OF EVENT AND REMS PERIOD
PER 10,000 PERSON-YEARS**

		PRE-IMPLEMENTATION PERIOD		ACTIVE PERIOD		UNADJUSTED INCIDENCE RATE RATIO, ACTIVE VS PRE-IMPLEMENTATION PERIOD		ADJUSTED INCIDENCE RATE RATIO, ACTIVE VS PRE-IMPLEMENTATION PERIOD	
		INCIDENCE RATE	95% CI	INCIDENCE RATE	95% CI	INCIDENCE RATE RATIO	95% CI	INCIDENCE RATE RATIO	95% CI
OPIOID OVERDOSE AMONG ER/LA OPIOID USERS	HIRD								
	All users								
	Treated time	84.6	76.5-93.5	86.8	75.0-99.9	1.03	0.86-1.22	0.83	0.70-0.99 ¹
	All	60.9	55.6-66.6	72.7	63.4-83.0	1.19	1.02-1.40	0.83	0.71-0.98 ²
	New users								
	Treated time	88.8	73.6-106.2	116.6	85.4-155.5	1.31	0.93-1.84	1.06	0.78-1.45 ³
	All	43.1	36.7-50.2	63.3	47.6-82.7	1.51	1.16-1.95	0.97	0.71-1.33 ⁴
	Non-new users								
	Treated time	82.9	73.3-93.4	80.4	68.0-94.4	0.97	0.78-1.20	0.79	0.65-0.97 ⁵
	All	76.9	68.8-85.8	76.4	65.2-89	0.99	0.82-1.19	0.76	0.63-0.92 ⁶
	Medicaid								
	All users								
	Treated time	244.6	182.7-320.7	261.9	202.9-322.5	1.07	0.75-1.54	0.81	0.59-1.18 ⁴
	All	203.2	156.8-259	219.7	170.6-278.5	1.08	0.77-1.52	0.80	0.52-1.21 ^{4X}

Models adjusted for:

1. Region, Deyo-Charlson comorbidity index, use of benzodiazepines, use of sleep medications, chronic pain, alcohol abuse, anxiety disorder, bipolar disorder, depression, history of overdose, post-traumatic stress disorder and addiction to opioids or other drugs.
2. Current ER/LA opioid exposure, region, Deyo-Charlson comorbidity index, use of benzodiazepines, use of sleep medications, chronic pain, alcohol abuse, bipolar disorder, depression, and history of suicide attempt.
3. Use of sleep medications, chronic pain, alcohol abuse, anxiety disorder, depression, drug use and history of overdose.
4. Deyo-Charlson comorbidity index, use of sleep medications, chronic pain, alcohol abuse, anxiety disorder, bipolar disorder, depression, current ER/LA opioid exposure and history of overdose.
5. Region, Deyo-Charlson comorbidity index, use of benzodiazepines, use of sleep medications, chronic pain, alcohol abuse, addiction to opioids or other drugs, bipolar disorder, depression, and history of overdose.
6. Region, Deyo-Charlson comorbidity index, use of benzodiazepines, use of sleep medications, chronic pain, alcohol abuse, anxiety disorder, depressive disorder, bipolar disorder, post-traumatic stress disorder, history of overdose and ER/LA opioid exposure.

In all users during a treatment episode, the incidence rate ratio comparing the active period versus the pre-implementation period was 0.83 (95% CI 0.70 – 0.99) after adjusting for region, Deyo-Charlson comorbidity index, use of benzodiazepines, use of sleep medications, chronic pain, alcohol abuse, anxiety disorder, depressive disorder, bipolar disorder and history of overdose. In new users during exposed person-time, the incidence rate ratio comparing the active period versus the pre-implementation period was 1.06 (95% CI 0.78 – 1.45) after adjusting for use of sleep medications, chronic pain, alcohol abuse, anxiety disorder, depressive disorder and history of overdose.

In a sensitivity analysis in which patients who used opioid formulations available with abuse deterrent properties were removed, incidence rates were consistently higher than in the main analysis (95.1, 95% CI 84.4 – 106.7 the pre-implementation period, 94.9, 95% CI 79.9 – 112.0) in the active period for all users during current exposure. Adjusted incidence rate ratio estimates did not differ from the main analysis.

4.6.1.4. Results for Medicaid Patients

We identified 3,488 ER/LA opioid analgesic users in the pre-implementation period, 3,746 in the implementation period and 3,625 in the active period.

4.6.1.5. Medicaid Patient Demographic and Clinical Characteristics

Age in Medicaid cohort members was lower than the commercially-insured population, with a mean of 43 to 45 years, and 59% were female. A large majority of patients had a back pain diagnosis at baseline. Over 90% used ER/LA and immediate release opioids concomitantly during follow-up across all REMS periods. Like the commercially-insured population, concomitant and prior use of non-opioid medications of abuse potential, especially benzodiazepines and sleep medications, was common.

Several patient characteristics changed significantly from the Pre-implementation to the Active period. Baseline opioid dependence was recorded for 28.4% of the patients during the pre-implementation and 35.4% during the active period. Increases across the REMS periods were also observed for several psychiatric comorbidities, including anxiety disorders (47.6% to 60.4%), depressive disorders (45.8% to 56.0%), sleep disorders (38.5% to 50.7%), alcoholism (14.7% to 19.3%), and other drug dependence (33.2% to 37.9%).

Among all ER/LA opioid users, the incidence of opioid overdose or poisoning was substantially higher than what was observed for commercially-insured patients: 244.6 (95% CI 182.7 – 320.7) per 10,000 person-years in the pre-implementation period, 235.5 (95% CI 173.6 – 312.3) in the implementation period, and 261.9 (95% CI 202.9 – 322.5) in the active period during a treatment episode (Table 16).

Adjusted for use of sleep medications, alcohol abuse, bipolar disorder, depressive disorder and history of overdose, the incidence rate ratio was 0.81 (95% CI 0.59 – 1.18) for the active period versus the pre-implementation period.

4.6.1.6. Summary of Results

The unadjusted rate of opioid overdose during treatment episodes increased after the REMS became active but there were large changes in the patient characteristics that are risk factors for opioid overdose from pre-implementation to the active REMS period. After adjustment for these confounding characteristics, the incidence rate ratio was 0.8 for both Medicaid and HIRD databases, but it is difficult to assign causal attribution to these results.

4.6.1.7. Limitations

Because the REMS study periods are perfectly correlated with calendar time, and not all time-varying covariates are identifiable, there is the possibility of confounding by unmeasured factors that change over the study periods. Although region of residence was taken into account as a possible covariate, we were unable to capture and address factors such as changes in physician preferences, use of Prescription Drug Monitoring Programs, or local regulatory environments. Additionally, there were policy changes in 2012

in the state where Medicaid data were available. In 2012, a Drug Action Committee was convened, with various follow-up items including linkage to PDMPs, law enforcement education, provider education, and public action and engagement components. As is true elsewhere in the study, various factors changed over time and place which likely influenced trends in opioid use and overdose over time.

The patient population in the post-REMS period had a higher prevalence of risk factors associated with opioid overdose, such as substance use disorder, depression, and low back pain. While the study controlled for these measured confounders, there may have been other unmeasured confounders that were not included in the adjustment. As such, residual confounding could lead to an underestimation of the adjusted decrease in opioid overdose observed after the REMS became active.

Our estimates of incidence may be subject to diagnostic bias. It is plausible, for example, that increased awareness of the serious risks of ER/LA opioid analgesics among the medical community could result in more widespread attribution of overdose events to opioids and the familiarity with and use of opioid-specific ICD-9-CM diagnosis overdose codes. Were that the case, an opioid overdose event may be more likely to be recorded as such in the implementation and active periods.

This study utilized an administrative claims database, and it is subject to the limitations inherent in the use of such data. The majority of analyses were conducted using a database that is representative of the commercially-insured population in the US and is therefore not representative of individuals without medical insurance. A small population of Medicaid program members was also included, and efforts are in progress to increase the size of this subgroup for future analyses. Given differences in patient characteristics between commercially and Medicaid insured individuals and a substantially higher rate of overdose in Medicaid patients, better characterization of this at-risk population is important.

Finally, although all patients were required to have a pharmacy benefit, patients for the main analyses of ER/LA opioid analgesic users were identified on the basis of submitted pharmacy claims, excluding patients who chose not to use their pharmacy benefit from the cohort. Insurance coverage typically presents a strong financial incentive for use of the pharmacy benefit; however it is possible that patients more likely to abuse opioids (who are therefore at higher risk for overdose, poisoning and death) could chose to pay for some or all of their prescriptions with cash.

Despite these limitations, this study provides insight on the incidence of opioid overdose and poisoning in the context of the class-wide ER/LA Opioid Analgesics REMS in a large population. Also, we were able to describe and control for important differences between patients receiving ER/LA opioid analgesics in different time periods related to the REMS.

4.6.2. Poison Center Programs

Poison Center Program data were used to assess 2 components of the ER/LA Opioid Analgesics REMS:

- Intentional exposures among adolescents and adults, including severity and deaths
- Unintentional exposures among infants and children, including severity and deaths

Both of these components utilize the RADARS[®] System Poison Center Program which obtains data from individuals within the general population and from healthcare providers who are seeking advice regarding potential toxic exposures, including prescription opioids and prescription stimulants. The objectives of the Poison Center Program are to detect product-specific prescription drug abuse and misuse in near-real-time and to identify geographic sites with disproportionately high rates of abuse and misuse. Poison center data collected through the RADARS[®] System provide an estimate of change in intentional abuse, misuse, and deaths associated with these drugs. The Poison Center Program gathers data from 49 regional US Poison Centers in 46 states, including urban, suburban, and rural regions (covering over 90% of the US population). Investigators at each participating poison center collect data using a nationally standardized electronic health record. In addition to obtaining exposure and substance data, the Poison Center Program collects demographic, clinical effects, treatment, and medical outcomes information. The Poison Center

Program was initiated in 2002. For purposes of this analysis pediatric was defined as children under 6 and adolescent was defined as cases 13-19 years old or with an age code of teen.

Additional background on the Poison Center Program, including Principal Investigator biographies can be found in [Appendix 10](#) and [Appendix 11](#).

4.6.2.1. Methods

The following outcomes listed were measured using Poison Center data.

- **Abuse** – an exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high euphoric effect or some other psychotropic effect
- **Misuse** – an exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of psychotropic effect
- **Major Medical Outcome, Hospitalization, Death** – an exposure resulting in a major medical outcome or death or any exposure with a level of healthcare facility coded as: admitted to critical care, admitted to non-critical care, or admitted to psychiatric care facility
- **Death** – an exposure with an outcome of death
- **Under 20 Years Treated/Evaluated and Released** – an exposure case in someone under 20 years old with a level of healthcare coded as treated/evaluated and released
- **Adult Treated/Evaluated and Released** – an adult exposure with a level of healthcare coded as treated/evaluated and released
- **Pediatric Unintentional Exposures** – unintentional therapeutic errors and unintentional general exposures occurring in a subject under six years of age
- **Child and Adolescent Unintentional Exposures** – unintentional therapeutic errors and unintentional general exposures occurring in subjects 6-19 years of age
- **Adult Unintentional Exposure** – unintentional therapeutic errors and unintentional general exposures occurring in individuals 20 years of age and older
- **Unintentional Therapeutic Error** – 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
- **Pediatric Unintentional General Exposures** – defined as those cases in children under 6 with a reason code of unintentional general which consists primarily of accidental unsupervised ingestions such as a toddler getting into a grandparent's prescription medicine
- **Pediatric Unintentional General Exposures Major Medical Outcome, Hospitalization, or Death** – defined as those cases in children under 6 with a reason code of unintentional general and an exposure resulting in a major medical outcome or death will be defined as a Major Medical Outcome, Hospitalization or Death and any case with a level of healthcare coded as: admitted to critical care, admitted to non-critical care, or admitted to psychiatric care facility
- **Pediatric Unintentional General Exposures Treated/Evaluated and Released** – defined as those cases in children under 6 with a reason code of unintentional general and level of healthcare coded as treated/evaluated and released
- **Adolescent Intentional Abuse** – defined as cases 13-19 years old or with an age code of teen that have a reason for exposure of intentional abuse

4.6.2.2. Statistical Methods

Crude (observed) and adjusted mean rates for these outcomes, with 95% CIs, based on 2 denominators: the population in rate per 100,000 and the number of prescriptions dispensed per 1,000. [Table 18](#) through [Table 45](#) show these rates for the class REMS ER/LA opioid analgesics and comparator drugs for the pre-implementation and active REMS time periods based on RADARS[®] Poison Center data from Q32 2010

through Q4 of 2014. Poisson regression was used to calculate the pre-implementation to active period percent changes in the rates, the 95% CIs, and the associated p-values for ER/LA opioid analgesics and the comparators. In addition the statistical model captured the p-value associated with the interaction between the ER/LA opioid analgesics and each of the other 2 drug types.

4.6.2.3. Results

[Table 17](#) shows a summary of the outcomes where there were significant differences in outcomes between the pre-implementation and active period and between the ER/LA opioids and one or more comparator drugs.

Additional results for the RADARS[®] Poison Center data can be found in [Appendix 12](#).

**TABLE 17: SUMMARY OF OUTCOMES FROM ANALYSES OF RADARS®
POISON CENTER DATA**

OUTCOMES WITH SIGNIFICANT DIFFERENCES BETWEEN PRE-IMPLEMENTATION AND ACTIVE PERIOD FOR ER/LA OPIOIDS	OUTCOMES WITH SIGNIFICANT DIFFERENCES BETWEEN ER/LA OPIOIDS AND COMPARATOR(S)	
	IR PRESCRIPTION OPIOIDS	PRESCRIPTION STIMULANTS
Abuse	Abuse	Abuse
Misuse	Misuse [#]	Misuse*
Major Medical Outcome, Hospitalization, Or Death	Major Medical Outcome, Hospitalization, Or Death	Major Medical Outcome, Hospitalization, Or Death
Death	Death [#]	
Under 20 Treated/Evaluated and Released	Under 20 Treated/Evaluated and Released	Under 20 Treated/Evaluated and Released
Adult Treated/Evaluated and Released	Adult Treated/Evaluated and Released [#]	Adult Treated/Evaluated and Released
Pediatric Unintentional Exposure		Pediatric Unintentional Exposure*
Adult Unintentional Exposure	Adult Unintentional Exposure [#]	
Unintentional Therapeutic Error	Unintentional Therapeutic Error [#]	Unintentional Therapeutic Error*
Pediatric Unintentional General Exposure		Pediatric Unintentional General Exposure*
Pediatric Unintentional General Exposure Treated/Evaluated And Released [#]	Pediatric Unintentional General Exposure Treated/Evaluated And Released [#]	
Adolescent Intentional Abuse Exposure	Adolescent Intentional Abuse Exposure	Adolescent Intentional Abuse Exposure

* Significant only for population data

Significant only for prescription data

4.6.2.4. Abuse Exposure Results

Table 18 shows that the mean rate of ER/LA opioid analgesic intentional abuse (adjusted for population) fell 44.04% compared to 30.89% for IR prescription opioids and 13.35% for prescription stimulants. The reduction in rates for ER/LA opioid analgesics was significantly greater than the reductions for IR prescription opioids and prescription stimulants.

TABLE 18: MEAN INTENTIONAL ABUSE RATE PER 100,000 POPULATION FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.123	0.069	-44.04% (-50.57%,-36.64%)	<.001	.
IR Prescription Opioids	0.276	0.191	-30.89% (-36.40%,-24.90%)	<.001	0.006
Prescription Stimulants	0.148	0.129	-13.35% (-19.35%, -6.90%)	<.001	<.001

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

Table 19 shows that the mean rate of ER/LA opioid analgesic intentional abuse (adjusted for prescriptions) fell 44.42% compared to 24.99% for IR prescription opioids and 26.25% for prescription stimulants. The reduction in rates for ER/LA opioid analgesics was significantly greater than the reductions for IR prescription opioids and prescription stimulants.

TABLE 19: MEAN INTENTIONAL ABUSE RATE PER 1,000 PRESCRIPTIONS DISPENSED FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.064	0.035	-44.42% (-50.34%,-37.79%)	<.001	.
IR Prescription Opioids	0.018	0.013	-24.99% (-30.45%,-19.10%)	<.001	<.001
Prescription Stimulants	0.032	0.023	-26.25% (-32.50%,-19.41%)	<.001	<.001

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

4.6.2.5. Misuse Results

Table 20 shows that the mean rate of ER/LA opioid analgesic misuse (adjusted for population) fell 22.49% compared to 17.94% for IR prescription opioids and 1.46 for prescription stimulants. Mean decreases for ER/LA opioid analgesics and IR prescription opioids were statistically significant.

TABLE 20: MEAN MISUSE RATE PER 100,000 POPULATION FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.236	0.183	-22.49% (-29.32%,-15.01%)	<.001	.
IR Prescription Opioids	1.226	1.006	-17.94% (-21.54%,-14.19%)	<.001	0.275
Prescription Stimulants	1.195	1.177	-1.46% (-6.57%, 3.94%)	0.589	<.001

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

Table 21 shows that the mean rate of ER/LA opioid analgesic misuse (adjusted for prescriptions) fell 23.03% compared to 10.93% for IR prescription opioids and 16.12% for prescription stimulants. All mean decreases were statistically significant.

TABLE 21: MEAN MISUSE RATE PER 1,000 PRESCRIPTIONS DISPENSED FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.122	0.094	-23.03% (-28.97%,-16.59%)	<.001	.
IR Prescription Opioids	0.079	0.070	-10.93% (-14.97%,-6.70%)	<.001	0.002
Prescription Stimulants	0.256	0.214	-16.12% (-20.14%,-11.90%)	<.001	0.074

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

4.6.2.6. Major Medical Outcome, Hospitalization, or Death Results

Table 22 shows that the mean rate of ER/LA opioid analgesic major medical outcome, hospitalization, or death (adjusted for population) fell 24.88% compared to 12.47% for IR prescription opioids while prescription stimulant rates increased 13.39. The mean decreases for ER/LA opioid analgesics and IR prescription opioids and the increase for prescription stimulants were all statistically significant.

TABLE 22: MEAN MAJOR MEDICAL OUTCOME, HOSPITALIZATION, OR DEATH RATE PER 100,000 POPULATION FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.250	0.188	-24.88% (-29.33%, -20.15%)	<.001	.
IR Prescription Opioids	1.220	1.068	-12.47% (-15.02%, -9.85%)	<.001	<.001
Prescription Stimulants	0.387	0.438	13.39% (6.19%, 21.09%)	<.001	<.001

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

Table 23 shows that the mean rate of ER/LA opioid analgesic major medical outcome, hospitalization, or death (adjusted for prescriptions) fell 25.40% compared to 4.99% for IR prescription opioids and 3.48% for prescription stimulants. Only mean decreases for ER/LA REMS opioids and IR prescription opioids were statistically significant.

TABLE 23: MEAN MAJOR MEDICAL OUTCOME, HOSPITALIZATION, OR DEATH RATE PER 1,000 PRESCRIPTIONS DISPENSED FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.129	0.096	-25.40% (-29.68%, -20.85%)	<.001	.
IR Prescription Opioids	0.078	0.074	-4.99% (-7.63%, -2.28%)	<.001	<.001
Prescription Stimulants	0.083	0.080	-3.48% (-7.72%, 0.95%)	0.122	<.001

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

4.6.2.7. Death Results

Table 24 shows that the mean rate of ER/LA opioid analgesic death (adjusted for population) fell 42.39% compared to 17.66% for IR prescription opioids while prescription stimulants increased 1.31%. Only the decrease observed for ER/LA REMS opioids was significant.

TABLE 24: MEAN DEATH RATE PER 100,000 POPULATION FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.004	0.002	-42.39% (-59.22%, -18.61%)	0.002	.
IR Prescription Opioids	0.012	0.010	-17.66% (-31.11%, -1.57%)	0.033	0.072
Prescription Stimulants	0.002	0.002	1.31% (39.02%, 68.31%)	0.960	0.072

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

Table 25 shows that the mean rate of ER/LA opioid analgesic death (adjusted for prescriptions) fell 42.78% compared to 10.62% for IR prescription opioids and 13.77% for prescription stimulants. Only the mean rate decrease observed for ER/LA REMS opioids was statistically significant.

TABLE 25: MEAN DEATH RATE PER 1,000 PRESCRIPTIONS DISPENSED FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.002	0.001	-42.78% (-59.43%, -19.30%)	0.001	.
IR Prescription Opioids	<.001	<.001	-10.62% (-25.63%, 7.42%)	0.231	0.025
Prescription Stimulants	<.001	<.001	-13.77% (-48.75%, 45.10%)	0.577	0.197

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

4.6.2.8. Under 20 Years Treated/Evaluated and Released Results

Table 26 shows that the mean rate of ER/LA opioid analgesic treated/evaluated and released for patients under 20 years of age (adjusted for population) fell 32.42% compared to 6.80% for IR prescription opioids while prescription stimulants increased 0.60%. The mean rate decreases observed for ER/LA REMS opioids and IR prescription opioids were statistically significant.

TABLE 26: MEAN RATE PER 100,000 POPULATION OF TREATED/EVALUATED AND RELEASED FOR PATIENTS UNDER 20 YEARS FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.107	0.072	-32.42% (-45.99%, -15.44%)	<.001	.
IR Prescription Opioids	0.727	0.677	-6.80% (-11.30%, -2.08%)	0.005	0.006
Prescription Stimulants	1.270	1.278	0.60% (-5.29%, 6.86%)	0.846	<.001

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

Table 27 shows that the mean rate of ER/LA opioid analgesic treated/evaluated and released for patients under 20 years of age (adjusted for prescriptions) fell 34.04% while IR prescription opioid rates remained constant and prescription stimulant rates fell 15.86%. Only the decreases observed for ER/LA REMS opioids and prescription stimulants were statistically significant.

TABLE 27: MEAN RATE PER 1,000 PRESCRIPTIONS DISPENSED OF TREATED/EVALUATED AND RELEASED FOR PATIENTS UNDER 20 YEARS FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.015	0.010	-34.04% (-46.92%, -18.04%)	<.001	.
IR Prescription Opioids	0.012	0.012	-0.60% (-5.86%, 4.97%)	0.830	<.001
Prescription Stimulants	0.073	0.061	-15.86% (-20.19%, -11.28%)	<.001	0.033

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

4.6.2.9. Adult Treated/Evaluated and Released Results

Table 28 shows that the mean rate of ER/LA opioid analgesic treated/evaluated and released for adults (adjusted for population) fell 26.54% compared to 16.01% for IR prescription opioids while prescription stimulant rates increased 6.55%. Only the mean decrease for ER/LA REMS opioids and IR prescription opioids were statistically significant.

TABLE 28: MEAN RATE PER 100,000 POPULATION OF ADULT TREATED/EVALUATED AND RELEASED FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.123	0.090	-26.54% (-35.37%,-16.50%)	<.001	.
IR Prescription Opioids	0.582	0.489	-16.01% (-19.44%,-12.42%)	<.001	0.051
Prescription Stimulants	0.140	0.149	6.55% (-0.40%, 13.99%)	0.065	<.001

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

Table 29 shows that the mean rate of ER/LA REMS opioid analgesic treated/evaluated and released for adults (adjusted for prescriptions) fell 26.53% compared to 8.19% for IR prescription opioids and 8.66% for prescription stimulants. All mean decreases were statistically significant.

TABLE 29: MEAN RATE PER 1,000 PRESCRIPTIONS DISPENSED OF ADULT TREATED/EVALUATED AND RELEASED FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.046	0.034	-26.53% (-34.67%,-17.38%)	<.001	.
IR Prescription Opioids	0.027	0.025	-8.19% (-11.26%,-5.01%)	<.001	<.001
Prescription Stimulants	0.022	0.020	-8.66% (-15.85%,-0.87%)	0.030	0.003

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

4.6.2.10. Pediatric Unintentional Exposure Results

Table 30 shows that the mean rate of ER/LA REMS opioid analgesic pediatric unintentional exposure (adjusted for population) fell 20.76% compared to 15.89% for IR prescription opioids and 1.05% for prescription stimulants. Mean decreases for ER/LA REMS opioids and IR prescription opioids were statistically significant.

TABLE 30: MEAN PEDIATRIC UNINTENTIONAL EXPOSURE RATE PER 100,000 POPULATION FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES [#]
ER/LA REMS Opioids	0.530	0.420	-20.76% (-32.37%, -7.16%)	0.004	.
IR Prescription Opioids	3.895	3.276	-15.89% (-21.52%, -9.84%)	<.001	0.499
Prescription Stimulants	5.511	5.453	-1.05% (-5.09%, 3.16%)	0.619	0.008

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

[#]The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

Table 31 shows that the mean rate of ER/LA REMS opioid analgesic pediatric unintentional exposure (adjusted for prescriptions) fell 22.39% compared to 9.96% for IR prescriptions and 16.94% for prescription stimulants. All mean decreases were statistically significant.

TABLE 31: MEAN PEDIATRIC UNINTENTIONAL EXPOSURE RATE PER 1,000 PRESCRIPTIONS DISPENSED FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES [#]
ER/LA REMS Opioids	0.021	0.016	-22.39% (-33.09%, -9.97%)	<.001	.
IR Prescription Opioids	0.019	0.018	-9.96% (-15.78%, -3.74%)	0.002	0.074
Prescription Stimulants	0.092	0.076	-16.94% (-22.79%, -10.65%)	<.001	0.421

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

[#]The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

4.6.2.11. Child and Adolescent Unintentional Exposure Results

Table 32 shows that the mean rate of ER/LA REMS opioid analgesic child and adolescent unintentional (adjusted for population) fell 19.35% compared to 7.39% for IR prescription opioids while prescription stimulants increased 5.60%. No mean decreases observed were statistically significant.

TABLE 32: MEAN CHILD AND ADOLESCENT UNINTENTIONAL EXPOSURE RATE PER 100,000 POPULATION FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.026	0.021	-19.35% (-41.39%, 10.98%)	0.187	.
IR Prescription Opioids	0.334	0.309	-7.39% (-14.28%, 0.04%)	0.051	0.409
Prescription Stimulants	2.590	2.735	5.60% (-2.28%, 14.11%)	0.168	0.108

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

Table 33 shows that the mean rate of ER/LA REMS opioid analgesic child and adolescent unintentional exposure (adjusted for prescriptions) fell 21.35% while IR prescription opioid rates remained constant and prescription stimulant rates fell 11.75%. Only the mean decrease for prescription stimulants was statistically significant. Only the mean decrease for prescription stimulants was statistically significant.

TABLE 33: MEAN CHILD AND ADOLESCENT UNINTENTIONAL EXPOSURE RATE PER 1,000 PRESCRIPTIONS DISPENSED FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.003	0.002	-21.35% (-42.01%, 6.66%)	0.122	.
IR Prescription Opioids	0.004	0.004	-1.31% (-9.20%, 7.27%)	0.757	0.159
Prescription Stimulants	0.105	0.093	-11.75% (-16.35%, -6.89%)	<.001	0.465

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

4.6.2.12. Adult Unintentional Exposure Results

Table 34 shows that the mean rate of ER/LA REMS opioid analgesic adult unintentional exposure (adjusted for population) fell 15.55% compared to 12.77% for IR prescription opioids and 8.65% for prescription stimulants. All mean decreases observed were statistically significant.

TABLE 34: MEAN ADULT UNINTENTIONAL EXPOSURE RATE PER 100,000 POPULATION FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.159	0.134	-15.55% (-21.80%, -8.81%)	<.001	.
IR Prescription Opioids	0.593	0.517	-12.77% (-17.19%, -8.13%)	<.001	0.493
Prescription Stimulants	0.221	0.202	-8.65% (-14.88%, -1.96%)	0.012	0.140

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

Table 35 shows that the mean rate of ER/LA REMS opioid analgesic adult unintentional exposure (adjusted for prescriptions) fell 15.54% compared to 4.65% for IR prescription opioids and 21.70% for prescription stimulants. Only mean decreases for ER/LA REMS opioids and prescription stimulants were statistically significant.

TABLE 35: MEAN ADULT UNINTENTIONAL EXPOSURE RATE PER 1,000 PRESCRIPTIONS DISPENSED FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.060	0.051	-15.54% (-21.36%, -9.29%)	<.001	.
IR Prescription Opioids	0.028	0.027	-4.65% (-10.11%, 1.13%)	0.113	0.010
Prescription Stimulants	0.035	0.027	-21.70% (-27.79%, -15.09%)	<.001	0.170

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

4.6.2.13. Unintentional Therapeutic Error Results

Table 36 shows that the mean rate of ER/LA REMS opioid analgesic unintentional therapeutic error (adjusted for population) fell 16.57% compared to 11.83% for IR prescription opioids while prescription stimulants increased 0.51%. Mean decreases for both ER/LA REMS opioids and IR prescription opioids were statistically significant.

TABLE 36: MEAN UNINTENTIONAL THERAPEUTIC ERROR RATE PER 100,000 POPULATION FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.134	0.112	-16.57% (-23.10%, -9.49%)	<.001	.
IR Prescription Opioids	0.570	0.502	-11.83% (-16.67%, -6.70%)	<.001	0.274
Prescription Stimulants	0.700	0.703	0.51% (-6.02%, 7.49%)	0.883	<.001

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

Table 37 shows that the mean rate of ER/LA REMS opioid analgesic unintentional therapeutic error (adjusted for prescriptions) fell 17.14% compared to 4.30% for IR prescription opioids and 14.45% for prescription stimulants. Mean decreases for both ER/LA REMS opioids and prescription stimulants were statistically significant.

TABLE 37: MEAN UNINTENTIONAL THERAPEUTIC ERROR RATE PER 1,000 PRESCRIPTIONS DISPENSED FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.069	0.057	-17.14% (-23.11%, -10.72%)	<.001	.
IR Prescription Opioids	0.037	0.035	-4.30% (-10.05%, 1.83%)	0.165	0.004
Prescription Stimulants	0.150	0.128	-14.45% (-18.85%, -9.81%)	<.001	0.493

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

4.6.2.14. Pediatric Unintentional General Exposure Results

Table 38 shows that the mean rate of ER/LA REMS opioid analgesic pediatric unintentional exposure (adjusted for population) fell 21.54% compared to 18.27% for IR prescription opioids and 0.69% for prescription stimulants. Mean decreases for both ER/LA REMS opioids and IR prescription opioids were statistically significant.

TABLE 38: MEAN PEDIATRIC UNINTENTIONAL GENERAL EXPOSURE RATE PER 100,000 POPULATION FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.520	0.408	-21.54% (-33.29%, -7.73%)	0.003	.
IR Prescription Opioids	3.504	2.864	-18.27% (-24.71%, -11.28%)	<.001	0.659
Prescription Stimulants	5.001	4.967	-0.69% (-4.86%, 3.67%)	0.753	0.006

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

Table 39 shows that the mean rate of ER/LA REMS opioid analgesic pediatric unintentional exposure (adjusted for prescriptions) fell 23.15% compared to 12.51% for IR prescription opioids and 16.63% for prescription stimulants. All mean decreases were statistically significant.

TABLE 39: MEAN PEDIATRIC UNINTENTIONAL GENERAL EXPOSURE RATE PER 1,000 PRESCRIPTIONS DISPENSED FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.021	0.016	-23.15% (-34.01%, -10.52%)	<.001	.
IR Prescription Opioids	0.017	0.015	-12.51% (-19.25%, -5.21%)	0.001	0.140
Prescription Stimulants	0.083	0.069	-16.63% (-22.76%, -10.02%)	<.001	0.349

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

4.6.2.15. Pediatric Unintentional General Exposures Major Medical Outcome, Hospitalization, or Death Results

Table 40 shows that the mean rate of ER/LA REMS opioid analgesic pediatric unintentional general exposure major medical outcome, hospitalization, or death (adjusted for population) fell 0.57% compared to 3.29% for IR prescription opioids while prescription stimulants increased 2.48%. No mean decreases were statistically significant.

TABLE 40: MEAN PEDIATRIC UNINTENTIONAL GENERAL EXPOSURE MAJOR MEDICAL OUTCOME, HOSPITALIZATION, OR DEATH RATE PER 100,000 POPULATION FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.158	0.157	-0.57% (-18.56%, 21.39%)	0.955	.
IR Prescription Opioids	0.182	0.176	-3.29% (-16.01%, 11.36%)	0.642	0.824
Prescription Stimulants	0.618	0.633	2.48% (-5.02%, 10.57%)	0.527	0.781

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

Table 41 shows that the mean rate of ER/LA REMS opioid analgesic pediatric unintentional exposure major medical outcome, hospitalization, or death (adjusted for prescriptions) fell 2.61% while IR prescription opioids increased 3.53% and prescription stimulant fell 13.97%. Only the mean decrease observed for prescription stimulants was statistically significant.

TABLE 41: MEAN PEDIATRIC UNINTENTIONAL GENERAL EXPOSURE MAJOR MEDICAL OUTCOME, HOSPITALIZATION, OR DEATH RATE PER 1,000 PRESCRIPTIONS DISPENSED FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.006	0.006	-2.61% (-20.33%, 19.03%)	0.796	.
IR Prescription Opioids	<.001	<.001	3.53% (-10.04%, 19.14%)	0.629	0.625
Prescription Stimulants	0.010	0.009	-13.97% (-21.99%, -5.14%)	0.003	0.276

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

4.6.2.16. Pediatric Unintentional General Exposures Treated/Evaluated and Released Results

Table 42 shows that the mean rate of ER/LA REMS opioid analgesic pediatric unintentional exposure treated/evaluated and released (adjusted for population) fell 22.04% compared to 5.77% for IR prescription opioids while prescription stimulants increased 0.15%. No mean decreases were statistically significant.

TABLE 42: MEAN RATE PER 100,000 POPULATION OF UNINTENTIONAL GENERAL EXPOSURE TREATED/EVALUATED AND RELEASED FOR PEDIATRIC PATIENTS FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.203	0.158	-22.04% (-40.25%, 1.72%)	0.067	.
IR Prescription Opioids	1.349	1.271	-5.77% (-12.81%, 1.83%)	0.133	0.180
Prescription Stimulants	2.043	2.046	0.15% (-5.32%, 5.94%)	0.958	0.071

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

Table 43 shows that the mean rate of ER/LA REMS opioid analgesic pediatric unintentional exposure treated/evaluated and released (adjusted for prescriptions) fell 23.64% while IR prescription opioids remained constant and prescription stimulants fell 15.93%. Mean decreases for ER/LA REMS opioids and prescription stimulants were statistically significant.

TABLE 43: MEAN RATE PER 1,000 PRESCRIPTIONS DISPENSED OF UNINTENTIONAL GENERAL EXPOSURE TREATED/EVALUATED AND RELEASED FOR PEDIATRIC PATIENTS FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.008	0.006	-23.64% (-41.03%, -1.13%)	0.041	.
IR Prescription Opioids	0.007	0.007	0.87% (-6.81%, 9.18%)	0.831	0.043
Prescription Stimulants	0.034	0.029	-15.93% (-22.79%, -8.46%)	<.001	0.488

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

4.6.2.17. Adolescent Intentional Abuse Results

Table 44 shows that the mean rate of rate of ER/LA REMS opioid analgesic adolescent intentional abuse exposure (adjusted for population) fell 61.85% compared to 36.62% for IR prescription opioids and 28.99% for prescription stimulants. All mean decreases were statistically significant.

TABLE 44: MEAN ADOLESCENT INTENTIONAL ABUSE EXPOSURE RATE PER 100,000 POPULATION FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.187	0.071	-61.85% (-69.47%, -52.33%)	<.001	.
IR Prescription Opioids	0.525	0.333	-36.62% (-48.01%, -22.73%)	<.001	<.001
Prescription Stimulants	0.647	0.459	-28.99% (-40.15%, -15.74%)	<.001	<.001

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

Table 45 shows that that the mean rate of ER/LA REMS opioid analgesic adolescent intentional abuse exposure (adjusted for prescriptions) fell 62.29% compared to 31.52% for IR prescription opioids and 39.84% for prescription stimulants. All mean decreases were statistically significant.

TABLE 45: MEAN ADOLESCENT INTENTIONAL ABUSE EXPOSURE RATE PER 1,000 PRESCRIPTIONS DISPENSED FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.009	0.004	-62.29% (-69.66%, -53.13%)	<.001	.
IR Prescription Opioids	0.003	0.002	-31.52% (-43.67%, -16.76%)	<.001	<.001
Prescription Stimulants	0.014	0.008	-39.84% (-49.63%, -28.15%)	<.001	0.001

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

4.6.2.18. Poison Center Program Summary

The mean intentional abuse population rate for the ER/LA REMS opioid group declined 44.0% compared to 30.9% for the IR prescription opioids and 13.4% for prescription stimulants. The reduction in rates for ER/LA opioid analgesics was significantly greater than the reductions for IR prescription opioids and prescription stimulants.

For all other outcome variables (intentional misuse, unintentional general exposures, unintentional therapeutic errors, major medical outcomes or hospitalization, and deaths) there were significant decreases from the pre period to the post period in the mean population and prescription adjusted rates in the ER/LA opioids. However, mean decreases were also seen for IR prescription opioids. The comparison

of the mean decreases for the ER/LA opioids to the mean decreases for the IR opioids was significant for population and prescription adjusted rates of intentional abuse and major medical outcomes or hospitalization. Additionally mean prescription adjusted rates decreases were larger for the ER/LA opioid compared to the IR opioids for intentional misuse, unintentional therapeutic errors, and deaths.

4.6.2.19. Poison Center Program Results without Abuse Deterrent Formulations

To explore the effect of abuse deterrent technology on changes in abuse and misuse rates, data were reanalyzed excluding opioids that are recognized by FDA as having abuse deterrent properties (OxyContin[®], Embeda[®]) along with reformulated opioids not recognized by FDA as having abuse deterrent properties (EXALGO[®], Opana[®] ER, OXAYDO[®], Nucynta[®] ER, and Zohydro[®] ER).

The mean rate of ER/LA REMS opioid analgesic abuse exposure (adjusted for population) fell 30.8% after data on ADF drugs were removed. Due to low rates of dispensed prescriptions for OXAYDO, the only IR abuse deterrent product, rates were little changed from those reported for IR prescription opioids that included this ADF. As there were no abuse deterrent resistant stimulants on the market during the study period, this sub-analysis was not conducted. The difference between ER/LA REMS opioid and IR prescription opioid groups was attenuated from 44.0% to 30.8% without inclusion of abuse deterrent products. The declines for the ER/LA REMS opioids compared to the IR prescription opioids were no longer statistically significant. The comparison of the declines for the ER/LA REMS opioid group and for the prescription stimulants remained significant.

For Intentional Abuse rates adjusted for the number of prescriptions and without abuse deterrent products, the ER/LA REMS opioid analgesic mean rates (adjusted for prescriptions) fell 35.0%. The attenuation in the difference in ER/LA REMS opioid rates resulted in the comparison between declines in IR prescription opioids and prescription stimulants becoming non-significant.

For all other outcome variables: intentional misuse, unintentional general exposures, unintentional therapeutic errors, major medical outcomes or hospitalization, and deaths, when analyses were repeated excluding labeled and purported ADFs, the mean change in death rates for the ER/LA REMS opioids was attenuated and no longer significant for either population or prescription adjusted rates. The comparison of mean decreases for the ER/LA REMS opioids and IR prescription opioids was no longer significant for both population and prescription adjusted rates for intentional abuse. Population rates for major medical outcomes or hospitalization and prescription rates for death also lost significance. Thus, only prescription adjusted rates of intentional misuse, unintentional therapeutic errors, and major medical outcome or hospitalizations were robust to removal of ADFs.

See [Appendix 12](#) for details on the results without abuse deterrent formulations.

4.6.3. Rates of People in Substance Abuse Treatment Programs Abusing ER/LA Opioid Analgesics

Two vendors examined rates of ER/LA opioid analgesic abuse among individuals in substance abuse treatment abuse treatment programs. NAVIPPRO[®] used data from 2 proprietary data streams, the ASI-MV[®] for adults and CHAT for adolescents, to compare ER/LA opioid analgesic abuse with abuse of IR opioids and benzodiazepines, including data on the source of the ER/LA opioid analgesics. RADARS[®] System Treatment Center Programs provided data on abuse of ER/LA opioid analgesic compared with IR opioids.

Results from NAVIPPRO[®] suggest that ER/LA opioid analgesics are reported as abused within the ASI-MV[®] and CHAT programs less often in the active period compared to the pre-REMS time frame ($p = 0.001$ for ASI-MV[®] data; $p = 0.02$ for CHAT data). In addition, past 30-day abuse of ER/LA opioid analgesics reported from the ASI-MV[®] per 100,000 U.S. population yielded directionally similar results as that from the pre-implementation period to the active period, reports of past 30-day abuse of ER/LA opioid analgesics observed within the ASI-MV[®] systems decreased per 100,000 U.S. population ($RR =$

0.80; -20.5% reduction); a reduction that was statistically significant ($p < 0.001$). Across the same time period, change was examined for IR opioids as a group and benzodiazepines (as collected by the ASI-MV[®] and CHAT). Analyses of the ASI-MV[®] adult substance abuse treatment data revealed a significant decrease from pre-REMS to the active period for these 3 groups (i.e., ER/LA opioid analgesics, IR opioids, and benzodiazepines). As for the adolescent CHAT assessments, change in reported prevalence for IR opioids and benzodiazepines did not reach significance.

4.6.3.1. NAVIPPRO[®] Drug Treatment Center Study

The main objective of this study was to monitor and evaluate patterns of abuse of ER/LA opioid analgesics among a sentinel population of adults assessed for substance use problems for treatment planning. To better understand ER/LA opioid analgesic abuse patterns, secondary analyses examined the ER/LA opioid analgesics together and by compound (ER/LA opioid analgesics included in the class-wide REMS and, at the compound or sub-group level for morphine ER, oxymorphone ER, methadone, transdermal fentanyl, transdermal buprenorphine, oxycodone ER, hydromorphone ER, tapentadol ER, and hydrocodone ER). Secondary objectives compared abuse of ER/LA opioid analgesics as a group to IR opioids and to benzodiazepines. Tertiary analyses assessed abuse patterns of ER/LA opioid analgesics as a group and at the compound level over time as well as patterns in source of procurement among those individuals reporting past 30-day abuse of ER/LA opioid analgesics. Sources of procurement, evaluated as part of the tertiary objective, included: one's own prescription, one's own prescription from several doctors, family member or friend and "illicit" (i.e., bought it online without a doctor's visit, bought it from a dealer [a known seller], wrote or bought a fake prescription, stole them, traded for it, and "other").

This cross-sectional, observational surveillance study using data collected by the NAVIPPRO[®] ASI-MV[®] system was analyzed using the same strategy established for the other safety surveillance activities for time periods (e.g., pre-implementation, implementation, active period). In addition, secondary analyses also compare ER/LA opioid analgesics and "benzodiazepines" in order to potentially understand secular trends when evaluating changes in abuse patterns over time. The ASI-MV[®] and CHAT do not collect data for benzodiazepines as a single category but rather group them in a general category. In the prior report of data through 2013, the unit of analysis was individual ASI-MV assessment. Based on FDA guidance, the 2014 data analysis plan includes the unit of analysis of the patient-home 3-digit ZIP code level (spatial) and quarter (time).

4.6.3.1.1. NAVIPPRO[®] Results Related to Adults

A total of 263,485 patients were included in the analysis based on having an available valid zip code.

Of the total 263,485 patients, the majority were male (64.7%), Caucasian (60.0%), and had never been married (57.1%). Approximately 47% were 21 to 34 years of age, followed by approximately 36% who were 35 to 54 years of age. The greatest proportion of individuals indicated employment in occupations involving skilled or semi-skilled labor (30.9%). Approximately 60% of the population had been prompted by the criminal justice system to enter a substance abuse treatment program. A chronic medical problem was indicated by 29.6% of individuals and 32.6% reported a pain problem.

During the 6-quarter active period, past 30-day abuse of ER/LA opioid analgesics was 8.7 cases per 100 ASI-MV[®] assessments (July 2013 – December 2014). From the pre-REMS baseline to the active period, reports of past 30-day abuse of ER/LA opioid analgesics among individuals assessed by the ASI-MV[®] decreased (RR = 0.93; -6.7% reduction); a reduction that was statistically significant ($p = 0.001$). Comparison of the active period to the pre-REMS period showed a decrease in the past 30-day abuse of IR opioids among individuals assessed by the ASI-MV[®] (RR = 0.94; -6.3% change) a change that was significant ($p = 0.0003$). During the active period, past 30-day abuse of benzodiazepines as captured by the ASI-MV[®] maintained the decreased prevalence (10.3 cases per 100 ASI-MV[®] assessments) observed in the pre-REMS to implementation period. Thus, the pre-REMS to active period decrease (RR = 0.90; -9.5% decrease) was significant ($p < 0.0001$).

Three sensitivity analyses were also conducted. The first sensitivity analysis was restricted to those sites within the total ASI-MV[®] network of sites which had contributed data (i.e., at least one ASI-MV[®] assessment) during the study period and looked to evaluate changes in the prevalence of abuse of ER/LA opioid analgesic products as a group among a shared set of sites across the study period. These data indicate results similar to those observed among all ASI-MV[®] assessments described above in that a significant decrease was observed from the pre-REMS period to the active period (- 4.7% reduction; $p = 0.0317$).

To explore any potential impact of changes in the underlying population being assessed over time as it relates to drug problem severity ratings, a stratified analysis was conducted which evaluated reports of past 30-day abuse of extended release opioids among low, moderate and high drug severity ratings during each REMS study period. A decrease in past 30-day ER/LA opioid analgesic abuse was observed within each strata of drug severity (low, moderate and high) over time, from the pre-REMS period in relation to the active period. Of note is that of the 3 drug severity categories, the highest proportion of ER/LA opioid analgesic abuse was observed among those individuals with the highest drug severity ratings (23.73 cases of ER/LA opioid analgesic abuser per 100 ASI-MV[®] assessments during the pre-REMS period and 21.78 cases of ER/LA opioid analgesic abuser per 100 ASI-MV[®] assessments during the active period). The greatest percent reduction in ER/LA opioid analgesic abuse over time was observed among those individuals with the lowest severity rating (-38% from the pre-REMS period to the active period).

Lastly, an evaluation of ER/LA opioid analgesic abuse within each of these treatment settings over time was conducted. A decrease in reports of past 30-day abuse of ER/LA opioid analgesics was observed within each treatment modality setting, with the exception of those evaluated within a residential/inpatient setting where no change was observed. Among those evaluated within a methadone maintenance setting, a -28.9% reduction in past 30-day abuse of ER/LA opioid analgesics was observed from the pre-REMS period to the active period. A significant reduction (-13.9%; $p < 0.0001$) was observed among those in an outpatient/non-methadone setting.

Analyses were also performed using the total U.S. Census population in the 3-digit ZIP codes associated with the home location of those individuals who presented to take at an ASI-MV[®] assessment. From the pre-REMS baseline to the active period, reports of past 30-day abuse of ER/LA opioid analgesics observed within the ASI-MV[®] systems decreased per 100,000 U.S. population (RR = 0.80; 20.5% reduction); a reduction that was statistically significant ($p < 0.001$). Directionally consistent findings were seen for IR opioids and benzodiazepines when using the U.S. Census denominator versus the 100 ASI-MV[®] denominator.

When restricting this analysis to those sites which had contributed data (i.e., at least one ASI-MV[®] assessment) during the study periods, the data indicate a significant decrease from the pre-REMS period to the active period (-13.5%; $p < 0.0001$). It should be noted that for this analysis, incorporating both the over-dispersion parameter along with the zip code random effect results in estimates which were substantially different from those derived from the standard Poisson model without random effects. It should be noted however, that the final model that incorporated the over-dispersion parameter and zip code random effects did yield a superior fit as compared to the standard model.

A stratified analysis which evaluated reports of past 30-day abuse of ER/LA opioid analgesics among individuals with low, moderate and high drug severity ratings was conducted for each REMS study period. Results indicated directionally consistent findings overall in that past 30-day abuse of ER/LA opioid analgesics decreased within each strata of drug severity, per 100,000 population, from the pre-REMS period to the active period. Decreases in past 30-day abuse of ER/LA opioid analgesics are observed within each treatment modality setting reviewed, with the exception of residential/inpatient which increased from the pre-REMS period to the active period (+14.9%; $p = 0.0002$).

4.6.3.1.2. CHAT Results Related to Adolescents

A total of 12,510 adolescents, generally between 10 and 18 years of age, comprised the CHAT population during the study period. The majority of the population was male (67.2% - 69.7%), 15 to 18 years of age (77.9% - 80.6%), Caucasian (67.3% - 68.9%), and reported usually living with one or both biological parents (78.0% - 80.2%). In addition, the majority of individuals who completed a CHAT assessment reported current enrollment in a school program (83.0% - 84.2%), of which most reported public school as the type of school program (71.5% - 73.0%). A total of 33% to 36% of CHAT participants indicated having been in a controlled environment (e.g., juvenile detention center, substance abuse treatment) in the 30 days prior to completing the assessment. Between 28% to 32% of the CHAT population indicated that they were currently taking a prescribed medication for an emotional, behavioral, or learning problem. Approximately 28% of CHAT respondents during each analysis period reported a current physical problem or illness. A current pain problem was reported by 20.8% of CHAT participants in the Pre-REMS period and 18.9% in the active period.

The prevalence of past 30-day ER/LA opioid analgesic abuse in the active REMS phase (2.61 per 100 CHAT assessments) was lower than the prevalence of past 30-day abuse of ER/LA opioid analgesics during the pre-REMS baseline period (3.51). In general, during each of the 3 analysis periods, the prevalence of past 30-day abuse of IR opioids within the CHAT population was higher than the prevalence of past 30-day abuse of ER/LA opioid analgesics. During the pre-REMS period, past 30-day ER/LA opioid analgesic abuse prevalence was similar to that of benzodiazepines (3.51 and 3.63 respectively). By the active period, ER/LA opioid analgesic abuse prevalence had decreased (2.61) while prevalence of benzodiazepine abuse increased (4.35).

Data to examine the proportion of the source of drug for ER/LA opioid analgesic prescription opioids was also collected. The percentage of those who obtained ER/LA opioid analgesics from one's own prescription was similar in the pre-REMS period (4.27%) and the active REMS period (4.26%). Obtaining ER/LA opioid analgesics from multiple doctors was indicated by 1.71% of past 30-day abusers in the pre-REMS period and less than 1% of past 30-day ER/LA opioid analgesic abusers in the active period. The percentage of those who obtained ER/LA opioid analgesics from a family member or friend was lowest during the active period (49.65%). The percentage of those who obtained ER/LA opioid analgesics from 'other' sources during the active period was 71.63%, similar to the pre-REMS period (70.09%).

4.6.3.2. RADARS® Drug Treatment Center Study

The RADARS® System Treatment Center program data was also used to evaluate trends in abuse of ER/LA opioid analgesics before and after the shared REMS intervention was implemented.

The Treatment Center Programs combined provide data from two distinct RADARS® System programs: Opioid Treatment Program and Survey of Key Informants' Patients Program. These programs use the same core data collection form and complement each other by providing information from patients entering both private and public opioid addiction treatment programs. Patients enrolling in the study are voluntarily recruited and complete a self-administered anonymous questionnaire within the first week of admission. The objectives of these programs are to estimate 1-month prevalence and the injection rate of prescription and illicit opioid and non-opioid drugs among patients admitted to opioid treatment programs. In addition, the surveys seek to determine the patient's drug of choice and the source of the primary drug.

The Opioid Treatment Program involves 77 methadone maintenance treatment programs in both urban and rural areas across 37 states. Formal data collection began in 2005. The Survey of Key Informants' Patients Program involves 155 substance abuse treatment programs covering 47 states. These primarily private treatment centers are balanced geographically with representation from urban, suburban, and rural centers. Survey of Key Informants' Patient Program became a RADARS® System Program in 2008.

Additional background on the Drug Treatment Center Study, including Principal Investigator biographies can be found in [Appendix 10](#) and [Appendix 11](#).

4.6.3.3. RADARS® Treatment Center Abuse Results

Full results for the RADARS® Treatment Center data can be found in [Appendix 12](#).

[Table 46](#) and [Table 47](#) show crude (observed) and adjusted mean rates of past 30 day mention rate, with 95% CIs, based on 2 denominators: the population in rate per 100,000 and the number of prescriptions dispensed per 1,000. These rates are shown for the class REMS ER/LA opioid analgesics and comparator drugs for the pre-implementation and active REMS time periods based on RADARS® Treatment Center data from Q32 2010 through Q4 of 2014.

[Table 46](#) shows that the mean rate of ER/LA REMS opioid analgesic past 30 day mention (adjusted for population) fell 47.02% compared to 12.09% for IR prescription opioids. The decrease for ER/LA opioid analgesics was statistically significant.

TABLE 46: MEAN PAST 30 DAY MENTION RATES PER 100,000 POPULATION FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	1.987	1.053	-47.02% (-60.00%, -29.81%)	<.001	.
IR Prescription Opioids	2.133	1.875	-12.09% (-27.31%, 6.32%)	0.184	0.003

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

[Table 47](#) shows that the mean rate of ER/LA REMS opioid analgesic past 30 day mention (adjusted for prescriptions) fell 46.31% compared to 2.27% for IR prescription opioids. The decrease for ER/LA opioid analgesics was statistically significant.

TABLE 47: MEAN PAST 30 DAY MENTION RATES PER 1,000 PRESCRIPTIONS DISPENSED FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.994	0.534	-46.31% (-59.60%, -28.64%)	<.001	.
IR Prescription Opioids	0.135	0.132	-2.27% (-18.78%, 17.60%)	0.808	<.001

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

4.6.4. RADARS® Treatment Center Abuse Summary

Mean rates of ER/LA Opioid use to get high within the past 30 days per 100,000 persons fell 47.02% compared to 12.09% for IR opioids. The reduction in rates for ER/LA opioids is significantly greater than the reductions for IR prescription opioids. Prescription-adjusted rates also showed a decrease. Mean rates of ER/LA Opioid use to get high within the past 30 days per 1,000 prescriptions fell 46.31% compared to 2.27% for IR prescription opioids. The reduction in rates for ER/LA opioids is significantly greater than the reductions for IR prescription opioids.

4.6.5. College Survey Program

RADARS® System College Survey program data was also used to evaluate trends in abuse of ER/LA opioid analgesics before and after the shared REMS intervention was implemented.

The College Survey Program is an online questionnaire that collects data from self-identified students attending a 2- or 4-year college, university, or technical school at least part-time during the specified sampling period. Data on non-medical use (abuse/misuse) of specific prescription drugs are collected at the completion of the fall and spring academic semesters/quarters and at the end of the summer. The objectives of the College Survey Program are to estimate the scope of non-medical prescription drug use among US college students, determine the drug source, and determine the route of drug administration among these students. A target of 2000 surveys is completed three times per year with enrollment stratified into the four US Census-regions to ensure nationwide distribution of respondents. A nationwide panel company is utilized to identify and target ideal responders. Students are sent an invitation to participate in the study and they receive credits upon completion of the survey. The survey inquires about the non-medical use of prescription drugs by capturing product specific endorsements. Data are national, timely, and drug specific. The College Survey was launched in 2008.

Additional background on the College Survey Program, including Principal Investigator biographies can be found in [Appendix 10](#) and [Appendix 11](#).

4.6.5.1. College Survey Results

Full results for the College Survey data can be found in [Appendix 12](#).

[Table 48](#) and [Table 49](#) show the observed and predicted population, prescription dispensed, and dosing unit mean past 90 day mention rates and 95% confidence intervals for ER/LA REMS opioids and comparator drugs during Pre-Implementation, Transition, and Active Period time periods based on data from RADARS® College Survey data from Q32 2010 through Q4 of 2014.

[Table 48](#) shows that the mean rates of ER/LA REMS opioid analgesic past 90 day mention (adjusted for population) increased 84.85% compared to 71.43% for IR prescription opioids and 7.72% for prescription stimulants. Mean increases for ER/LA REMS opioids and IR prescription opioids were statistically significant.

TABLE 48: MEAN PAST 90 DAY MENTION RATES PER 100,000 POPULATION FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.049	0.091	84.85% (22.07%, 179.93%)	0.004	.
IR Prescription Opioids	0.114	0.195	71.43% (30.88%, 124.54%)	<.001	0.765
Prescription Stimulants	0.177	0.191	7.72% (-25.25%, 55.23%)	0.690	0.056

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

Table 49 shows that that the mean rates of ER/LA REMS opioid analgesic past 90 day mention (adjusted for prescriptions) increased 85.10% compared to 87.52% for IR prescription opioids while prescription stimulants decreased 8.24%. Mean decreased for ER/LA REMS opioids and IR prescription opioids were statistically significant.

TABLE 49: MEAN PAST 90 DAY MENTION RATES PER 1,000 PRESCRIPTIONS FOR ER/LA REMS OPIOIDS AND COMPARATORS, 2010 - 2014

DRUG GROUP	MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
ER/LA REMS Opioids	0.027	0.049	85.10% (24.37%, 175.47%)	0.002	.
IR Prescription Opioids	0.008	0.014	87.52% (43.34%, 145.32%)	<.001	0.958
Prescription Stimulants	0.039	0.036	-8.24% (-38.05%, 35.90%)	0.668	0.014

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

4.6.5.2. College Survey Program Abuse Summary

College Survey mean changes for non-medical use in the past 90 days were increasing but not significantly.

4.6.6. Mortality Rates Resulting From Drug Poisoning

Medical Examiner data were obtained from death indexes in the state of Washington. The objective of the Medical Examiner Program was to detect changes in mortality rates relative to the implementation of the ER/LA REMS. Of the states contacted, only Washington State was able to provide death data within the timeframe required to evaluate and analyze the data for the last FDA Assessment Report.

4.6.6.1. Death Rates for Prescription Opioids with an ER/LA Formulation Excluding Hydrocodone

Table 50 through Table 51 show crude (observed) and adjusted mean death rates, with 95% CIs, based on 2 denominators: the population in rate per 100,000 and the number of prescriptions dispensed per 1,000. These rates are shown for the class REMS ER/LA opioid analgesics without hydrocodone, all hydrocodone formulations as a separate category and benzodiazepines as a comparator for the pre-implementation and active REMS time periods based on Washington State Medical Examiner data from Q1 2005 through Q4 of 2013. Hydrocodone was excluded because prior to 2014, all hydrocodone products were IR only.

Table 50 shows that the mean death rate for ER/LA opioid analgesics excluding hydrocodone (adjusted for population) fell 29.82% compared to 28.06% for hydrocodone and 18.88% for Benzodiazepine. Only the mean decrease over time for all ER/LA opioid analgesics excluding hydrocodone was statistically significant.

TABLE 50: MEAN POPULATION-ADJUSTED DEATH RATES FOR PRESCRIPTION OPIOIDS WITH AN ER/LA FORMULATION AND COMPARATORS, 2005 - 2013

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
Prescription Opioids with an ER/LA Formulation excluding Hydrocodone	1.930	1.355	-29.82% (-39.84%, -18.14%)	<.001	.
Hydrocodone	0.276	0.199	-28.06% (-50.78%, 5.15%)	0.089	0.906
Benzodiazepine	0.656	0.532	-18.88% (-38.44%, 6.88%)	0.137	0.369

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the prescription opioids with an ER/LA formulation excluding hydrocodone group is not different than the corresponding difference in pairs of means for the comparator group.

Table 51 shows that the mean death rate for ER/LA opioid analgesics excluding hydrocodone (adjusted for prescriptions) fell 39.44% compared to 17.32% for hydrocodone. Only the mean decrease for all prescription opioids excluding hydrocodone over time was statistically significant.

TABLE 51: MEAN PRESCRIPTION-ADJUSTED DEATH RATES FOR PRESCRIPTION OPIOIDS WITH AN ER/LA FORMULATION EXCLUDING HYDROCODONE AND COMPARATORS, 2005 - 2013

DRUG GROUP	MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
Prescription Opioids with an ER/LA Formulation excluding Hydrocodone	0.217	0.131	-39.44% (-57.36%, -14.00%)	0.006	.
Hydrocodone	0.022	0.018	-17.32% (-54.48%, 50.17%)	0.526	0.372

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the prescription opioids with an ER/LA formulation excluding hydrocodone group is not different than the corresponding difference in pairs of means for the comparator group.

4.6.6.2. Death Rates for All Prescription Opioids excluding Hydrocodone

Table 52 shows that the mean death rate for all prescription opioids excluding hydrocodone (adjusted for population) fell 35.46% compared to 28.06% for hydrocodone and 18.88% for benzodiazepine. Only the mean decrease for all prescription opioids excluding hydrocodone over time was statistically significant.

TABLE 52: MEAN POPULATION-ADJUSTED DEATH RATES FOR ALL PRESCRIPTION OPIOIDS EXCLUDING HYDROCODONE AND COMPARATORS, 2005 - 2013

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
All Prescription Opioids excluding Hydrocodone	2.341	1.511	-35.46% (-46.18%, -22.61%)	<.001	.
Hydrocodone	0.276	0.199	-28.06% (-50.78%, 5.15%)	0.089	0.613
Benzodiazepine	0.656	0.532	-18.88% (-38.44%, 6.88%)	0.137	0.175

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the all prescription opioids excluding hydrocodone group is not different than the corresponding difference in pairs of means for the comparator group.

Table 53 shows that the mean death rate for all prescription opioids excluding hydrocodone (adjusted for prescriptions) fell 47.26% compared to 17.32% for hydrocodone. Only the mean decrease for all prescription opioids excluding hydrocodone over time was statistically significant.

TABLE 53: MEAN PRESCRIPTION-ADJUSTED DEATH RATES FOR ALL PRESCRIPTION OPIOIDS EXCLUDING HYDROCODONE AND COMPARATORS, 2005 - 2013

DRUG GROUP	PRE MEAN RATE	ACTIVE MEAN RATE	% CHANGE (95% CI)	WITHIN DRUG CONTRAST P-VALUES*	BETWEEN DRUG INTERACTION P-VALUES#
All Prescription Opioids excluding Hydrocodone	0.222	0.117	-47.26% (-65.86%, -18.52%)	0.005	.
Hydrocodone	0.022	0.018	-17.32% (-54.48%, 50.17%)	0.526	0.228

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the all prescription opioids excluding hydrocodone group is not different than the corresponding difference in pairs of means for the comparator group.

4.6.6.3. Mortality Rates Conclusion

Compared to the pre-implementation period, in the active period, the mean mortality rate per 100,000 persons for ER/LA opioids (excluding hydrocodone) fell 29.82%, while benzodiazepines fell 18.88% and hydrocodone fell 28.06%. The reduction in rates for ER/LA opioids was not statistically different from the reductions for hydrocodone and benzodiazepines.

When looking at prescription-adjusted mean death rates during the same time period, the rate for ER/LA opioids (excluding hydrocodone) fell 39.44%. Hydrocodone mean death rates per 1,000 prescriptions fell 17.32%. The reduction in rates for ER/LA opioids was not significantly different from the reduction reductions for hydrocodone.

5. FUNCTIONAL COMPONENTS

5.1. REMS Call Center

Upon approval of the ER/LA Opioid Analgesics REMS Program, a centralized Call Center was launched on July 23, 2012 to provide REMS Program support to consumers and HCPs. After one year of data collection, RPC requested that FDA consider removal of the requirement for the Call Center and to utilize an Interactive Voice Response System (IVRS). The rationale for the request included:

- The Call Center had handled a total of 268 calls during the first 4 months of operation (July 23, 2012 – November 8, 2012).
- Call volume was highest during the first 3 weeks immediately following Call Center go-live (July 23, 2012 – August 10, 2012) which also corresponded to distribution of approximately 1.3 million Dear DEA-Registered Prescriber and Dear Professional Organization/Licensing Board letters. Call Center volume had since been consistently low since that time, averaging 10 calls per week.
- The ER/LA Opioid Analgesics REMS website, which contains approved frequently asked questions (FAQs), was fully functional and available 24 hours a day, 7 days a week. As of November 8, 2012, there had been no downtime.
- In addition to the FAQs that were anticipated prior to go-live, the RPC Call Center Team had developed new FAQs and enhanced existing FAQs in response to inquiries received from stakeholders. FAQs for all stakeholders were easily available on the website. The current list of FAQs presented on the website had a robust amount of information and responded to common (and not so common) inquiries. The RPC continues to assess and address stakeholder issues and concerns and, when possible, creates new, or revises current FAQs for the website.
- There were a total of 7 abandoned calls, and the RPC does not consider this abandonment rate as an explanation for the consistently low call volume.
- Three requests to fulfill Patient Counseling Document orders had been received and no requests were made for Dear DEA-Registered Prescriber and Dear Professional Organization/Licensing Board letters, indicating this was not a primary route stakeholders are using to access these documents.

The request to modify the centralized Call Center to utilize an IVRS was acceptable to FDA. The centralized Call Center was decommissioned and the IVRS went live on March 19, 2014. The IVRS is available 24 hours/7 days a week and utilizes the same toll-free telephone number that was established for the centralized Call Center. The IVRS guides callers through a series of prompts for general REMS questions and specific FAQs for each stakeholder type. Using data collected from incoming calls to the previous centralized Call Center, the most often selected FAQs and responses for each stakeholder type are recorded, and stakeholders have the option to leave a voicemail if their questions are not addressed via the FAQs. The IVRS has been fully functional since its launch on March 19, 2014.

5.2. Dear DEA-Registered Prescriber Letter

A series of Dear DEA-Registered Prescriber Letters were utilized as part of the prescriber outreach for the REMS.

- The first Dear DEA-Registered Prescriber Letter announced the approval of the ER/LA Opioid Analgesics REMS.
- The second Dear DEA-Registered Prescriber Letter was used to announce availability of ER/LA Opioid Analgesics REMS-related CE opportunities.

- The third Dear DEA-Registered Prescriber Letter, distributed during this reporting period, was used to announce the existence of the ER/LA Opioid Analgesics REMS and availability of ER/LA Opioid Analgesics REMS-related CE opportunities to newly DEA-registered Schedule II and III narcotic prescribers.

To date, a total of 4 Dear DEA-Registered Prescriber Letters have been sent to stakeholders. Each letter included a copy of the Patient Counseling Document. Distribution details are included in [Table 54](#).

TABLE 54: DISTRIBUTION OF DEAR DEA-REGISTERED PRESCRIBER LETTERS

	TARGET NUMBER OF RECIPIENTS	DELIVERED*
Dear DEA-Registered Prescriber Letter 1 (2012) Email, Fax or United States Postal Service (USPS)		
Unique DEA-Registered Prescribers	1,321,019	1,299,888 (98.4%)
Hospitals and Pharmacies	82,651	80,768 (97.7%)
Dear DEA-Registered Prescriber Letter 2 (2013) Email, Fax, or USPS		
Unique DEA-Registered Prescribers	1,342,173	1,314,968 (98%)
Hospitals and Pharmacies	15,561	15,468 (99.4%)
Dear DEA-Registered Prescriber Letter 3 (2013) Email, Fax, or USPS		
Unique DEA-Registered Prescribers	84,009	78,888 (93.9%)
Hospitals and Pharmacies	799	760 (95.1%)
Dear DEA-Registered Prescriber Letter 3 (2014) Email, Fax, or USPS		
Unique DEA-Registered Prescribers	109,208	104,404 (95.6%)
Hospitals and Pharmacies	1,014	973 (96%)

* Delivered is defined as not bouncing back via email, receiving an "OK" transmission notice via fax, or no mail returned as undeliverable via USPS.

Undelivered letters to all recipients are put through the following 3 step process before considered undeliverable:

1. Search the Communications Vendor Practitioners Database to identify potential secondary methods of contact and execute the communication.
2. Use several additional data assets including the AMA, Group Practice and other files to identify potential secondary methods of contact and execute the communication.
3. The Communications Vendor commits to using all available avenues to secure secondary communication methods for undeliverable mail.

Additionally, the RPC distributed a letter to relevant Learned Societies and Professional Associations on August 24, 2012, 46 days after REMS approval and on January 24, 2014, 34 days prior to the start of CE activities. These letters also included a copy of the Patient Counseling Document. The recipients of this letter included the leadership of organizations shown in the table below.

**TABLE 55: LEARNED SOCIETIES AND PROFESSIONAL ASSOCIATIONS
RECEIVING REMS LETTER***

American Academy of Neurology*	American Board of Medical Specialties*	American Osteopathic Association of Addiction Medicine*
American Academy of Addiction Psychiatry*	American Board of Orofacial Pain*	American Pain Society*
American Academy of Family Physicians*	American College of Rheumatology*	American Society for Pain Management Nursing*
American Academy of Hospice and Palliative Medicine*	American College of Emergency Physicians	American Society of Addiction Medicine*
American Academy of Nurse Practitioners	American College of Nurse Practitioners*	American Society of Anesthesiologists
American Academy of Nursing*	American College of Osteopathic Family Physicians*	American Society of Pain Educators*
American Academy of Orofacial Pain*	American College of Physicians*	Association of American Medical Colleges*
American Academy of Pain Management*	American Dental Association*	Council of Medical Specialty Societies
American Academy of Pain Medicine*	American Dental Education Association*	Hospice and Palliative Nurses Association*
American Academy of Physical Medicine and Rehabilitation*	American Medical Association Hospice and Palliative Nurses Association	National Association of Managed Care Physicians
American Academy of Physician Assistants*	American Medical Association*	National Association of State Controlled Substances Authorities
American Association of Colleges of Osteopathic Medicine*	American Medical Directors Association*	National Commission on Certification of Physician Assistants
American Association of Colleges of Nursing*	American Nurses Association*	National Hospice and Palliative Care Organization
American Association of Nurse Practitioners	American Nurses Credentialing Center*	Society of Emergency Medicine Physician Assistants*
American Association of Poison Control Centers*	American Osteopathic Association*	

*Professional Organizations/Licensing Boards noted with an asterisk were sent both Letter 1 and Letter 2.

A letter similar to the Professional Organization/Licensing Board Letter was sent to the following 265 professional organizations and healthcare professional licensing boards on August 24, 2012, 46 days after REMS approval and January 24, 2013, 34 days prior to the start of CE activities.

- State Licensing Boards of:
 - Medicine (allopathic and osteopathic)
 - Nursing
 - Dentistry
- Associations of State Licensing Boards:

- Federation of State Medical Boards
- National Council of State Boards of Nursing
- American Association of Dental Boards

There was no indication of failed delivery for the 265 Dear Professional Organization/Licensing Board Letter 1's sent and only one of the 326 Dear Professional Organization/Licensing Board Letter 2's (South Dakota Osteopathic Association) was returned. Despite follow-up, a viable address could not be located.

5.3. Patient Counseling Document

The Patient Counseling Document on ER/LA opioid analgesics is a tool intended to facilitate important discussions between prescribers and patients for whom an ER/LA opioid analgesic is being prescribed. The Patient Counseling Document contains important safety information about the drug products covered by the REMS. Key messages outlined in the Patient Counseling Document include the importance of taking ER/LA opioid analgesics exactly as prescribed, the need to store ER/LA opioid analgesics safely and securely out of the reach of children, pets, and household acquaintances—to avoid risks from unintended exposure, the importance of not sharing these medications, even if someone has the same symptoms as the patient, and the proper methods of disposal of unneeded ER/LA opioid analgesics. The Patient Counseling Document is available in English and Spanish.

Electronic and hardcopy versions of the Patient Counseling Document continue to be readily accessible to all stakeholders through multiple modalities. A Portable Document Format version of the Patient Counseling Document available for download was posted on the website on July 23, 2012 (website launch). Patient Counseling Document access is summarized in [Table 56](#).

TABLE 56: PATIENT COUNSELING DOCUMENT ACCESS VIA WEBSITE

	SUCCESSFUL DOWNLOADS	
	ENGLISH	SPANISH
July 23, 2012-November 7, 2012	1,822	-
November 9, 2012-May 10, 2013	1,920	-
May 10, 2013-May 9, 2014	2,461	196
May 10, 2014-May 8, 2015	1,695	149

In addition to accessing the Patient Counseling Document online, a portal is available for prescribers to order copies of the Patient Counseling Document via an online order form or by fax. Larger orders (more than 3 Patient Counseling Document pads) can be requested by phone. Patient Counseling Document orders fulfilled to date are described in [Table 57](#).

TABLE 57: PATIENT COUNSELING DOCUMENT PAD FULFILLMENT

	ORDERS		
	ONLINE	FAX	PHONE
July 23, 2012-November 7, 2012	29	6	-
November 9, 2012-May 10, 2013	226	13	2
May 10, 2013-May 9, 2014	197	5	-
May 10, 2014-May 8, 2015	175	167	-

6. PROPOSED REMS RECOMMENDATIONS

The ER/LA Opioid Analgesics REMS is an education-based program with the goal of reducing serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. Its scope is unprecedented, with a broad range of assessment tools and data sources to measure impact. The RPC includes 23 companies of widely ranging sizes, with branded and generic medications, cooperating to design, implement, and refine the REMS. There have been significant accomplishments and much learned through this collaborative process. The RPC is committed to using what they have learned to improve upon the existing REMS.

The implementation of this complex, CE-focused ER/LA Opioid Analgesics REMS by a consortium of 23 companies, has led to a variety of lessons learned. These lessons can be leveraged to improve upon the existing REMS and to inform the design of other class-wide REMS program in the future. See [Table 58](#) for a summary of the lessons learned to date.

TABLE 58: ER/LA OPIOID ANALGESICS REMS LESSONS LEARNED

LESSON LEARNED	BACKGROUND
Importance of Collaboration	The 23 companies of the RPC, FDA, and the CE community have worked to ensure that nearly 839 accredited REMS-compliant continuing education courses have been offered. This has required engaging with accreditors, data providers for assessments, program managers, medical writers, and others in the course of design, implementation, and assessment of the program.
Importance of Project Management for Class-wide Initiatives	The scope of this REMS is unique, given the CE emphasis, number of participating companies, and varied assessments. Dedicated project management is essential to ensure forward motion, quality assurance, and that reporting requirements are fulfilled.
Importance of the Communication Plan	Awareness of the REMS was low. Identifying which elements had satisfactory or better reach and which were not effective is important to meet goals of the REMS. Alternative communication strategies should be explored.
Importance of Reviewing Data Collected Through Assessments in Order to Identify Areas for Improvement	Each assessment had identified weaknesses that are targets for improvement. Surveys: <ul style="list-style-type: none"> • Pre-specifying demographic data to collect on CE completers • Direct comparisons of knowledge for CE completers vs. non-completers • Enhanced recruitment efforts to ensure sample sizes are met and are representative • Survey questions answered correctly by a smaller proportion of participants were

LESSON LEARNED	BACKGROUND
	<p>should be shared with CE Providers to be considered for their next curriculum updates.</p> <p>Surveillance Studies:</p> <ul style="list-style-type: none"> • Expanding studies to include <ul style="list-style-type: none"> ○ Data on deaths ○ Different patient risk profiles • Evaluation of surveillance findings in the context of the external environment • Impacts of changes in the healthcare system • Changes in drug abuse patterns and their impacts on observed trends in abuse, misuse, death, and other key outcomes.
Create Short, Simple Materials Directed at Patients	Among the educational tools created for the REMS were a single-sheet medication guide for patients to be distributed with each prescription, and a 1-page Patient Counseling Document. Reports of receipt and use of these documents were high.
Leverage Adult Education Best Practices	Healthcare provider associations report that the accredited REMS-compliant education is important, but lacks creativity to engage learners and is longer than other programs. For participation in the CE to increase and be effective, innovative training programs and using more case-based interactive learning techniques, linked to individual prescribers and practice needs, addressing knowledge gaps more specifically, should be considered.

In addition to the lessons learned since implementation of the ER/LA Opioid Analgesics REMS, RPC has also identified barriers to the REMS success. For example, accredited REMS-compliant CE activities are not the only educational offering available. A variety of competing and non-standardized CE courses for prescribers are available, which highlights the importance of making prescribers aware of the REMS and accredited REMS-compliant CE activities.

With these lessons learned in mind, and given the context of the data from the various REMS assessments, the RPC recommends six changes to enhance the REMS content and implementation and to better deliver education on safe ER/LA opioid analgesic prescribing to healthcare providers.

RPC Recommendations for REMS Enhancements:

1. Enhance REMS communication activities

To engage more HCPs in accredited REMS-compliant CE activities, it will be important to enhance communication about the REMS. One improvement will be to improve the accessibility of the ER/LA Opioid Analgesics REMS website, so that interested healthcare providers can more

easily access accredited REMS-compliant CE activity content. In addition, the RPC plans to launch an awareness campaign featuring a general-audience website and additional materials later in 2016; these will be shown at conferences and in journals targeted to specialties and provider groups who may not have been well-reached in the past.

2. Expand the REMS to include the extended healthcare team and increase awareness about the program.

The current goal of accredited REMS-compliant CE activities for this REMS involves a focus on educating ER/LA opioid analgesic prescribers. Education of all team members involved in patient care is critical for implementation of REMS learnings. This will include increasing awareness of the accredited REMS-compliant CE activities among non-prescribers and ensuring that all REMS training courses are accepted for CE credit by accrediting bodies for nurses, pharmacists and others.

The RPC also recommends the specific addition of accredited REMS-compliant education targeted to new healthcare providers and to those caring for patients in underserved communities, where patients may not have access to pain medicine specialists (e.g., targeting non-pain specialists). Awareness is crucial, so the RPC also suggests promoting accredited REMS-compliant CE activities at conferences targeted to all these specialties and provider groups.

The RPC would audit revised accredited REMS-compliant CE activities yearly and survey prescribers to assess the success of the trainings in terms of message consistency and prescriber knowledge.

3. Revise the FDA Blueprint for Prescriber Education to reflect evolving stakeholder input and feedback and to take into consideration the needs of adult learners.

The Blueprint is an important resource, and it should include the latest information and take into consideration adult learning best practices. Specifically, the RPC proposes to:

- include tools to manage opioid risks such as co-prescribing of naloxone
- condense content. An accredited REMS-compliant CE activity generally takes 3 hours to complete, while other opioid prescribing training – outside of the REMS – takes 1 or 2 hours to complete
- utilize case studies more in the trainings, since case studies are known to be effective tools in adult learning
- use adaptive approaches to ensure prescribers have necessary knowledge, such as a demonstration of prior knowledge to opt out of specific sections of the training
- emphasize general principles of safe ER/LA opioid analgesic prescribing rather than details of specific drugs, since most prescribers only regularly use 1 or 2 from within the class
- establishment of standard assessments across accredited REMS-compliant CE activities

4. The majority of RPC supports tying Schedule II and Schedule III Narcotics DEA registration and re-registration to either completion of prescription opioid education or other attestation of prior knowledge such as board certification in pain medicine. This would expand education to all ER/LA opioid analgesic prescribers and ensures a common base of knowledge about safe opioid prescribing, particularly around issues of abuse and misuse.

This type of targeted education is an approach to ensuring all prescribers have received appropriate training in pain management with opioids so their patients can continue to access

treatment options. The RPC understands that this would require cross-agency communication and congressional approval to implement.

5. The RPC encourages federal agencies to work together in developing an education solution to the public health problem of opioid abuse utilizing the principles of this REMS and the lessons that have been learned in its implementation.

Currently there are multiple continuing education courses offered by various federal agencies. All of these courses focus on safe prescribing of opioids for pain, but all vary somewhat in their approach. The RPC supports the development of a shared/common education that includes the REMS, as a part of an overall opioid strategy. In addition, consideration of more innovative approaches that use more case-based interactive learning techniques, linked to individual prescribers and practice needs and more specifically addressing knowledge gaps.

6. Evaluate the pros and cons of including IR opioids in the ER/LA Opioid Analgesics REMS

FDA recently noted that one item considered by the Advisory Committee in May will be to add IR opioids to this REMS program. The RPC supports careful consideration of the pros and cons and feasibility of this change in the REMS

The ER/LA Opioid Analgesics REMS is the first REMS to utilize accredited CE as a medium to deliver REMS education. It is also the first REMS to include such a large group of participating companies, including those of varying sizes, and with both brand and generic products. The RPC continues to work closely with the CE community and other stakeholders to enhance efforts to reach and train ER/LA opioid analgesic prescribers and other healthcare professionals responsible for patient treatment, as well as distributing the Medication Guide and Patient Counseling Document. In addition to tracking the accredited REMS-compliant CE activity completion, the RPC employs comprehensive assessments of a wide array of outcomes to evaluate whether the REMS is meeting the established goals. The RPC will continue to implement the REMS and measure its impact as one part of a national response to the opioid abuse problem, with the aim of reducing the serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of ER/LA opioid analgesics.

The RPC believes expanding the REMS in evidence-driven ways, based on lessons learned during REMS implementation, will help to educate providers on safe use of opioids and, as part of a larger public health strategy, further reduce inappropriate prescribing, misuse and abuse of these medications.

The RPC welcomes the opportunity to work with FDA, DEA, and other key stakeholders to develop actionable plans for these recommendations.

7. CONCLUSION

The sponsors (NDA and ANDA holders) of ER/LA opioid analgesics have collaborated to develop and fully implement all components of FDA's REMS, a novel program focused on education. Overall, REMS assessments indicate that since implementation there has been progress made in achieving the REMS goals, including high levels of prescriber knowledge and patient knowledge of ER/LA opioid analgesic risks, reductions in misuse, abuse, and major medical outcomes including death, as well as prescribing behaviors. However, the RPC is committed to improving the REMS to better educate HCPs and further reduce inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics, while preserving access to these medicines for appropriate use in people with severe pain. To illustrate the success of this implementation, the following summarizes the REMS assessments and functional components of the most recent ER/LA Opioid Analgesics REMS Assessment:

- **Prescriber Training:** The RPC has funded over 800 REMS-compliant CE activities to date in order to assure that this training was available in multiple formats to prescribers.
 - With regard to the FDA established goal of 80,000 ER/LA opioid analgesic prescribers completing training within 2 years following availability of the first REMS-compliant activity, a total of 37,512 ER/LA opioid analgesic prescribers, as defined in the REMS, have completed a REMS-compliant CE activity as of February 28, 2015 with a total of 66,219 completing through February 29, 2016.
 - Based on data from CE Providers, RPC is aware that 91,274 healthcare providers have completed a REMS-compliant activity but are not counted in this total number based on the inclusion criteria defined in the REMS (i.e., registered with DEA to prescribe Schedule II and/or III controlled substances and having prescribed at least one ER/LA opioid analgesic in the last year.) While not included in the metric, these 91,274 HCPs play a critical role in the safe use of ER/LA opioid analgesics (assessment and care of patients including important patient education) and can benefit from REMS-compliant CE. In addition, there are multiple instances when HCPs might actually prescribe an ER/LA opioid analgesic without themselves having an individual DEA registration (e.g., residents who utilize an institutional DEA number, physician assistants/nurse practitioners who may prescribe under the DEA number of a collaborating physician).
 - RPC is aware of many other CE activities that are educating ER/LA opioid analgesic prescribers—as well as other HCPs involved in the care of patients who are taking ER/LA opioid analgesics—about the safe use of opioids. RPC is actively engaged in working to increase REMS awareness among CE Providers who develop these non-RPC-supported activities to encourage them to be REMS-compliant.
 - RPC continues to explore ways to increase prescriber awareness and participation in REMS-compliant CE activities, including improvements to the REMS website and the REMS awareness campaign.
- **REMS-Compliant CE Audits:** RPC exceeded the 10% target for independent audit of REMS-compliant CE activities and 100% of the audited activities successfully complied with the REMS requirements for full/accurate inclusion of the FDA Blueprint content and the requisite knowledge assessments.
 - While fully compliant with Blueprint content, accuracy, and assessment requirements, 14 activities had non-content-related observations noted by the Accreditor. (These observations were limited to the manner in which the CE Provider stated financial disclosures for the CE activity and all have been remediated.)

- **Patient Survey:** Patient Survey results indicate that the REMS requirement to make available a Medication Guide continues to be achieved.
 - The majority of patients reported that they received, read, and understood the Medication Guide.
 - Nearly half of patients reported receiving the Patient Counseling Document, but only a quarter of those receiving it reported that their healthcare provider referenced the Patient Counseling Document. This may be due to the fact that prescribers did not specifically refer to the document as the “Patient Counseling Document.” In contrast the Prescriber Survey results show that prescribers are increasing their use of this tool.
 - Patients showed a high level of understanding on most tested messages. The only general knowledge questions that less than 80% of respondents answered correctly concerned storing ER/LA opioid analgesics away from other household medications, the need to read the Medication Guide at each pharmacy dispensing, never splitting or crushing pills (oral product users only), and informing a healthcare provider of fever (patch product users only).
 - Based on results from patient surveys, there is no indication that the REMS is having a negative impact on access.
- **Prescriber Surveys:**
 - Results from the Prescriber Survey showed that prescribers understood the assessment, management, and counseling requirements for patients who are being considered for treatment or being treated with ER/LA opioid analgesics, as indicated by at least 85% of prescribers correctly answering 80% or more questions regarding these topics.
 - Prescribers were less knowledgeable about initiation, modification, and discontinuation of ER/LA opioid analgesic therapy, and about product-specific information about ER/LA opioid analgesics.
 - Prescribers who were recruited through CE Providers and HCPs who prescribe a high volume of ER/LA opioid analgesics were significantly more likely to understand the risks and safety information relating to ER/LA opioid analgesics treatment.
 - Prescribers that completed a CE course within the past 6 to 12 months (Long-term Evaluation Survey respondents) demonstrated strong understanding of the monitoring and counseling requirements for patients who are being treated with ER/LA opioid analgesics, as indicated by at least 84.5% of prescribers correctly answering 80% or more questions testing knowledge of managing therapy with ER/LA opioid analgesics.
 - Prescribers were less knowledgeable about assessment of patients and initiation of treatment and general information about risks associated with ER/LA opioid analgesic products. Very few prescribers met the 80% correct response rate threshold regarding risk information for specific ER/LA opioid analgesic products.
 - For both prescriber surveys, the knowledge deficit in the area of product specific characteristics may be related to physician’s lack of familiarity with products they don’t routinely prescribe and the “real-world clinical practice” by HCPs who, understanding that prescribing information changes frequently, routinely access on-demand tools (e.g., RxList, Epocrates®) to retrieve information on specific products as needed.
 - Based on results from the prescriber survey, there is no indication that the REMS is having a negative impact on access.

- **Drug Utilization Patterns, Prescribing Behaviors and Changes to ER/LA Opioid Access:**

- Assessment of drug utilization data showed a significant decrease in the total ER/LA opioid analgesic prescription volume since the introduction of the REMS. Metrics of appropriate prescribing behaviors showed a reduction in prescriptions of ER/LA opioid analgesics to non-opioid tolerant patients that are indicated only for opioid-tolerant patients.
- Additionally, this finding is supported by the results of the Prescriber Survey. Respondents who reported changing the types of medications they prescribe since implementation of the REMS most often reported that they limit which ER/LA opioid analgesics they prescribe or that they prescribe more non-opioid medications.
- Drug utilization data from IMS showed a decrease in prescribing ER/LA opioid analgesics by those specialties with less compelling reasons to prescribe ER/LA opioids for which the REMS could be expected to have greater impact (e.g., dentists and emergency room specialists).
- An increase in prescribing was noted among nurse practitioners and physician assistants. This may be the result of changes in healthcare system practices, greater numbers of these HCPs, and expanded roles for these practitioners in managing patients requiring ER/LA opioid analgesics. These prescribers have been participating in REMS-compliant CE activities and accounted for approximately one third of all ER/LA opioid analgesic prescriber completers during this reporting period.

- **Surveillance Monitoring:**

- The incidence of opioid overdose or poisoning decreased slightly between the pre-implementation period and the active period after adjustment for demographic and clinical characteristics.
- Poison Center Program results showed a decrease in abuse, misuse, as well as reduction in calls for major medical outcomes, hospitalizations, and deaths.
- Surveillance monitoring of abuse in substance abuse treatment centers showed decreases in mean rates of ER/LA opioid analgesic use to get high within the past 30 days
- State Medical Examiner data show decreases in the mean mortality rate for ER/LA opioid analgesics.
- Surveillance findings cannot be causally attributed to the REMS due to other interventions aimed at decreasing opioid abuse and misuse and their consequences during the same time period, such as implementation of PDMPs, increased law enforcement, institution of guidelines by states or insurance companies, and introduction of ADFs. However, the REMS education is one important piece in efforts to curb negative outcomes associated with opioid use and abuse, and trends have shown improvements over the past 5 years.

- **Functional Components:**

- Dear DEA-Registered Prescriber Letter 3 sent in 2015 was sent to 104,404 new DEA registrants and a number of registered hospitals/clinics.
- Over 20,000 Patient Counseling Documents were downloaded, ordered and requested via fax in English and Spanish during this reporting period. This is likely a conservative estimate of Patient Counseling Document utilization, as once downloaded the document may be replicated multiple times for distribution.

- Overall REMS assessments indicated high levels of prescriber knowledge and patient knowledge of ER/LA opioid analgesic risks, reductions in misuse, abuse, and major medical outcomes including death, as well as prescribing behaviors.

The implementation of the ER/LA Opioid Analgesics REMS, has led to the following lessons learned, which can be leveraged to improve upon the existing REMS:

- The importance of collaboration
- The importance of project management for class-wide initiatives
- The importance of the communication plan
- The importance of reviewing data collected through assessments in order to identify areas for improvement
- The importance of creating short, simple materials directed at patients
- Leveraging adult education best practices

RPC proposes the following changes to the REMS content and educational implementation to reduce ER/LA opioid analgesic inappropriate prescribing, misuse and abuse without negatively affecting the access to pain medications for those who desperately need them.

- Enhance REMS communication activities to engage more HCPs in accredited REMS-compliant CE activities.
- Expand the REMS to include the extended healthcare team, including non-prescribers and increase awareness about the program. Education of all team members involved with patient care is critical for implementation of REMS learnings and ensuring the public health impact of the REMS.
- Revise the FDA Blueprint to reflect evolving stakeholder input and feedback and to take into consideration the needs of adult learners.
- The majority of RPC supports tying Schedule II and Schedule III Narcotics DEA registration and re-registration to either completion of prescription opioid education or other attestation of prior knowledge such as board certification in pain medicine. The RPC understands that this would require cross-agency communication and congressional approval to accomplish.
- The RPC encourages federal agencies to work together in developing an education solution to the public health problem of opioid abuse utilizing the principles of this REMS and the lessons that have been learned in its implementation. The RPC supports the development of a shared/common education that includes the accredited REMS-compliant CE component, as a part of an overall opioid strategy.
- Evaluate the pros and cons of including IR opioids in the ER/LA Opioid Analgesics REMS. Per the recent New England Journal of Medicine publication by Califf, Woodcock and Ostroff (2016)¹³, FDA announced that one item considered by the Advisory Committee in May will be to add IR opioids to this REMS program. The RPC supports careful consideration of the pros and cons and feasibility of this change in the REMS

¹³ Califf RM, Woodcock J, Ostroff S. A proactive response to prescription opioid abuse. N Engl J Med. 2016. doi:10.1056/NEJMSr1601307.

The RPC believes expanding the REMS in evidence-driven ways, based on lessons learned during REMS implementation, will help to educate providers on safe use of opioids and, as part of a larger public health strategy, further reduce inappropriate prescribing, misuse and abuse of these medications. It is imperative to address the public health issues of prescription opioid analgesic abuse and medically appropriate treatment of people with pain. The RPC welcomes the opportunity to work with FDA, DEA, and other key stakeholders to develop actionable plans for these recommendations.

APPENDIX 1 ER/LA OPIOID ANALGESICS REMS

Initial REMS Approval: 07/2012
Most Recent Modification: 10/2015

**EXTENDED-RELEASE (ER) AND LONG-ACTING (LA) OPIOID
ANALGESICS RISK EVALUATION AND MITIGATION
STRATEGY (REMS)**

GOAL

The goal of this REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of extended-release or long-acting (ER/LA) opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

I. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each ER/LA opioid analgesic prescription in accordance with 21 CFR § 208.24.

The Medication Guides for ER/LA opioids are part of the ER/LA Opioid Analgesic REMS program and will be available through the ER/LA Opioid Analgesic REMS website www.ER-LA-opioidREMS.com.

B. Elements to Assure Safe Use

1. Training will be made available to healthcare providers who prescribe ER/LA opioid analgesics.
 - a. Training will be considered “REMS-compliant training” under this REMS if: 1) it, for training provided by CE providers, is offered by an accredited provider to licensed prescribers, 2) it includes all elements of the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics (“FDA Blueprint”), 3) it includes a knowledge assessment of all of the sections of the FDA Blueprint, and 4) it is subject to independent audit to confirm that conditions of the REMS training have been met.
 - b. The NDA/ANDA holders of ER/LA opioid analgesic products (“NDA/ANDA holders”) will ensure that REMS-compliant training is made available to prescribers of ER/LA opioid analgesics and will achieve the following performance goals:
 - i. Not later than March 1, 2013, the first REMS-compliant training will be made available.
 - ii. Within two years from the time the first REMS-compliant training becomes available, 80,000 prescribers (based on 25% of the 320,000 active prescribers in 2011) will have been trained;
 - iii. Within three years from the time the first REMS-compliant training becomes available, 160,000 prescribers (based on 50% of the 320,000 active prescribers in 2011) will have been trained;
 - iv. Within four years from the time the first REMS-compliant training becomes available, 192,000 prescribers (based on 60%

of the 320,000 active prescribers in 2011) will have been trained.

- c. The content of the REMS-compliant training will be based on the learning objectives established by the FDA Blueprint. The FDA Blueprint contains core messages to be conveyed to prescribers in the training about the risks and appropriate prescribing practices for the safe use of ER/LA opioid analgesics. The NDA/ANDA holders will direct providers of REMS-compliant training to the FDA Blueprint, via the REMS website (www.ER-LA-opioidREMS.com), and via its Request for Grant Applications. No less than annually, NDA/ANDA holders will direct providers of REMS-compliant training to consult the FDA Blueprint for possible revisions (e.g., changes to the drug specific information).
- d. NDA/ANDA holders will ensure that independent audits of the educational materials used by the providers of REMS-compliant training are conducted. The audits must:
 - i. Be conducted by an auditor independent of the NDA/ANDA holders. (Accreditation bodies of CE providers would be considered independent of the NDA/ANDA holders and would be eligible to conduct the audits.)
 - ii. Evaluate:
 - 1. whether the content of the training covers all components of the FDA Blueprint approved as part of the REMS;
 - 2. whether the knowledge assessment measures knowledge of all sections of the FDA Blueprint; and
 - 3. for training conducted by CE providers, whether the training was conducted in accordance with the standards for CE of the Accreditation Council for Continuing Medication Education[®] (ACCME[®]), or of another CE accrediting body appropriate to the prescribers' medical specialty or healthcare profession.
 - iii. Be conducted on a random sample of 1) at least 10% of the training funded by the NDA/ANDA holders, and 2) REMS-compliant training not funded by the NDA/ANDA holders but that will be counted towards meeting the performance goals in section B.1.b.
- e. To facilitate prescriber awareness of the availability of the REMS and REMS-compliant training, within 30 calendar days of the approval of the REMS, the NDA/ANDA holders will make available, and then

maintain a web site that will contain information about the REMS specified below (www.ER-LA-opioidREMS.com):

- i. A current list of the REMS-compliant training that is supported by educational grants from the NDA/ANDA holders, when this information becomes available.
 - ii. A copy of the Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioid Analgesics.
 - iii. A copy of the Prescriber Letters 1, 2, and 3 (when mailed and for at least one year thereafter) (see section B.1.f).
- f. To make prescribers aware of the existence of the REMS and the prescriber training that will be made available under the REMS, the NDA/ANDA holders will electronically deliver (email or fax), or directly mail letters to all DEA-registered prescribers who are registered to prescribe Schedule II and III drugs:
 - i. Prescriber Letter 1 will be sent not later than 60 days after the initial approval of this REMS, notifying prescribers of the existence of the REMS and the fact that prescriber training will be offered, and providing a copy of the Patient Counseling Document (PCD).
 - ii. Prescriber Letter 2 will be sent not later than 30 days before the first prescriber REMS-compliant training required by the REMS is offered by providers and will notify prescribers of the imminent upcoming availability of accredited REMS CE courses.
 - iii. The prescribers will be identified via the DEA Registration Database.
 - iv. At least annually from the date of initial approval of the REMS, the DEA Registration Database will be reviewed and Prescriber Letter 3 will be sent to all newly DEA-registered prescribers who are registered to prescribe Schedule II and III drugs to inform them of the existence of the REMS, provide them the Patient Counseling Document (PCD), and notify them of the availability of the REMS-compliant training and how to find REMS-compliant courses.
- g. To further ensure that prescribers are aware of the existence of the ER/LA Opioid Analgesic REMS and the prescriber training that will be made available under the REMS, the NDA/ANDA holders will electronically deliver (email or fax), or directly mail the following two letters to the professional organizations and state licensing entities listed in section B.1.g.iii with a request that the information be disseminated to their members:

- i. Professional Organization/Licensing Board Letter 1 will be sent not later than 60 days after the approval of this REMS, notifying prescribers of the existence of the REMS and the fact that prescriber training will be offered, and providing a copy of the Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioids.
- ii. Professional Organization/Licensing Board Letter 2 will be sent not later than 30 days before the first prescriber REMS-compliant training required by the REMS is offered by providers and will notify prescribers of the imminent upcoming availability of accredited REMS CE courses.
- iii. The letter and enclosures referenced above, will be sent to the following entities:
 - a) State Licensing Boards of:
 - 1) Medicine (allopathic and osteopathic)
 - 2) Nursing
 - 3) Dentistry
 - b) Associations of State Licensing Boards:
 - 1) Federation of State Medical Boards
 - 2) National Council of State Boards of Nursing
 - 3) American Association of Dental Boards
 - c) Learned Societies and Professional Associations, including, but not limited to:
 - 1) American Academy of Addiction Psychiatry
 - 2) American Academy of Family Physicians
 - 3) American Academy of Hospice and Palliative Medicine
 - 4) American Academy of Neurology
 - 5) American Academy of Nurse Practitioners
 - 6) American Academy of Nursing
 - 7) American Academy of Orofacial Pain
 - 8) American Academy of Pain Management
 - 9) American Academy of Pain Medicine
 - 10) American Academy of Physical Medicine and Rehabilitation
 - 11) American Academy of Physician Assistants

- 12) American Association of Colleges of Osteopathic Medicine
- 13) American Association of Colleges of Nursing
- 14) American Association of Poison Control Centers
- 15) American Board of Medical Specialties
- 16) American Board of Orofacial Pain
- 17) American College of Nurse Practitioners
- 18) American College of Osteopathic Family Physicians
- 19) American College of Physicians
- 20) American College of Rheumatology
- 21) American Dental Association
- 22) American Dental Education Association
- 23) American Medical Association
- 24) American Medical Directors Association
- 25) American Nurses Association
- 26) American Nurses Credentialing Center
- 27) American Osteopathic Association
- 28) American Osteopathic Association of Addiction Medicine
- 29) American Pain Society
- 30) American Society of Addiction Medicine
- 31) American Society for Pain Management Nursing
- 32) American Society of Anesthesiologists
- 33) American Society of Pain Educators
- 34) Association of American Medical Colleges
- 35) Council of Medical Specialty Societies
- 36) Hospice and Palliative Nurses Association
- 37) National Association of Managed Care Physicians
- 38) National Association of State Controlled Substances Authorities
- 39) National Commission on Certification of Physician Assistants
- 40) National Hospice and Palliative Care Organization
- 41) American College of Emergency Physicians

42)Society of Emergency Medicine Physician Assistants

- h. NDA/ANDA holders will ensure that an interim single toll-free number call center is implemented no later than July 23, 2012, and a fully operational centralized call center is implemented no later than 90 calendar days after the approval of the REMS.

The following materials are part of the ER/LA Opioid Analgesic REMS and are appended:

- Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioid Analgesics
- FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics
- Prescriber Letter 1
- Prescriber Letter 2
- Prescriber Letter 3
- Professional Organization/Licensing Board Letter
- 1 - Professional Organization/Licensing Board
- Letter 2 - ER/LA Opioid Analgesic REMS website
(www.ER-LA-opioidREMS.com)

II. Implementation System

The ER/LA Opioid Analgesic REMS can be approved without the Elements to Assure Safe Use specifically described under FDCA 505-1(f)(3) (B), (C), and (D) of the Act; therefore an implementation system is not required.

III. Timetable for Submission of Assessments

REMS assessments will be submitted to the FDA at 6 months and 12 months after the initial approval date of the REMS (July 9, 2012), and annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment. The NDA holders will submit each assessment so that it will be received by the FDA on or before the due date based on the initial approval date of the REMS.

APPENDIX 2 LIST OF ER/LA OPIOID ANALGESICS

LIST OF CURRENT EXTENDED-RELEASE AND LONG-ACTING OPIOID ANALGESICS PRODUCTS

Product Name	Application Number	Application Holder	Added to REMS
Avinza (morphine sulfate)	NDA 021260	King Pharmaceuticals LLC	9-Jul-2012
Belbuca (buprenorphine)	NDA 207932	Endo Pharmaceuticals Inc	23-Oct-2015
Butrans (buprenorphine)	NDA 021306	Purdue Pharma LP	9-Jul-2012
Dolophine (methadone hydrochloride)	NDA 006134	Roxane Laboratories, Inc	9-Jul-2012
Duragesic (fentanyl transdermal system)	NDA 019813	Janssen Pharmaceuticals, Inc	9-Jul-2012
Embeda (morphine sulfate and naltrexone hydrochloride)	NDA 022321	Alpharma Pharmaceuticals LLS	9-Jul-2012
Exalgo (hydromorphone hydrochloride)	NDA 021217	Mallinckrodt INC The Pharmaceuticals Business of Covidien	9-Jul-2012
Hysingla ER (hydrocodone bitartrate)	NDA 206627	Purdue Pharma LP	20-Nov-2014
Kadian (morphine sulfate)	NDA 020616	Watson Laboratories, Inc.	9-Jul-2012
Methadose (methadone hydrochloride)	ANDA 040050	Mallinckrodt Pharmaceuticals	9-Jul-2012
Morphabond (morphine sulfate)	NDA 206544	Inspirion Delivery Technologies LLC	2-Oct-2015
MS Contin (morphine sulfate)	NDA 019516	Purdue Pharma LP	9-Jul-2012
Nucynta ER (tapentadol)	NDA 200533	Depomed, Inc.	9-Jul-2012
Opana ER (oxymorphone hydrochloride)	NDA 201655	Endo Pharmaceuticals Inc	9-Jul-2012
Opana ER (oxymorphone hydrochloride)	NDA 021610	Endo Pharmaceuticals Inc	9-Jul-2012
OxyContin (oxycodone hydrochloride)	NDA 022272	Purdue Pharma LP	9-Jul-2012
Targiniq ER (oxycodone and naloxone hydrochloride)	NDA 205777	Purdue Pharma LP	23-Jul-2014
Zohydro ER (hydrocodone)	NDA 202880	Zogenix, Inc	25-Oct-2013
fentanyl transdermal system	ANDA 076709	Watson Laboratories, Inc.	9-Jul-2012
fentanyl transdermal system	ANDA 077154	Mallinckrodt Pharmaceuticals	9-Jul-2012
fentanyl transdermal system	ANDA 077449	Aveva Drug Delivery Systems, Inc. (An Apotex Company)	14-Feb-2013
fentanyl transdermal system	ANDA 077775	Noven Pharmaceuticals, Inc.	9-Jul-2012
fentanyl transdermal system	ANDA 076258	Mylan Technologies Inc.	9-Jul-2012
fentanyl transdermal system	ANDA 077062	Par Pharmaceuticals, Inc.	9-Jul-2012
hydromorphone hydrochloride	ANDA 202144	Actavis Elizabeth LLC	12-May-2014
hydromorphone hydrochloride extended-release	ANDA 204278	Paddock Laboratories, LLC	6-Apr-2015
methadone hydrochloride	ANDA 040517	Mallinckrodt Pharmaceuticals	9-Jul-2012
methadone hydrochloride	ANDA 090635	The Pharma Network, LLC	9-Jul-2012
methadone hydrochloride	ANDA 087997	Roxane Laboratories, Inc	9-Jul-2012
methadone hydrochloride	ANDA 087393	Roxane Laboratories, Inc	9-Jul-2012
methadone hydrochloride	ANDA 089897	Roxane Laboratories, Inc	9-Jul-2012

Product Name	Application Number	Application Holder	Added to REMS
methadone hydrochloride	ANDA 090065	CorePharma, LLC	18-Aug-2015
methadone hydrochloride	ANDA 203502	Aurolife Pharma LLC	31-Aug-2015
methadone hydrochloride	ANDA 040241	Sandoz Inc.	9-Jul-2012
methadone hydrochloride	ANDA 090707	Watson Laboratories, Inc.	2-Nov-2012
morphine sulfate	ANDA 200824	Mylan Pharmaceuticals, Inc	9-Jul-2012
morphine sulfate extended release	ANDA 202104	Upsher-Smith Laboratories, Inc.	3-Jun-2013
morphine sulfate extended-release	ANDA 076412	Mallinckrodt Pharmaceuticals	9-Jul-2012
morphine sulfate extended-release	ANDA 076438	Mallinckrodt Pharmaceuticals	9-Jul-2012
morphine sulfate extended-release	ANDA 202718	Teva Pharmaceuticals USA	29-Dec-2014
morphine sulfate extended-release	ANDA 200812	Par Pharmaceuticals, Inc.	24-Apr-2013
morphine sulfate extended-release	ANDA 075295	Vintage Pharmaceuticals LLC, d/b/a Qualitest Pharmaceuticals and a subsidiary of Endo Pharmaceuticals Inc.	9-Jul-2012
morphine sulfate extended-release	ANDA 203602	Novel Laboratories, Inc.	16-Dec-2015
morphine sulfate extended-release	ANDA 203849	Actavis Elizabeth LLC	6-Apr-2015
morphine sulfate extended-release	ANDA 77855	Nesher Pharms	8-May-2015
morphine sulfate extended-release	ANDA 76720	Nesher Pharms	8-May-2015
morphine sulfate extended-release	ANDA 76733	Nesher Pharms	8-May-2015
morphine sulfate extended-release	ANDA 078761	Ranbaxy Pharmaceuticals Inc	15-Apr-2013
morphine sulfate extended-release	ANDA 074769	Rhodes Pharmaceuticals L.P.	9-Jul-2012
morphine sulfate extended-release	ANDA 074862	Rhodes Pharmaceuticals L.P.	9-Jul-2012
morphine sulfate extended-release	ANDA 079040	Actavis Elizabeth, LLC	16-Jan-2013
oxymorphone hydrochloride	ANDA 079087	Impax Laboratories, Inc.	12-Oct-2012
oxymorphone hydrochloride	ANDA 079046	Actavis Elizabeth, LLC	9-Jul-2012
oxymorphone hydrochloride	ANDA 202946	Mallinckrodt Pharmaceuticals	27-Jun-2014
oxymorphone hydrochloride	ANDA 200792	Par Pharmaceuticals, Inc.	24-Oct-2014
oxymorphone hydrochloride extended release	ANDA 200822	Roxane Laboratories, Inc	15-Jul-2013
oxymorphone hydrochloride extended-release	ANDA 203506	Sun Pharmaceutical Industries Limited	24-Apr-2015

APPENDIX 3 FDA BLUEPRINT

Introduction for the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics

In April 2011, FDA announced the elements of a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of extended-release and long-acting (ER/LA) opioid analgesics outweigh the risks. The REMS supports national efforts to address the prescription drug abuse epidemic.

As part of the REMS, all ER/LA opioid analgesic companies must provide:

- Education for prescribers of these medications, which will be provided through accredited continuing education (CE) activities supported by independent educational grants from ER/LA opioid analgesic companies.
- Information that prescribers can use when counseling patients about the risks and benefits of ER/LA opioid analgesic use.

FDA developed core messages to be communicated to prescribers in the Blueprint for Prescriber Education (FDA Blueprint), published the draft FDA Blueprint for public comment, and considered the public comments when finalizing the FDA Blueprint. This final FDA Blueprint contains the core educational messages. It is approved as part of the ER/LA Opioid Analgesic REMS and will remain posted on the FDA website for use by CE providers to develop the actual CE activity. A list of all REMS-compliant CE activities that are supported by independent educational grants from the ER/LA opioid analgesic companies to accredited CE providers will be posted at www.ER-LA-opioidREMS.com as that information becomes available.

The CE activities provided under the FDA Blueprint will focus on the safe prescribing of ER/LA opioid analgesics and consist of a core content of about three hours. The content is directed to prescribers of ER/LA opioid analgesics, but also may be relevant for other healthcare professionals (e.g., pharmacists). The course work is not intended to be exhaustive nor a substitute for a more comprehensive pain management course.

Accrediting bodies and CE providers will ensure that the CE activities developed under this REMS will be in compliance with the standards for CE of the Accreditation Council for Continuing Medical Education (ACCME) ¹⁻² or another CE accrediting body as appropriate to the prescribers' medical specialty or healthcare profession.

For additional information from FDA, including more detailed Questions and Answers about the REMS for ER/LA Opioid Analgesics, see <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm>.

¹ Accreditation Council for Continuing Medical Education. 2015. *Accreditation Requirements. Criteria for CME Providers-Accreditation Criteria*. Accessed on May 29, 2015.

² Accreditation Council for Continuing Medical Education. 2015. *Accreditation Requirements. Criteria for CME Providers-Standards for Commercial Support*. Accessed on May 29, 2015.

FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics

Why Prescriber Education is Important

Health care professionals who prescribe extended-release (ER) and long-acting (LA) opioid analgesics (hereafter referred to as ER/LA opioid analgesics) are in a key position to balance the benefits of prescribing ER/LA opioid analgesics to treat pain against the risks of serious adverse outcomes including addiction, unintentional overdose, and death. Opioid misuse and abuse, resulting in injury and death, has emerged as a major public health problem.

- Based on the 2010 National Survey on Drug Use and Health, public health experts estimate more than 35 million Americans age 12 and older used an opioid analgesic for non-medical use some time in their life—an increase from about 30 million in 2002.³
- In 2009, there were nearly 343,000 emergency department visits involving nonmedical use of opioid analgesics.⁴
- In 2008, nearly 36,500 Americans died from drug poisonings, and of these, nearly 14,800 deaths involved opioid analgesics.⁵
- Improper use of any opioid can result in serious side effects including overdose and death, and this risk can be greater with ER/LA opioid analgesics.

Appropriate prescribing practices and patient education are important steps to help address this public health problem. Health care professionals who prescribe ER/LA opioid analgesics have a responsibility to help ensure the safe and effective use of these drug products. ER/LA opioid analgesics should be prescribed only by health care professionals who are knowledgeable in the use of potent opioids for the management of pain.

The expected results of the prescriber education in this REMS are that the prescribers will:

- a. Understand how to assess patients for treatment with ER/LA opioid analgesics.
- b. Be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics.
- c. Be knowledgeable about how to manage ongoing therapy with ER/LA opioid analgesics.
- d. Know how to counsel patients and caregivers about the safe use of ER/LA opioid analgesics, including proper storage and disposal.
- e. Be familiar with general and product-specific drug information concerning ER/LA opioid analgesics.

I. Assessing Patients for Treatment with ER/LA Opioid Analgesic Therapy

- a. Prescribers should consider risks involved with ER/LA opioid analgesics and balance these against potential benefits. Risks include:
 - i. Overdose with ER/LA formulations, as most dosage units contain more opioid than immediate-release formulations.

³Substance Abuse and Mental Health Services Administration. 2011. *Results from the 2010 National Survey on Drug Use and Health: Detailed Table*, Table 7.1.a. Rockville, MD.

<http://www.samhsa.gov/data/NSDUH/2k10NSDUH/tabs/Sect7peTabs1to45.htm#Tab7.1A>. Accessed on May 29, 2015.

⁴Substance Abuse and Mental Health Services Administration. 2011. *Drug Abuse Warning Network, 2009: National Estimates of Drug-Related Emergency Department Visits*, Table 19. Rockville, MD.

<http://www.samhsa.gov/data/2k11/DAWN/2k9DAWNED/HTML/DAWN2k9ED.htm#Tab19>. Accessed on May 29, 2015.

⁵Warner M, Chen LH, Makuc DM, Anderson RN, and Miniño AM. 2011. Drug Poisoning Deaths in the United States, 1980–2008, in U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, *NCHS Data Brief, No 81*. December 2011. Hyattsville, MD. <http://www.cdc.gov/nchs/data/databriefs/db81.pdf>. Accessed on May 29, 2015.

- ii. Life-threatening respiratory depression
 - iii. Abuse by patient or household contacts
 - iv. Misuse and addiction.
 - v. Physical dependence and tolerance.
 - vi. Interactions with other medications and substances (See table in Section VI for product-specific information).
 - vii. Risk of neonatal opioid withdrawal syndrome with prolonged use during pregnancy.
 - viii. Inadvertent exposure/ingestion by household contacts, especially children.
- b. Prescribers should assess each patient's risk of abuse, including substance use and psychiatric history. Prescribers should:
 - i. Obtain a complete history and conduct a complete physical examination. The history should include assessment for a family history of substance abuse and psychiatric disorders, as well as special considerations regarding dose and adverse effects in geriatric patients, pregnant women, and children.
 - A history of substance abuse does not prohibit treatment with ER/LA opioid analgesics but may require additional monitoring and expert consultation.
 - ii. Be knowledgeable about risk factors for opioid abuse.
 - iii. Understand and appropriately use screening tools for addiction or abuse to help assess potential risks associated with chronic opioid therapy and to help manage patients using ER/LA opioid analgesics (e.g., structured interview tools).
 - iv. Adequately document all patient interactions and treatment plans.
- c. Prescribers should understand when to appropriately refer high risk patients to pain management specialists.
- d. Prescribers should understand opioid tolerance criteria as defined in the product labeling.
 - Prescribers should know which products and which doses are indicated for use only in opioid-tolerant patients. (See table in Section VI for product-specific information).

II. Initiating Therapy, Modifying Dosing, and Discontinuing Use of ER/LA Opioid Analgesics

- a. Prescribers should have awareness of federal and state regulations on opioid prescribing.
- b. Prescribers should be aware that:
 - i. Dose selection is critical, particularly when initiating therapy in opioid non-tolerant patients.
 - ii. Some ER/LA opioid analgesics are only appropriate for opioid-tolerant patients. (See table in Section VI for product-specific information)
 - iii. Dosage should be individualized in every case.
 - iv. Titration should be based on efficacy and tolerability. (See individual product labeling)
- c. Prescribers should be knowledgeable about when and how to supplement pain management with immediate-release analgesics, opioids and non-opioids.
- d. Prescribers should be knowledgeable about converting patients from immediate-release to ER/LA opioid products and from one ER/LA opioid product to another ER/LA opioid
- e. Prescribers should understand the concept of incomplete cross-tolerance when converting patients from one opioid to another.
- f. Prescribers should understand the concepts and limitations of equianalgesic dosing and follow patients closely during all periods of dose adjustments.

- g. Prescribers should understand the warning signs and symptoms of significant respiratory depression from opioids and monitor patients closely, especially at the time of treatment initiation and dose increases.
- h. Prescribers should understand that tapering the opioid dose is necessary to safely discontinue treatment with ER/LA opioid analgesics when therapy is no longer needed.

III. Managing Therapy with ER/LA Opioid Analgesics

- a. Prescribers should establish analgesic and functional goals for therapy and periodically evaluate pain control, functional outcomes, side-effect frequency and intensity, and health-related quality of life.
- b. Prescribers should be aware of the existence of Patient Prescriber Agreements (PPAs).
 - i. PPAs are documents signed by both prescriber and patient at the time an opioid is prescribed.
 - ii. PPAs can help ensure patients and caregivers understand the goals of treatment, the risks, and how to use the medications safely.
 - iii. PPAs can include commitments to return for follow-up visits, to comply with appropriate monitoring (such as random drug testing), and to safeguard the medication.
- c. Prescribers should monitor patient adherence to the treatment plan, especially with regard to misuse and abuse by:
 - i. Recognizing, documenting, and addressing aberrant drug-related behavior.
 - ii. Utilizing state Prescription Drug Monitoring Programs, where practical, to identify behaviors that may represent abuse.
 - iii. Understanding the utility and interpretation of drug testing (e.g., screening and confirmatory tests), and using it as indicated.
 - iv. Screening and referring for substance abuse treatment as indicated.
 - v. Performing medication reconciliation as indicated.
- d. Prescribers should understand how to anticipate and manage adverse events associated with ER/LA opioid analgesics.
- e. Prescribers should be aware that there are no adequate and well-controlled studies of ER/LA opioid analgesics in pregnant women. ER/LA opioid analgesics should be used during pregnancy only if the potential benefit justifies the risk to the fetus.
- f. Prescribers should be aware of the pregnancy status of their patients. If opioid use is required for a prolonged period in a pregnant woman, prescribers should advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.
- g. Prescribers treating patients with ER/LA opioid analgesics should periodically assess benefits and side effects of these drugs, and the continued need for opioid analgesics.
- h. Prescribers should understand the need for reevaluation of patient's underlying medical condition if the clinical presentation changes over time.
- i. Prescribers should be familiar with referral sources for the treatment of abuse or addiction that may arise from the use of ER/LA opioid analgesics.

IV. Counseling Patients and Caregivers about the Safe Use of ER/LA Opioid Analgesics

- a. Prescribers should use the Patient Counseling Document as part of the discussion when prescribing opioid analgesics.

- b. Prescribers should explain product-specific information about the prescribed ER/LA opioid analgesic.
- c. Prescribers should explain how to take the ER/LA opioid analgesic as prescribed.
- d. Prescribers should explain the importance of adherence to dosing regimen, how to handle missed doses, and to contact their prescriber should pain not be controlled.
- e. Prescribers should inform patients and caregivers to read the specific ER/LA opioid analgesic Medication Guide they receive from the pharmacy.
- f. Prescribers should warn patients and caregivers that under no circumstances should an oral ER/LA opioid analgesic be broken, chewed or crushed. In addition, patches and buccal films should not be cut, torn, or damaged prior to use. Manipulating the ER/LA opioid analgesic described above may lead to rapid release of the ER/LA opioid analgesic causing overdose and death. When a patient cannot swallow a capsule whole, prescribers should refer to the product labeling to determine if it is appropriate to sprinkle the contents of a capsule on applesauce or administer via a feeding tube.
- g. Prescribers should caution patients and caregivers that the use of other CNS depressants such as sedative-hypnotics and anxiolytics, alcohol, or illegal drugs with ER/LA opioid analgesics can cause overdose and death. Patients and caregivers should be instructed to only use other CNS depressants, including other opioids, under the instruction of their prescriber.
- h. Prescribers should instruct patients and caregivers to tell all of their doctors about all medications the patient is taking.
- i. Prescribers should warn patients and caregivers not to abruptly discontinue or reduce the ER/LA opioid analgesic and discuss how to safely taper the dose when discontinuing.
- j. Prescribers should caution patients and caregivers that ER/LA opioid analgesics can cause serious side effects that can lead to death, even when used as recommended. Prescribers should counsel patients and caregivers on the risk factors, signs, and symptoms of overdose and opioid-induced respiratory depression, gastrointestinal obstruction, and allergic reactions.
- k. Prescribers should counsel patients and caregivers on the most common side effects of ER/LA opioid analgesics, and about the risk of falls, working with heavy machinery, and driving.
- l. Patients or caregivers should call their prescriber for information about managing side effects.
- m. Prescribers should explain to patients and caregivers that sharing ER/LA opioid analgesics with others may cause them to have serious side effects including death, and that selling or giving away ER/LA opioid analgesics is against the law.
- n. Prescribers should counsel patients and caregivers to store ER/LA opioid analgesics in a safe and secure place away from children, family members, household visitors, and pets.
- o. Prescribers should warn patients and caregivers that ER/LA opioid analgesics must be protected from theft.
- p. Prescribers should counsel patients and caregivers to dispose of any ER/LA opioid analgesics when no longer needed by flushing them down the toilet.
- q. Prescribers should counsel patients and caregivers to inform them about side effects.
- r. Adverse events should be reported to the FDA at 1-800-FDA-1088 or via <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf>.

V. General Drug Information for ER/LA Opioid Analgesic Products

Prescribers should be knowledgeable about general characteristics, toxicities, and drug interactions for ER/LA opioid analgesic products. For example,

- a. ER/LA opioid analgesic products are scheduled under the Controlled Substances Act and

- can be misused and abused.
- b. Respiratory depression is the most important serious adverse effect of opioids as it can be immediately life-threatening.
 - c. Constipation is the most common long-term side effect and should be anticipated.
 - d. Drug-drug interaction profiles vary among the products. Knowledge of particular opioid-drug interactions, and the underlying pharmacokinetic and pharmacodynamic mechanisms, allows for the safer administration of opioid analgesics.
 - i. Central nervous system depressants (alcohol, sedatives, hypnotics, tranquilizers, tricyclic antidepressants) can have a potentiating effect on the sedation and respiratory depression caused by opioids.
 - ii. Some ER opioid formulations may rapidly release opioid (dose dump) when exposed to alcohol. Some drug levels may increase without dose dumping when exposed to alcohol. See individual product labeling.
 - iii. Using opioids with monoamine oxidase inhibitors (MAOIs) may result in possible increase in respiratory depression. Using certain opioids with MAOIs may cause serotonin syndrome.
 - iv. Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone (ADH).
 - v. Some opioids (methadone, buprenorphine) can prolong the QTc interval.
 - vi. Concomitant drugs that act as inhibitors or inducers of various cytochrome P450 enzymes can result in higher or lower than expected blood levels of some opioids.
 - vii. See table in Section VI for product-specific information.
 - e. Tolerance to sedating and respiratory-depressant effects of opioids is critical to the safe use of ER/LA opioid analgesics.
 - i. For ER products, patients must meet the criteria for opioid tolerance, described in the table in Section VI, before using:
 - a. certain products,
 - b. certain strengths,
 - c. certain daily doses, and
 - d. in specific indicated patient populations (e.g., pediatric patients).
 - ii. See the table in Section VI for product-specific information.
 - f. ER/LA opioid analgesic tablets must be swallowed whole. ER/LA opioid analgesic capsules should be swallowed intact or when necessary, the pellets from some capsules can be sprinkled on applesauce and swallowed without chewing.
 - g. For transdermal products, external heat, fever, and exertion can increase absorption of the opioid, leading to fatal overdose. Transdermal products with metal foil backings are not safe for use in MRIs.
 - h. For buccal film products, the film should not be applied if it is cut, damaged, or changed in any way. Use the entire film.
 - i. Follow the instructions for conversion in the Dosage and Administration section (2.1) in the *Prescribing Information* of each product when converting patients from one opioid to another.

VI. Specific Drug Information for ER/LA Opioid Analgesic Products

Prescribers should be knowledgeable about specific characteristics of the ER/LA opioid analgesic products they prescribe, including the drug substance, formulation, strength, dosing interval, key instructions, specific information about conversion between products where available, specific drug interactions, use in opioid-tolerant patients, product-specific safety concerns, and relative potency to morphine. The attached table is a reference. For detailed information, prescribers can refer to prescribing information available online via DailyMed at www.dailymed.nlm.nih.gov or Drugs@FDA at www.fda.gov/drugsatfda.

Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Avinza (morphine sulfate ER capsules) Belbuca (buprenorphine buccal film) Butrans (buprenorphine transdermal system) Dolophine (methadone HCl tablets) Duragesic (fentanyl transdermal system) Embeda (morphine sulfate ER-naltrexone capsules) Exalgo (hydromorphone HCl ER tablets) Hysingla ER (hydrocodone bitartrate ER tablets) Kadian (morphine sulfate ER capsules)	MorphaBond (morphine sulfate ER tablets) MS Contin (morphine sulfate ER tablets) Nucynta ER (tapentadol HCl ER tablets) Opana ER (oxycodone HCl ER tablets) OxyContin (oxycodone HCl ER tablets) Targiniq ER (oxycodone HCl/naloxone HCl ER tablets) Zohydro ER (hydrocodone bitartrate ER capsules)
Dosing Interval	<ul style="list-style-type: none"> Refer to individual product information.
Key Instructions	<ul style="list-style-type: none"> Limitations of usage: <ul style="list-style-type: none"> Reserve for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. Not for use as an as-needed analgesic. Not for mild pain or pain not expected to persist for an extended duration. Not for use in treating acute pain. Individually titrate to a dose that provides adequate analgesia and minimizes adverse reactions. The times required to reach steady-state plasma concentrations are product specific; refer to product information for titration interval. Continually reevaluate to assess the maintenance of pain control and the emergence of adverse reactions. During chronic therapy, especially for non-cancer-related pain, periodically reassess the continued need for opioids. If pain increases, attempt to identify the source, while adjusting the dose. When an ER/LA opioid analgesic is no longer required, gradually titrate downward to prevent signs and symptoms of withdrawal in the physically-dependent patient. Do not abruptly discontinue these products. Solid oral dosage forms: <ul style="list-style-type: none"> Swallow tablets and capsules whole: crushing, chewing, breaking, cutting or dissolving may result in rapid release and absorption of a potentially fatal dose of opioid. Some capsules can be opened and pellets sprinkled on applesauce for patients who can reliably swallow without chewing and used immediately. See individual product information. Exposure of some products to alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of opioid. Dispose of unused product by flushing down the toilet. Transdermal dosage forms: <ul style="list-style-type: none"> Avoid exposure to external heat. Patients with fever must be monitored for signs or symptoms of increased opioid exposure. Location of application must be rotated. Prepare skin by clipping, not shaving hair, and washing area only with water. Buccal film dosage form: <ul style="list-style-type: none"> Do not use if the package seal is broken or the film is cut, damaged, or changed in any way. See individual product information for the following: <ul style="list-style-type: none"> Dosage reduction for hepatic or renal impairment.

Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Drug Interactions Common to the Class	<ul style="list-style-type: none"> Concurrent use with other central nervous system depressants (sedatives, hypnotics, general anesthetics, antiemetics, phenothiazines, other tranquilizers, and alcohol) can increase the risk of respiratory depression, hypotension, profound sedation, or coma. Reduce the initial dose of one or both agents. Avoid concurrent use of mixed opioid agonist/antagonists (i.e., pentazocine, nalbuphine, and buprenorphine) or partial opioid agonists (buprenorphine) in patients who have received or are receiving a course of therapy with a full opioid agonist. In these patients, mixed opioid agonist/antagonists and partial opioid agonists may reduce the analgesic effect and/or may precipitate withdrawal symptoms. Opioids may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. Concurrent use with anticholinergic medication increases the risk of urinary retention and severe constipation, which may lead to paralytic ileus.
Use in Opioid-Tolerant Patients	<ul style="list-style-type: none"> Adult patients considered opioid-tolerant are those receiving, for one week or longer: <ul style="list-style-type: none"> at least 60 mg oral morphine/day 25 mcg transdermal fentanyl/hour 30 mg oral oxycodone/day 8 mg oral hydromorphone/day 25 mg oral oxymorphone/day Pediatric patients (11 years and older) considered opioid-tolerant are those who are already receiving and tolerating a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent (applicable to OxyContin's pediatric indication only) See individual product information for which products: <ul style="list-style-type: none"> Have strengths or total daily doses only for use in opioid-tolerant patients. Are only for use in opioid-tolerant patients at all strengths.
Contraindications	<ul style="list-style-type: none"> Significant respiratory depression Acute or severe asthma in an unmonitored setting or in the absence of resuscitative equipment Known or suspected paralytic ileus Hypersensitivity (e.g., anaphylaxis) See individual product information for additional contraindications.
Relative Potency To Oral Morphine	<ul style="list-style-type: none"> These are intended as general guides. Follow conversion instructions in individual product information. Incomplete cross-tolerance and inter-patient variability require the use of conservative dosing when converting from one opioid to another - halve the calculated comparable dose and titrate the new opioid as needed.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Avinza	Morphine Sulfate ER Capsules, 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 120 mg
Dosing Interval	Once a day
Key Instructions	<ul style="list-style-type: none"> Initial dose in opioid non-tolerant patients is 30 mg. Titrate in increments of not greater than 30 mg using a minimum of 3 to 4 day intervals. Swallow capsule whole (do not chew, crush, or dissolve). May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing; use immediately. Maximum daily dose: 1600 mg due to risk of serious renal toxicity by excipient, fumaric acid.
Specific Drug Interactions	<ul style="list-style-type: none"> Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. P-gp inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	90 mg and 120 mg capsules are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Belbuca	Buprenorphine Buccal Film, 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, and 900 mcg
Dosing Interval	Every 12 hours (or once every 24 hours for initiation in opioid naïve patients and patients taking less than 30 mg oral morphine sulfate equivalents)
Key Instructions	<ul style="list-style-type: none"> Opioid-naïve patients or patients taking less than 30 mg oral morphine sulfate equivalents: Initiate treatment with a 75 mcg buccal film, once daily, or if tolerated, every 12 hours. <ul style="list-style-type: none"> Titrate to 150 mcg every 12 hours no earlier than 4 days after initiation. Individual titration to a dose that provides adequate analgesia and minimizes adverse reactions should proceed in increments of 150 mcg every 12 hours, no more frequently than every 4 days. When converting from another opioid, first taper the current opioid to no more than 30 mg oral morphine sulfate equivalents per day prior to initiating Belbuca. <ul style="list-style-type: none"> If prior daily dose before taper was 30 mg to 89 mg oral morphine sulfate equivalents, initiate with 150 mcg dose every 12 hours. If prior daily dose before taper was 90 mg to 160 mg oral morphine sulfate equivalents, initiate with 300 mcg dose every 12 hours. Titration of the dose should proceed in increments of 150 mcg every 12 hours, no more frequently than every 4 days. Maximum dose: 900 mcg every 12 hours due to the potential for QTc prolongation Severe Hepatic Impairment: Reduce the starting and incremental dose by half that of patients with normal liver function. Oral Mucositis: Reduce the starting and incremental dose by half that of patients without mucositis Do not use if the package seal is broken or the film is cut, damaged, or changed in any way
Specific Drug Interactions	<ul style="list-style-type: none"> CYP3A4 inhibitors may increase buprenorphine levels. CYP3A4 inducers may decrease buprenorphine levels. Benzodiazepines may increase respiratory depression. Class IA and III antiarrhythmics, other potentially arrhythmogenic agents, may increase risk for QTc prolongation and torsades de pointes

Use in Opioid-Tolerant Patients	Belbuca 600 mcg, 750 mcg, and 900 mcg are for use following titration from lower doses of Belbuca.
Product-Specific Safety Concerns	<ul style="list-style-type: none"> QTc prolongation and torsade de pointes Hepatotoxicity
Relative Potency To Oral Morphine	Equipotency to oral morphine has not been established.
Butrans	Buprenorphine Transdermal System, 5 mcg/hr, 7.5 mcg/hr, 10 mcg/hr, 15 mcg/hr, 20 mcg/hr
Dosing Interval	One transdermal system every 7 days
Key Instructions	<ul style="list-style-type: none"> Initial dose in opioid non-tolerant patients when converting from less than 30 mg morphine equivalents, and in mild to moderate hepatic impairment - 5 mcg/hr dose. When converting from 30 mg to 80 mg morphine equivalents - first taper to 30 mg morphine equivalent, then initiate with 10 mcg/hr dose. Titrate in 5 mcg/hour or 10 mcg/hour increments by using no more than two patches of the 5 mcg/hour or 10-mcg/hour system(s) with a minimum of 72 hours between dose adjustments. The total dose from all patches should not exceed 20 mcg/hour Maximum dose: 20 mcg/hr due to risk of QTc prolongation. Application <ul style="list-style-type: none"> Apply only to sites indicated in the Full Prescribing Information. Apply to intact/non-irritated skin. Skin may be prepped by clipping hair, washing site with water only Rotate site of application a minimum of 3 weeks before reapplying to the same site. Do not cut. Avoid exposure to heat. Dispose of used/unused patches by folding the adhesive side together and flushing down the toilet.
Specific Drug Interactions	<ul style="list-style-type: none"> CYP3A4 Inhibitors may increase buprenorphine levels. CYP3A4 Inducers may decrease buprenorphine levels. Benzodiazepines may increase respiratory depression. Class IA and III antiarrhythmics, other potentially arrhythmogenic agents, may increase risk for QTc prolongation and torsade de pointe.
Use in Opioid-Tolerant Patients	Butrans 7.5 mcg/hr, 10 mcg/hr, 15 mcg/hr, and 20 mcg/hr transdermal systems are for use in opioid- tolerant patients only.
Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Drug-Specific Safety Concerns	<ul style="list-style-type: none"> QTc prolongation and torsade de pointe. Hepatotoxicity Application site skin reactions
Relative Potency To Oral Morphine	Equipotency to oral morphine has not been established.
Dolophine	Methadone Hydrochloride Tablets, 5 mg and 10 mg
Dosing Interval	Every 8 to 12 hours

Key Instructions	<ul style="list-style-type: none"> Initial dose in opioid non-tolerant patients: 2.5 to 10 mg Conversion of opioid-tolerant patients using equianalgesic tables can result in overdose and death. Use low doses according to the table in the full prescribing information. Titrate slowly, with dose increases no more frequent than every 3 to 5 days. Because of high variability in methadone metabolism, some patients may require substantially longer periods between dose increases (up to 12 days). High inter-patient variability in absorption, metabolism, and relative analgesic potency. Opioid detoxification or maintenance treatment shall only be provided in a federally certified opioid (addiction) treatment program (Code of Federal Regulations, Title 42, Sec 8).
Specific Drug Interactions	<ul style="list-style-type: none"> Pharmacokinetic drug-drug interactions with methadone are complex. <ul style="list-style-type: none"> CYP 450 inducers may decrease methadone levels. CYP 450 inhibitors may increase methadone levels. Anti-retroviral agents have mixed effects on methadone levels. Potentially arrhythmogenic agents may increase risk for QTc prolongation and torsade de pointe. Benzodiazepines may increase respiratory depression
Use in Opioid-Tolerant Patients	Refer to full prescribing information.
Product-Specific Safety Concerns	<ul style="list-style-type: none"> QTc prolongation and torsade de pointe. Peak respiratory depression occurs later and persists longer than analgesic effect. Clearance may increase during pregnancy. False positive urine drug screens possible.
Relative Potency To Oral Morphine	Varies depending on patient's prior opioid experience.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)

Duragesic	Fentanyl Transdermal System, 12, 25, 37.5*, 50, 62.5*, 75, 87.5*, and 100 mcg/hr (*These strengths are available only in generic form)
Dosing Interval	Every 72 hours (3 days)
Key Instructions	<ul style="list-style-type: none"> Use product specific information for dose conversion from prior opioid Use 50% of the dose in mild or moderate hepatic or renal impairment, avoid use in severe hepatic or renal impairment Application <ul style="list-style-type: none"> Apply to intact/non-irritated/non-irradiated skin on a flat surface. Skin may be prepped by clipping hair, washing site with water only Rotate site of application. Titrate using a minimum of 72 hour intervals between dose adjustments. Do not cut. Avoid exposure to heat. Avoid accidental contact when holding or caring for children. Dispose of used/unused patches by folding the adhesive side together and flushing down the toilet. <p>Specific contraindications:</p> <ul style="list-style-type: none"> Patients who are not opioid-tolerant. Management of acute or intermittent pain, or in patients who require opioid analgesia for a short period of time. Management of post-operative pain, including use after out-patient or day surgery. Management of mild pain.

Specific Drug Interactions	<ul style="list-style-type: none"> ▪ CYP3A4 inhibitors may increase fentanyl exposure. ▪ CYP3A4 inducers may decrease fentanyl exposure. ▪ Discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration.
Use in Opioid-Tolerant Patients	All doses of Duragesic are indicated for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	<ul style="list-style-type: none"> ▪ Accidental exposure due to secondary exposure to unwashed/unclothed application site. ▪ Increased drug exposure with increased core body temperature or fever. ▪ Bradycardia ▪ Application site skin reactions
Relative Potency To Oral Morphine	See individual product information for conversion recommendations from prior opioid
Embeda	Morphine Sulfate ER-Naltrexone Capsules, 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, 100 mg/4 mg
Dosing Interval	Once a day or every 12 hours
Key Instructions	<ul style="list-style-type: none"> ▪ Initial dose as first opioid: 20 mg/0.8 mg. ▪ Titrate using a minimum of 1 to 2 day intervals. ▪ Swallow capsules whole (do not chew, crush, or dissolve) ▪ Crushing or chewing will release morphine, possibly resulting in fatal overdose, and naltrexone, possibly resulting in withdrawal symptoms. ▪ May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. ▪ P-gp inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	Embeda 100 mg/4 mg capsule is for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Exalgo	Hydromorphone Hydrochloride Extended-Release Tablets, 8 mg, 12 mg, 16 mg or 32 mg
Dosing Interval	Once a day
Key Instructions	<ul style="list-style-type: none"> ▪ Use the conversion ratios in the individual product information. ▪ Start patients with moderate hepatic impairment on 25% dose that would be prescribed for a patient with normal hepatic function. ▪ Start patients with moderate renal impairment on 50%, and patients with severe renal impairment on 25% of the dose that would be prescribed for a patient with normal renal function. ▪ Titrate in increments of 4 to 8 mg using a minimum of 3 to 4 day intervals ▪ Swallow tablets whole (do not chew, crush, or dissolve). ▪ Do not use in patients with sulfite allergy—contains sodium metabisulfite.
Specific Drug Interactions	None
Use in Opioid-Tolerant Patients	All doses of Exalgo are indicated for opioid-tolerant patients only.
Drug-Specific Adverse Reactions	Allergic manifestations to sulfite component.
Relative Potency To Oral Morphine	Approximately 5:1 oral morphine to hydromorphone oral dose ratio, use conversion recommendations in the individual product information.
Hysingla ER	Hydrocodone bitartrate Extended-Release Tablets, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 100 mg, and 120 mg
Dosing Interval	Every 24 hours (once-daily)

Key Instructions	<ul style="list-style-type: none"> ▪ Opioid-naïve patients: initiate treatment with 20 mg orally once daily. During titration, adjust the dose in increments of 10 mg to 20 mg every 3 to 5 days until adequate analgesia is achieved. ▪ Swallow tablets whole (do not chew, crush, or dissolve). ▪ Consider use of an alternative analgesic in patients who have difficulty swallowing or have underlying gastrointestinal disorders that may predispose them to obstruction. ▪ Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth. ▪ Use 1/2 of the initial dose and monitor closely for adverse events, such as respiratory depression and sedation, when administering Hysingla ER to patients with severe hepatic impairment or patients with moderate to severe renal impairment.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ CYP3A4 inhibitors may increase hydrocodone exposure. ▪ CYP3A4 inducers may decrease hydrocodone exposure ▪ Concomitant use of Hysingla ER with strong laxatives (e.g., Lactulose) that rapidly increase GI motility may decrease hydrocodone absorption and result in decreased hydrocodone plasma levels. ▪ The use of MAO inhibitors or tricyclic antidepressants with Hysingla ER may increase the effect of either the antidepressant or Hysingla ER.
Use in Opioid-Tolerant Patients	A single dose of Hysingla ER greater than or equal to 80 mg is only for use in opioid tolerant patients.
Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Product-Specific Safety Concerns	<ul style="list-style-type: none"> ▪ Use with caution in patients with difficulty swallowing the tablet or underlying gastrointestinal disorders that may predispose patients to obstruction. ▪ Esophageal obstruction, dysphagia, and choking have been reported with Hysingla ER. ▪ In nursing mothers, discontinue nursing or discontinue drug. ▪ QTc prolongation has been observed with Hysingla ER following daily doses of 160 mg. Avoid use in patients with congenital long QTc syndrome. This observation should be considered in making clinical decisions regarding patient monitoring when prescribing Hysingla ER in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong the QTc interval. In patients who develop QTc prolongation, consider reducing the dose.
Relative Potency To Oral Morphine	See individual product information for conversion recommendations from prior opioid
Kadian	Morphine Sulfate Extended-Release Capsules, 10 mg, 20mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 100 mg, 130 mg, 150 mg, and 200 mg
Dosing Interval	Once a day or every 12 hours
Key Instructions	<ul style="list-style-type: none"> ▪ Product information recommends not using as first opioid. ▪ Titrate using a minimum of 2-day intervals. ▪ Swallow capsules whole (do not chew, crush, or dissolve). ▪ May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. ▪ P-gp inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	Kadian 100 mg, 130 mg, 150 mg, and 200 mg capsules are for use in opioid-tolerant-patients only
Product-Specific Safety	None

MorphaBond	Morphine Sulfate Extended-release Tablets, 15 mg, 30 mg, 60 mg, 100 mg
Dosing Interval	Every 8 hours or every 12 hours
Key Instructions	<ul style="list-style-type: none"> Product information recommends not using as first opioid. Titrate using a minimum of 1 to 2-day intervals. Swallow tablets whole (do not chew, crush, or dissolve).
Specific Drug Interactions	P-gp inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	MorphaBond 100 mg tablets are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
MS Contin	Morphine Sulfate Extended-release Tablets, 15 mg, 30 mg, 60 mg, 100 mg, and 200 mg
Dosing Interval	Every 8 hours or every 12 hours
Key Instructions	<ul style="list-style-type: none"> Product information recommends not using as first opioid. Titrate using a minimum of 1 to 2-day intervals. Swallow tablets whole (do not chew, crush, or dissolve).
Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Specific Drug Interactions	P-gp inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	MS Contin 100 mg and 200 mg tablet strengths are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Nucynta ER	Tapentadol Extended-Release Tablets, 50 mg, 100mg, 150 mg, 200 mg, and 250 mg
Dosing Interval	Every 12 hours
Key Instructions	<ul style="list-style-type: none"> Use 50 mg every 12 hours as initial dose in opioid nontolerant patients Titrate by 50 mg increments using a minimum of 3-day intervals. Maximum total daily dose is 500 mg Swallow tablets whole (do not chew, crush, or dissolve). Take one tablet at a time and with enough water to ensure complete swallowing immediately after placing in the mouth. Dose once daily in moderate hepatic impairment with 100 mg per day maximum Avoid use in severe hepatic and renal impairment.
Specific Drug Interactions	<ul style="list-style-type: none"> Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of tapentadol. Contraindicated in patients taking MAOIs.
Use in Opioid-Tolerant Patients	No product-specific considerations.
Product-Specific Safety Concerns	<ul style="list-style-type: none"> Risk of serotonin syndrome Angioedema
Relative Potency To Oral Morphine	Equipotency to oral morphine has not been established.
Opana ER	Oxymorphone Hydrochloride ER Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg
Dosing Interval	Every 12h dosing, some may benefit from asymmetric (different dose given in AM than in PM) dosing.

Key Instructions	<ul style="list-style-type: none"> Use 5 mg every 12 hours as initial dose in opioid non-tolerant patients and patients with mild hepatic impairment and renal impairment (creatinine clearance < 50 mL/min) and patients over 65 years of age Swallow tablets whole (do not chew, crush, or dissolve). Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth. Titrate in increments of 5 to 10 mg using a minimum of 3 to 7-day intervals. Contraindicated in moderate and severe hepatic impairment.
Specific Drug Interactions	<ul style="list-style-type: none"> Alcoholic beverages or medications containing alcohol may result in the absorption of a potentially fatal dose of oxymorphone.
Use in Opioid-Tolerant Patients	No product specific considerations.
Product-Specific Safety Concerns	<ul style="list-style-type: none"> Use with caution in patients who have difficulty in swallowing or have underlying GI disorders that may predispose them to obstruction, such as a small gastrointestinal lumen.
Relative Potency To Oral Morphine	Approximately 3:1 oral morphine to oxymorphone oral dose ratio
OxyContin	Oxycodone Hydrochloride Extended-release Tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg
Dosing Interval	<ul style="list-style-type: none"> Every 12 hours

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Key Instructions	<ul style="list-style-type: none"> For Adults: <ul style="list-style-type: none"> Initial dose in opioid-naïve and opioid non-tolerant patients is 10 mg every 12 hours. If needed, adult dosage may be adjusted in 1 to 2 day intervals. When a dose increase is clinically indicated, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose. For Pediatric patients (11 years and older): Use only in <u>opioid-tolerant</u> patients (see below, <i>Use in Opioid-Tolerant Patients</i> for dosing information). For all patients: <ul style="list-style-type: none"> Hepatic impairment: start with one third to one half the usual dosage Renal impairment (creatinine clearance <60 mL/min): start with one half the usual dosage. Consider use of other analgesics in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction. Swallow tablets whole (do not chew, crush, or dissolve). Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth.
Specific Drug Interactions	<ul style="list-style-type: none"> CYP3A4 inhibitors may increase oxycodone exposure. CYP3A4 inducers may decrease oxycodone exposure.

Use in Opioid-Tolerant Patients	<ul style="list-style-type: none"> For Adults: <ul style="list-style-type: none"> Single dose greater than 40 mg or total daily dose greater than 80 mg are for use in adult patients in whom tolerance to an opioid of comparable potency has been established. For Pediatric patients (11 years and older): <ul style="list-style-type: none"> For use only in <u>opioid-tolerant</u> pediatric patients already receiving and tolerating opioids for at least 5 consecutive days with a minimum of 20 mg per day of oxycodone or its equivalent for at least two days immediately preceding dosing with OxyContin. If needed, pediatric dosage may be adjusted in 1 to 2 day intervals. When a dose increase is clinically indicated, the total daily oxycodone dose usually can be increased by 25% of the current total daily dose.
Product-Specific Safety Concerns	<ul style="list-style-type: none"> Choking, gagging, regurgitation, tablets stuck in the throat, difficulty swallowing the tablet. Contraindicated in patients with gastrointestinal obstruction.
Relative Potency To Oral Morphine	Approximately 2:1 oral morphine to oxycodone oral dose ratio.
Targiniq ER	Oxycodone Hydrochloride / Naloxone Hydrochloride Extended-release tablets, 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg
Dosing Interval	<ul style="list-style-type: none"> Every 12 hours

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Key Instructions	<ul style="list-style-type: none"> Opioid-naïve patients: initiate treatment with 10 mg/5 mg every 12 hours. Titrate using a minimum of 1 to 2 day intervals. Do not exceed 80 mg/40 mg total daily dose (40 mg/20 mg q12) of Targiniq ER May be taken with or without food. Swallow tablets whole. Do not chew, crush, split, or dissolve, as this will release oxycodone, possibly resulting in fatal overdose, and naloxone, possibly resulting in withdrawal symptoms. Hepatic impairment: contraindicated in moderate and severe hepatic impairment. In patients with mild hepatic impairment, start with one third to one half the usual dosage. Renal impairment (creatinine clearance < 60 mL/min): start with one half the usual dosage.
Specific Drug Interactions	<ul style="list-style-type: none"> CYP3A4 inhibitors may increase oxycodone exposure. CYP3A4 inducers may decrease oxycodone exposure
Use in Opioid-Tolerant Patients	<ul style="list-style-type: none"> Single dose greater than 40 mg/20 mg or total daily dose of 80 mg/40 mg are for use in opioid-tolerant patients only
Product-Specific Safety Concerns	<ul style="list-style-type: none"> Contraindicated in patients with moderate to severe hepatic impairment.
Relative Potency To Oral Morphine	<ul style="list-style-type: none"> See individual product information for conversion recommendations from prior opioid.
Zohydro ER	Hydrocodone Bitartrate Extended-Release Capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50
Dosing Interval	<ul style="list-style-type: none"> Every 12 hours
Key Instructions	<ul style="list-style-type: none"> Initial dose in opioid non-tolerant patient is 10 mg. Titrate in increments of 10 mg using a minimum of 3 to 7 day intervals. Swallow capsules whole (do not chew, crush, or dissolve).
Specific Drug Interactions	<ul style="list-style-type: none"> Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of hydrocodone. CYP3A4 inhibitors may increase hydrocodone exposure. CYP3A4 inducers may decrease hydrocodone exposure.

Use in Opioid-Tolerant Patients	▪ Single dose greater than 40 mg or total daily dose greater than 80 mg are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Relative Potency To Oral Morphine	Approximately 1.5:1 oral morphine to hydrocodone oral dose ratio.
For detailed information, refer to prescribing information available online via DailyMed at www.dailymed.nlm.nih.gov or Drugs@FDA at www.fda.gov/drugsatfda .	

APPENDIX 4 ER/LA OPIOID ANALGESICS REMS WEBSITE

ER/LA Opioid Analgesics REMS

The Extended-Release and Long-Acting Opioid
Analgesics Risk Evaluation and Mitigation Strategy

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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure that the benefits of a drug outweigh its risks.

The FDA has required a REMS for extended-release and long-acting (ER/LA) opioid analgesics.

Under the conditions specified in this REMS, **prescribers of ER/LA opioid analgesics are strongly encouraged to do all of the following:**

- **Train (Educate Yourself)** - Complete a [REMS-compliant education program](#) offered by an accredited provider of continuing education (CE) for your discipline
- **Counsel Your Patients** - Discuss the safe use, serious risks, storage, and disposal of ER/LA opioid analgesics with patients and/or their caregivers every time you prescribe these medicines. Click here for the [Patient Counseling Document \(PCD\)](#)
- **Emphasize Patient and Caregiver Understanding of the Medication Guide** - Stress to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an ER/LA opioid is dispensed to them
- **Consider Using Other Tools** - In addition to the PCD, there are other publicly available tools to improve patient, household and community safety, as well as compliance with conditions of treatment, including Patient-Prescriber Agreement (PPA) and risk assessment instruments



[Click here for a complete list of products covered under the ER/LA Opioid Analgesics REMS Program](#)

For additional information about the ER/LA Opioid REMS Program, call 800-503-0784.

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Analgesics Risk Evaluation and Mitigation Strategy

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REMS-Compliant CE for ER/LA Opioid Analgesics

Health care professionals who prescribe ER/LA opioid analgesics have a responsibility to help ensure the safe and effective use of ER/LA opioid analgesics. REMS-compliant training programs will focus on the safe prescribing of ER/LA opioid analgesics.

REMS-compliant training will: (a) be delivered by accredited CE providers; (b) cover all elements of the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics ("FDA Blueprint"); (c) include a knowledge assessment; and (d) be subject to independent audit of content and compliance with applicable accrediting standards.

The FDA has developed core messages to be communicated to prescribers in the [FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics \("FDA Blueprint"\)](#), which will be used by Continuing Education (CE) providers to develop the REMS-compliant training programs.

These core messages include:

- Understand how to assess patients for treatment with ER/LA opioid analgesics.
- Be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics.
- Be knowledgeable about how to manage ongoing therapy with ER/LA opioid analgesics.
- Know how to counsel patients and caregivers about the safe use of ER/LA opioid analgesics, including proper storage and disposal.
- Be familiar with general and product-specific drug information concerning ER/LA opioid analgesics.

The first prescriber REMS-compliant training programs are anticipated to be available by March 1, 2013.

[Click here for a listing of available REMS-compliant training activities supported by educational grants from the ER/LA opioid analgesics companies and offered by accredited CE providers.](#)

Links

[Listing of Accredited CME/CE
REMS-Compliant Activities
Supported by RPC](#) ^{UPDATED}

[FDA Blueprint for Prescriber
Education for Extended-Release
and Long-Acting Opioid Analgesics
\("FDA Blueprint"\)](#)

[If you are a CE provider, click here
for more information](#)

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<h2>ER/LA Opioid Analgesics REMS</h2> <p>The Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy</p>	
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Patient Counseling Document

What is the Patient Counseling Document?

The Patient Counseling Document (PCD) on Extended-Release/Long Acting (ER/LA) Opioid Analgesics is a tool unique to this REMS designed to facilitate important discussions with your patients for whom you select an ER/LA opioid analgesic. The PCD should be provided to and reviewed with the patient and/or their caregiver at the time of prescribing. It contains important safety information about the drug products subject to this REMS and includes space for you to write additional information to help your patients use their ER/LA opioid analgesic safely.

How can I obtain copies of the PCD?

Printed copies of the PCD can be ordered either through an on-line order or via fax. Detailed instructions for both methods of ordering printed copies of the PCD can be found in the PCD Order Form, and an electronic version of the Patient Counseling Document (PCD) is also available for download.

Materials for Download

[Patient Counseling Document \(PCD\) - English](#)

[Patient Counseling Document \(PCD\) - Spanish](#)

[PCD Order Form](#)

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Dear DEA-Registered Prescriber Letter

Click on the letter title below to open a PDF version of that letter.

- [Dear DEA-Registered Prescriber Letter 3 - Announcing REMS approval and REMS-related CME/CE opportunities to newly DEA-registered Schedule II and III Prescribers](#)

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Products covered under the ER/LA Opioid Analgesics REMS Program

Brand Name Products

Trade Name	Generic Name	Company	Contact	Links

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Generic Name Products

Trade Name	Generic Name	Company	Contact	Links

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The RPC attests that the table above will only include products listed in the link titled 'List of approved application numbers and sponsors' on the FDA Approved REMS website.

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Selected Important Safety Information

ABUSE POTENTIAL AND RISK OF LIFE-THREATENING RESPIRATORY DEPRESSION

The branded and generic drug products subject to this REMS include *all*:

- extended-release, oral dosage forms containing
 - hydrocodone,
 - hydromorphone,
 - morphine,
 - oxycodone,
 - oxymorphone, or
 - tapentadol;
- fentanyl and buprenorphine-containing transdermal delivery systems; *and*
- methadone tablets and solutions as well as buprenorphine-containing buccal films that are indicated for use as analgesics.

These drug products will be collectively referred to as Extended-Release and Long-Acting (ER/LA) prescription opioid analgesics.

ER/LA prescription opioid analgesics are opioid agonists and Schedule II or, Schedule III, as is the case with transdermal and buccal film buprenorphines, controlled substances with abuse liabilities similar to other opioid agonists. Schedule II and Schedule III opioid substances have high potential for abuse and risk of fatal overdose due to respiratory depression.

ER/LA opioid analgesics can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing ER/LA opioid analgesics in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse, abuse and addiction.

ER/LA opioid analgesics containing buprenorphine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Extended-release oxycodone (OxyContin) is also indicated in pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent. **ER/LA opioid analgesics are not indicated for acute pain.**

Because of the risks of addiction, abuse and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release formulations, reserve ER/LA opioid analgesics reserved for use in patients for whom alternative treatment options (e.g. non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise be inadequate to provide sufficient management of pain. For some of the ER/LA opioid analgesics, certain strengths, certain daily doses, and in specific indicated patient populations (e.g., pediatric patients) are for use in opioid-tolerant patients only. Consult the individual Full Prescribing Information for the definition of opioid tolerance and dosing instructions for patients. ER/LA opioid analgesics are not intended for acute pain, pain that is mild or moderate, or pain that is expected to persist for an extended period of time, or for use on an as-needed basis.

ER/LA opioid analgesic formulations have product specific dosage and administration instructions. Refer to the individual Full Prescribing Information for specific doses and dosing recommendations.

ER/LA oral dosage forms must be swallowed whole and must not be cut, broken, chewed, crushed, or dissolved. Taking cut, broken, chewed, crushed or dissolved oral dosage forms leads to rapid release and absorption of a potentially fatal dose of the opioid agonist. For patients who have difficulty swallowing their medication whole, certain oral products may be opened and sprinkled on applesauce—refer to the product-specific Full Prescribing Information.

Transdermal dosage forms must not be cut, damaged, chewed, swallowed or used in ways other than indicated since this may cause choking or overdose resulting in death. Avoid direct external heat sources to transdermal application site and surrounding area.

As stated in the **Boxed Warning**, prescribers need to be aware of the following:

- **ER/LA Opioid Analgesics exposes users to risks of addictions, abuse and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing and monitor regularly for development of these behaviors and conditions.**
- **Serious life-threatening or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow ER/LA Opioid Analgesics tablets whole to avoid exposure/ingestion to a potentially fatal dose.**
- **Accidental ingestion of ER/LA Opioid Analgesics, especially in children, can result in fatal overdose.**
- **Prolonged use of ER/LA Opioid Analgesics during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.**
- **Initiation of CYP 3A4 inhibitors (or discontinuation of CYP 3A4 inducers) can result in a fatal overdose.**

ER/LA opioid analgesics are contraindicated in patients with a known hypersensitivity to any of the components of ER/LA opioid analgesics, including the respective active ingredients, or in any situation where opioids are contraindicated; in patients who have significant respiratory depression; in patients who have acute or severe bronchial asthma; or in patients who have or are suspected of having paralytic ileus. **These contraindications are not all-inclusive of those for each individual ER/LA opioid analgesic;** therefore, the Full Prescribing Information for the individual ER/LA opioid analgesics must be consulted.

The concomitant use of ER/LA opioid analgesics containing buprenorphine, fentanyl, methadone, or oxycodone with cytochrome P450 3A4 inhibitors may result in increased opioid plasma concentrations and may cause potentially fatal respiratory depression.

Adverse Reactions

Serious adverse reactions of ER/LA opioid analgesics include life threatening respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, and death.

Accidental exposure/ingestion of ER/LA opioids, especially in children, can result in death.

With methadone, cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. A positive-controlled study of the effects of transdermal buprenorphine on the QTc interval in healthy subjects demonstrated no clinically meaningful effect at a transdermal buprenorphine dose of 10 mcg/hour; however, a transdermal buprenorphine dose of 40 mcg/hour (given as two 20 mcg/hour transdermal buprenorphine systems) was observed to prolong the QTc interval.

The most common adverse reactions of ER/LA opioid analgesics include constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, asthenia, and sweating. Additionally, the following have been reported with transdermal buprenorphine and fentanyl products: application site pruritus, application site erythema, and application site rash. Refer to the individual Full Prescribing Information for all product-specific adverse reactions.

Adverse Event Reporting

Please report all suspected adverse reactions associated with the use of the specific ER/LA opioid analgesic to the appropriate company. You may also report adverse events directly to the FDA's MedWatch Reporting System:

- by calling 1-800-FDA-1088 (1-800-332-1088),
- online at <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm> or
- by mail using the fillable portable document format (PDF) Form FDA 3500, available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf>

Patient Counseling Document and Medication Guide

The Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioids is a tool unique to this REMS designed to facilitate important discussions with your patients and their caregivers for whom you select an ER/LA opioid analgesic. The PCD should be provided to the patient and/or their caregiver at the time of prescribing. It contains important safety information about the drug products subject to this REMS and includes space for you to write additional information to help your patients use their ER/LA opioid analgesic safely.

Patients and their caregivers should be counseled on: the importance of taking these medicines exactly as you prescribe them, the need to store ER/LA opioid analgesics safely and securely—out of the reach of children, pets, and household acquaintances to avoid risks from unintended exposure, the importance of not sharing these medications, even if someone has the same symptoms as the patient, and the proper methods of disposal of unneeded ER/LA opioid analgesics.

It is important that you encourage your patients and their caregivers to read the relevant Medication Guide when they pick up their prescription from the pharmacy. The Medication Guide provides important information on the safe and effective use of the specific ER/LA opioid analgesic prescribed.

ER/LA Opioid Analgesics REMS

The Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy

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Interstitial Popup

The interstitial pop-up is displayed when a website visitor clicks on non-RPC member links on the website pages. The interstitial pop-up is not displayed when a website visitor clicks on the Medication Guides or the U.S. Prescribing Information links on the Products covered under the ER/LA Opioid Analgesics REMS Program page.

Thank you for visiting www.er-la-opioidrems.com.

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Safety Labeling Change Popup

IMPORTANT SAFETY LABEL CHANGES!

Revised Indication:

- For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Revised Warnings:

- ADDICTION, ABUSE and MISUSE
- LIFE-THREATENING RESPIRATORY DEPRESSION
- ACCIDENTAL INGESTION
- CYTOCHROME P450 3A4 INTERACTION.

New Warning:

- NEONATAL OPIOID WITHDRAWAL SYNDROME

Please click on the [U.S. Prescribing Information](#) link for the complete label for each ER/LA opioid drug.

[Continue](#)

APPENDIX 5 DEAR DEA-REGISTERED PRESCRIBER LETTER 3

FDA-Required REMS Program for Serious Drug Risks

Subject: Risk Evaluation and Mitigation Strategy (REMS) for all extended-release/long-acting opioid analgesic drug products due to their risks of misuse, abuse, addiction, and overdose

Dear DEA-Registered Prescriber:

You are receiving this letter because you recently registered with DEA to prescribe Schedule II or III drugs. The purpose of this letter is to inform you about a Risk Evaluation and Mitigation Strategy (REMS) that has been required by the U.S. Food and Drug Administration (FDA) for all extended-release and long-acting (ER/LA) opioid analgesic drug products.

ER/LA opioid analgesics are used for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Because of the risks of addiction, abuse and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release formulations, reserve ER/LA opioid analgesics for use in patients for whom alternative treatment options (e.g. non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.

They can be safe and effective in appropriately selected patients when used as directed. However, opioid analgesics are also associated with serious risks and are at the center of a major public health crisis of increased misuse, abuse, addiction, overdose, and death.

FDA determined that a REMS was necessary to ensure that the benefits of ER/LA opioid analgesics continue to outweigh their risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse. A REMS is a strategy to manage a known or potential serious risk associated with a drug product. In the interest of public health and to minimize the burden on the healthcare delivery system of having multiple unique REMS programs, the pharmaceutical companies subject to this REMS have joined together to implement the REMS for all ER/LA opioid analgesic drug products.

The ER/LA Opioid Analgesic REMS has three principal components:

- a) prescriber training on all ER/LA opioid analgesics,
- b) a *Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics* (PCD), and
- c) a unique Medication Guide for each ER/LA opioid analgesic drug product.

The branded and generic drug products subject to this REMS include *all*:

- extended-release, oral-dosage forms containing
 - hydrocodone,
 - hydromorphone,
 - morphine,
 - oxycodone,
 - oxymorphone, or
 - tapentadol;
- fentanyl and buprenorphine-containing transdermal delivery systems; and
- methadone tablets and solutions that are indicated for use as analgesics.

Prescriber Action

Under the REMS, you are **strongly encouraged** to do **all** of the following:

- **Train (Educate Yourself)** - Complete REMS-compliant training on the ER/LA opioid analgesics offered by an accredited provider of continuing education (CE) for your discipline. *REMS-compliant training* will: (a) be delivered by accredited CE providers; (b) cover all elements of the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics ("FDA Blueprint"); (c) include a knowledge assessment; and (d) be subject to independent audit of content and compliance with applicable accrediting standards.
- **Counsel Your Patients** – Discuss the safe use, serious risks, storage, and disposal of ER/LA opioid analgesics with patients and their caregivers every time you prescribe these medicines. Use the enclosed *Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics* (PCD) to facilitate these discussions.

Prescriber Letter #3

- **Emphasize Patient and Caregiver Understanding of the Medication Guide** - Stress to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an ER/LA opioid analgesic is dispensed to them, as information may have changed.
- **Consider Using Other Tools** - In addition to the PCD, there are other publicly available tools to improve patient, household and community safety when using ER/LA opioid analgesics, as well as compliance with conditions of treatment, including Patient-Prescriber Agreements (PPAs) and risk assessment instruments.

REMS-compliant Training Programs

REMS-compliant training is a critical component of the ER/LA Opioid Analgesics REMS program. REMS-compliant training will focus on the safe prescribing of ER/LA opioid analgesics. The FDA developed core messages to be communicated to prescribers in the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics ("FDA Blueprint"), which is being used by accredited CE providers to develop the REMS-compliant training courses. The Blueprint is available at <http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM277916.pdf>

REMS-compliant training for prescribers includes both general and product-specific drug information, as well as information on weighing the benefits and risks of opioid therapy, appropriate patient selection, managing and monitoring patients, and counseling patients on the safe use of these drugs. In addition, the education includes information on how to recognize evidence of, and the potential for, opioid misuse, abuse, addiction, and overdose. REMS-compliant training may also be offered by academic institutions or learned societies independent of REMS-related funding. We encourage you to successfully complete REMS-compliant training from an accredited CE provider to improve your ability to prescribe these medications more safely.

For a listing of available REMS-compliant training offered by accredited CE providers under the REMS, visit www.ER-LA-opioidREMS.com.

The Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics (PCD)

Enclosed with this letter is the Patient Counseling Document that was developed under the REMS for ER/LA opioid analgesics and designed to assist you in having important conversations with patients for whom you select an ER/LA opioid analgesic. It contains important safety information common to the drug products subject to this REMS, and includes space for you to write additional information to help your patients use their ER/LA opioid analgesic safely. The PCD should be provided to the patient or their caregiver at the time of prescribing. Patients and their caregivers should be counseled on:

- the importance of taking these medicines exactly as you prescribe them,
- the need to store ER/LA opioid analgesics safely and securely – out of the reach of children, pets, and household members– to avoid risks from unintended exposure,
- the importance of not sharing these medications, even if someone has the same symptoms as the patient, *and*
- the proper methods of disposal of unneeded ER/LA opioid analgesics.

You can re-order or print additional copies of the PCD from www.ER-LA-opioidREMS.com.

Adverse Event Reporting

To report all suspected adverse reactions associated with the use of the ER/LA opioid analgesics, contact:

- the pharmaceutical company that markets the specific product, or
- the FDA MedWatch program:
 - by phone at 1-800-FDA-1088 (1-800-332-1088) or
 - online at www.fda.gov/medwatch/report.htm

More information about this REMS can be obtained at: www.ER-LA-opioidREMS.com or by calling the ER/LA Opioid Analgesic REMS Call Center at 1-800-503-0784.

Sincerely,

APPENDIX 6 PATIENT COUNSELING DOCUMENT

Patient Counseling Document (PCD)

Patient Counseling Document on Extended-Release / Long-Acting Opioid Analgesics
Patient Name:
The DOs and DON'Ts of Extended-Release / Long - Acting Opioid Analgesics
DO: <ul style="list-style-type: none">• Read the Medication Guide• Take your medicine exactly as prescribed• Store your medicine away from children and in a safe place• Flush unused medicine down the toilet• Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
Call 911 or your local emergency service right away if: <ul style="list-style-type: none">• You take too much medicine• You have trouble breathing, or shortness of breath• A child has taken this medicine
Talk to your healthcare provider: <ul style="list-style-type: none">• If the dose you are taking does not control your pain• About any side effects you may be having• About all the medicines you take, including over-the-counter medicines, vitamins, and dietary supplements
DON'T: <ul style="list-style-type: none">• Do not give your medicine to others• Do not take medicine unless it was prescribed for you• Do not stop taking your medicine without talking to your healthcare provider• Do not cut, break, chew, crush, dissolve, snort, or inject your medicine. If you cannot swallow your medicine whole, talk to your healthcare provider.• Do not drink alcohol while taking this medicine
For additional information on your medicine go to: dailymed.nlm.nih.gov

Patient Counseling Document on Extended-Release / Long-Acting Opioid Analgesics
Patient Name:
Patient Specific Information
Take this card with you every time you see your healthcare provider and tell him/her: <ul style="list-style-type: none">• Your complete medical and family history, including any history of substance abuse or mental illness• If you are pregnant or are planning to become pregnant• The cause, severity, and nature of your pain• Your treatment goals• All the medicines you take, including over-the-counter (non-prescription) medicines, vitamins, and dietary supplements• Any side effects you may be having
Take your opioid pain medicine exactly as prescribed by your healthcare provider.

<p>Documento de orientación al paciente sobre medicamentos narcóticos para el dolor, también llamados analgésicos opiáceos (<i>opioid analgesics en inglés</i>), de liberación extendida y/o acción prolongada</p>
<p>Nombre del paciente:</p>
<p><u>LO QUE DEBE HACER y NO DEBE HACER</u> con los medicamentos narcóticos para el dolor, también llamados analgésicos opiáceos (<i>opioid analgesics en inglés</i>), de liberación extendida y/o acción prolongada</p>
<p><u>LO QUE DEBE HACER:</u></p> <ul style="list-style-type: none">• Lea la Guía del Medicamento• Use su medicina siguiendo exactamente las instrucciones de como ha sido indicada• Guarde su medicina fuera del alcance de los niños y en un lugar seguro• Arroje la medicina que le ha sobrado en el servicio sanitario/el inodoro/la taza del baño y vacíelo para asegurarse que no queden residuos de la medicina en el mismo• En caso de reacciones a su medicina, comuníquese inmediatamente con su médico o proveedor de salud. Usted tiene la opción de reportar reacciones a su medicina a la FDA al 1-800-FDA-1088
<p><u>Llame inmediatamente al 911 o a su centro/servicio local de emergencia, si:</u></p> <ul style="list-style-type: none">• Tomó demasiada medicina• Siente dificultad al respirar o siente que le falta el aire• Un niño ha tomado la medicina
<p><u>Hable con su médico o proveedor de salud:</u></p> <ul style="list-style-type: none">• Si la dosis recetada no controla su dolor• Sobre cualquier reacción que tenga a su medicina• Acerca de todas las medicinas que está tomando, incluyendo medicinas sin receta médica, vitaminas y suplementos nutricionales
<p><u>LO QUE NO DEBE HACER:</u></p> <ul style="list-style-type: none">• No debe dar su medicina a otras personas• No debe tomar medicinas a menos que se las hayan recetado específicamente a usted• No debe dejar de tomar su medicina sin antes consultar con su médico o proveedor de salud• No debe cortar, moler/triturar, quebrar, disolver, masticar, inhalar ni inyectar su medicina. Si usted no puede tragar/ingerir su medicina entera, comuníquese con su médico o proveedor de salud• No debe tomar bebidas alcohólicas mientras esté tomando esta medicina
<p>Para obtener información adicional sobre su medicina, visite: dailymed.nlm.nih.gov</p>

<p>Documento de orientación al paciente sobre medicamentos narcóticos para el dolor, también llamados analgésicos opiáceos (<i>opioid analgesics en inglés</i>), de liberación extendida y/o acción prolongada</p>
<p>Nombre del paciente:</p>
<p>Información específica del paciente</p>
<p>Lleve estas instrucciones cada vez que visite a su médico o proveedor de salud e infórmele:</p> <ul style="list-style-type: none">• Su historia médica completa y la de su familia, incluyendo cualquier antecedente de abuso de sustancias o enfermedades de salud mental• Si está embarazada o tiene planes de quedar embarazada• La causa, los síntomas y el grado de severidad de su dolor• Los resultados que espera de su tratamiento• Acerca de todas las medicinas que está tomando, incluyendo medicinas sin receta médica, vitaminas y suplementos nutricionales• Sobre cualquier reacción que usted está teniendo a su medicina <p>Tome sus medicamentos narcóticos para el dolor, también llamados analgésicos opiáceos (<i>opioid analgesics en inglés</i>), de liberación extendida y/o acción prolongada exactamente como han sido indicados por su médico o proveedor de salud.</p>

APPENDIX 7 PATIENT SURVEY QUESTIONS

PATIENT SURVEY QUESTION/ITEMS AND PROPORTION ANSWERING CORRECTLY ORDERED HIGH TO LOW

Table 1 Patient Survey Question/Items and Proportion Answering Correctly Ordered High to Low

QUESTION/ITEMS AND CORRECT ANSWERS	% OF PATIENTS THAT ANSWERED CORRECTLY (N=423)
Do not give ER/LA opioid analgesics to other people who have the same condition as you.	98.1
Selling or giving away ER/LA opioid analgesics is against the law.	97.6
Seek emergency medical help for side effects such as trouble breathing, shortness of breath, fast heartbeat, chest pain, or swelling of their face, tongue, or throat after taking or using ER/LA opioid analgesics.	97.4
Talk to a healthcare provider about taking or using more ER/LA opioid analgesics if the current dose doesn't control the pain.	95.7
Overdoses may cause life-threatening breathing problems, respiratory depression, or abnormally slow breathing that can lead to death.	93.1
It is not okay to drink alcohol while taking or using ER/LA opioid analgesics.	93.1
Inform healthcare provider about all the other medications being used.	93.1
Do not throw any unused ER/LA opioid analgesic in the trash.	92.9
A child could die if they take or use the respondent's ER/LA opioid analgesics.	92.9
Do not take more when it is time for the next dose if a dose of ER/LA opioid analgesics was missed. ¹	92.5
Inform healthcare provider about any history of abuse of street or prescription drugs, alcohol addiction, or mental health problems.	90.3
Do not cut ER/LA opioid analgesic patches in half to use less medicine. ²	90.1
Seek emergency medical help for ER/LA opioid analgesic overdose, even if the respondent feels fine.	88.4
Inform healthcare provider about over-the-counter medicines, vitamins, and dietary supplements.	87.2
Talk to a healthcare provider prior to stopping ER/LA opioid analgesics.	84.4
ER/LA opioid analgesics can make you dizzy, lightheaded, or sleepy.	80.9
Do not use a hot tub or sauna while using ER/LA opioid analgesics if pain persists. ²	77.2

QUESTION/ITEMS AND CORRECT ANSWERS	% OF PATIENTS THAT ANSWERED CORRECTLY (N=423)
ER/LA opioid analgesic pills should not be split or crushed if the respondent is having trouble swallowing their medication. ¹	76.1
Do not store ER/LA opioid analgesics in a medicine cabinet with other medications in the household.	70.9
Inform healthcare provider of any fever. ²	70.3
Read the attached MG every time an ER/LA opioid prescription is filled.	54.9
It is okay to drink caffeine while using ER/LA opioid analgesics.	48.9

¹ Survey questions only asked of non-methadone oral drugs only respondents (N = 268)

² Survey questions only asked of patch and no methadone respondents (N = 101)

APPENDIX 8 PRESCRIBER SURVEY QUESTIONS

DISTRIBUTION OF CORRECT SCORES FOR THE QUESTIONS/ITEMS AMONG PRESCRIBERS IN THE PRESCRIBER SURVEY

Table 1 Distribution of Correct Scores for the Questions/Items among Prescribers in the Prescriber Survey

QUESTIONS/ITEMS AND CORRECT ANSWERS	PRESCRIBER SURVEY		
	RECRUITMENT METHOD		OVERALL
	% OF PRESCRIBERS RECRUITED THROUGH CE PROVIDERS THAT ANSWERED CORRECTLY % (N=301)	% OF PRESCRIBERS RECRUITED THROUGH IMS THAT ANSWERED CORRECTLY (N=311)	% OF ALL PRESCRIBERS THAT ANSWERED CORRECTLY (N=612)
Which of the following are important factors to consider when selecting an initial dose of an ER/LA opioid analgesic? (General medical status of the patient-Yes)	99.7	100.0	99.8
How should prescribers reassess patients maintained on ER/LA opioid analgesics during follow-up visits? (Evaluate pain control and functional improvement.-True)	99.7	100.0	99.8
Which of the following can potentiate the risk of a serious overdose or death when taken with an ER/LA opioid analgesic? (Alcohol- Yes)	99.7	99.7	99.7
How should prescribers reassess patients maintained on ER/LA opioid analgesics during follow-up visits? (Periodically assess the continued need for opioid analgesics.-True)	99.7	99.4	99.5
Which of the following can potentiate the risk of a serious overdose or death when taken with an ER/LA opioid analgesic? (Illegal drugs- Yes)	99.7	99.4	99.5
Which of the following can potentiate the risk of a serious overdose or death when taken with an ER/LA opioid analgesic? (Sedative hypnotics-Yes)	99.7	97.7	98.7
Which of the following are important factors to consider when selecting an initial dose of an ER/LA opioid analgesic? (Concurrent medication- Yes)	99.3	99.7	99.5
How should prescribers reassess patients maintained on ER/LA opioid analgesics during follow-up visits? (Evaluate for changes in the patient's medical condition.-True)	99.3	99.4	99.3

QUESTIONS/ITEMS AND CORRECT ANSWERS	PRESCRIBER SURVEY		
	RECRUITMENT METHOD		OVERALL
	% OF PRESCRIBERS RECRUITED THROUGH CE PROVIDERS THAT ANSWERED CORRECTLY % (N=301)	% OF PRESCRIBERS RECRUITED THROUGH IMS THAT ANSWERED CORRECTLY (N=311)	% OF ALL PRESCRIBERS THAT ANSWERED CORRECTLY (N=612)
Which of the following are risk factors for opioid abuse? (A personal history of past or current alcohol or drug abuse)	99.3	98.7	99
When counseling patients about the safe use of ER/LA opioid analgesics, prescribers should inform patients of the following. (The importance of adhering to a dosage regimen as prescribed)	99.0	98.7	98.9
When counseling patients about the safe use of ER/LA opioid analgesics, prescribers should inform patients of the following. (It is illegal to sell or give away ER/LA opioid analgesics)	99.0	98.1	98.5
PPAs may include commitments regarding follow-up visits, monitoring for misuse, and safeguarding the medication. (True)	98.7	99.0	98.9
Which of the following are important factors to consider when selecting an initial dose of an ER/LA opioid analgesic? (The patient's degree of opioid experience- Yes)	98.7	98.7	98.7
Central nervous system depressants can have a potentiating effect on the sedation and respiratory depression caused by opioids. (True)	98.7	98.1	98.4
Which of the following are the warning signs and symptoms of respiratory depression from ER/LA opioid analgesics? (Decreased rate of respiration)	98.7	97.1	97.9
How should prescribers monitor patient adherence to the treatment plan, especially with regard to misuse and abuse? (Document any 'drug seeking' behavior)	97.7	97.4	97.5
All ER/LA opioids reach steady state plasma concentration at the same time. (False)	97.7	92.9	95.3
PPAs can include information about treatment goals, risks, and safe use of the ER/LA opioid. (True)	97.3	97.1	97.2

QUESTIONS/ITEMS AND CORRECT ANSWERS	PRESCRIBER SURVEY		
	RECRUITMENT METHOD		OVERALL
	% OF PRESCRIBERS RECRUITED THROUGH CE PROVIDERS THAT ANSWERED CORRECTLY % (N=301)	% OF PRESCRIBERS RECRUITED THROUGH IMS THAT ANSWERED CORRECTLY (N=311)	% OF ALL PRESCRIBERS THAT ANSWERED CORRECTLY (N=612)
When evaluating patients for treatment with ER/LA opioid analgesics, which of the following are important risks to consider? The patient's current opioid tolerance Respiratory depression, particularly in elderly or debilitated patients Interactions with other medications the patient may be taking Inadvertent exposure, especially in children present in the home all of the above	97.3	93.6	95.4
How should prescribers monitor patient adherence to the treatment plan, especially with regard to misuse and abuse? (Periodically re-evaluate therapy)	97.0	97.4	97.2
Federal regulations stipulate which of the following when writing a prescription for an ER/LA opioid? (Refills for an ER/LA opioid prescription can be phoned into a pharmacy.- False)	96.7	95.8	96.2
How should prescribers monitor patient adherence to the treatment plan, especially with regard to misuse and abuse? (Utilize state Prescription Drug Monitoring Programs)	96.7	93.2	94.9
It is not necessary to re-evaluate a patient's underlying medical condition if the clinical presentation changes over time. (False)	96.3	95.5	95.9
After thorough clinical evaluation, it is appropriate for prescribers to refer a patient at high risk for drug abuse to a pain management specialist. (True)	96.0	95.8	95.9
PPAs are signed by both prescriber and patient at the time an opioid is initially prescribed. (True)	95.7	94.2	94.9

QUESTIONS/ITEMS AND CORRECT ANSWERS	PRESCRIBER SURVEY		
	RECRUITMENT METHOD		OVERALL
	% OF PRESCRIBERS RECRUITED THROUGH CE PROVIDERS THAT ANSWERED CORRECTLY % (N=301)	% OF PRESCRIBERS RECRUITED THROUGH IMS THAT ANSWERED CORRECTLY (N=311)	% OF ALL PRESCRIBERS THAT ANSWERED CORRECTLY (N=612)
How should prescribers monitor patient adherence to the treatment plan, especially with regard to misuse and abuse? (Use drug testing for both screening and confirmatory tests)	95.7	91.6	93.6
Which of the following can potentiate the risk of a serious overdose or death when taken with an ER/LA opioid analgesic? (Anxiolytics- Yes)	95.0	91.0	93.0
Concomitant drugs that act as inhibitors or inducers of various cytochrome P450 enzymes can result in higher or lower than expected blood levels of some opioids. (true)	94.7	90.4	92.5
Which of the following are the warning signs and symptoms of respiratory depression from ER/LA opioid analgesics? (Profound sedation)	94.4	94.5	94.4
A patient should not cut an extended release tablet in half to reduce the dose. (True)	94.4	93.6	94.0
When starting a patient who is currently taking a sedative on an ER/LA opioid analgesic, reduce the dose of one or both. (true)	94.4	91.3	92.8
Fatal respiratory depression may occur, with the highest risk at initiation and when the dose is increased (True)	94.4	90.7	92.5
The underlying pharmacokinetic and pharmacodynamic mechanisms are the same for all ER/LA opioids. (False)	93.7	88.7	91.2
Some opioids can increase the QTc interval. (True)	92.7	86.8	89.7
Federal regulations stipulate which of the following when writing a prescription for an ER/LA opioid? (Any prescription for a Schedule II product can be faxed to the pharmacy.-False)	92.0	92.6	92.3
Which of the following are the warning signs and symptoms of respiratory depression from ER/LA opioid analgesics? (Reduced urge to breathe)	91.7	91.0	91.3

QUESTIONS/ITEMS AND CORRECT ANSWERS	PRESCRIBER SURVEY		
	RECRUITMENT METHOD		OVERALL
	% OF PRESCRIBERS RECRUITED THROUGH CE PROVIDERS THAT ANSWERED CORRECTLY % (N=301)	% OF PRESCRIBERS RECRUITED THROUGH IMS THAT ANSWERED CORRECTLY (N=311)	% OF ALL PRESCRIBERS THAT ANSWERED CORRECTLY (N=612)
Chewing a solid, oral dosage form of an ER/LA opioid analgesic can result in rapid release and absorption of a potentially fatal dose of opioid. (True)	91.7	85.9	88.7
The Controlled Substances Act includes ER/LA opioids because of the potential risk for abuse. (True)	90.7	91.6	91.2
Federal regulations stipulate which of the following when writing a prescription for an ER/LA opioid? (Refills are not allowed for Schedule II products.- True)	90.4	87.5	88.9
Which of the following should prescribers do when initiating a patient on ER/LA opioid analgesics? (Titrate doses based on efficacy and tolerability)	90.0	86.2	88.1
How should prescribers monitor patient adherence to the treatment plan, especially with regard to misuse and abuse?(Perform medication reconciliation by counting leftover drug supplies)	90.0	84.9	87.4
For methadone, the peak of respiratory depression can occur later and can persist longer than the analgesic effects. (True)	89.7	81.4	85.5
The most common long-term side effects of ER/LA opioid analgesics is constipation. (True)	86.7	89.4	88.1
For which of the following conditions are ER/LA opioid analgesics indicated? (Chronic non-cancer pain)	86.4	86.2	86.3
A patient with a history of substance abuse must not be prescribed an ER/LA opioid analgesic. (False)	85.7	80.1	82.8
Which of the following are risk factors for opioid abuse? (A personal history of psychiatric disorders)	85.4	84.6	85
Which of the following are risk factors for opioid abuse? (A family history of illicit drug use or alcohol abuse)	85.0	86.5	85.8

QUESTIONS/ITEMS AND CORRECT ANSWERS	PRESCRIBER SURVEY		
	RECRUITMENT METHOD		OVERALL
	% OF PRESCRIBERS RECRUITED THROUGH CE PROVIDERS THAT ANSWERED CORRECTLY % (N=301)	% OF PRESCRIBERS RECRUITED THROUGH IMS THAT ANSWERED CORRECTLY (N=311)	% OF ALL PRESCRIBERS THAT ANSWERED CORRECTLY (N=612)
Which of the following are the warning signs and symptoms of respiratory depression from ER/LA opioid analgesics? (“Sighing” pattern of breathing)	84.1	83.9	84.0
Monoamine oxidase inhibitors (MAOIs) are the preferred antidepressants for use with ER/LA opioid analgesics. (False)	83.7	78.5	81.0
Patients who are not opioid tolerant can initiate opioid therapy with any type of ER/LA opioid analgesic. (False)	82.4	74.3	78.3
Some ER opioid formulations may rapidly release opioid (dose dump) when exposed to alcohol. (True)	81.7	62.7	72.1
Conversion of patients to or from methadone using equianalgesic tables can result in overdose and death. (True)	81.1	68.5	74.7
For some ER products, patients must be opioid tolerant before using certain strengths or certain daily doses. (True)	78.7	75.2	77.0
Which of the following should prescribers do when initiating a patient on ER/LA opioid analgesics? (Consider a rescue medication for break-through pain)	75.7	74.3	75.0
ER/LA opioid analgesic transdermal patches that have a matrix formulation may be cut prior to use. (False)	74.1	76.2	75.2
Which of the following can potentiate the risk of a serious overdose or death when taken with an ER/LA opioid analgesic? (Caffeine- No)	73.1	63.3	68.1
Dispose of transdermal patches by cutting into small pieces and throwing in the trash. (False)	72.8	65.0	68.8
Patients considered opioid-tolerant are those (Who are taking at least 60 mg oral morphine/day or an equianalgesic dose of another opioid for one week or longer)	71.4	66.6	69.0
PPAs are a legal requirement. (False)	64.1	61.4	62.7

QUESTIONS/ITEMS AND CORRECT ANSWERS	PRESCRIBER SURVEY		
	RECRUITMENT METHOD		OVERALL
	% OF PRESCRIBERS RECRUITED THROUGH CE PROVIDERS THAT ANSWERED CORRECTLY % (N=301)	% OF PRESCRIBERS RECRUITED THROUGH IMS THAT ANSWERED CORRECTLY (N=311)	% OF ALL PRESCRIBERS THAT ANSWERED CORRECTLY (N=612)
Patients must be opioid tolerant before using any strength of transdermal fentanyl or ER hydromorphone. (True)	55.8	45.7	50.7
What should be done if a patient treated with a transdermal opioid develops a high fever? (Monitor the patient closely for opioid side effects and reduce the dose of the patch if necessary.)	54.8	54.3	54.6
What is the recommended way to safely convert an opioid-tolerant patient from a parenteral opioid, such as morphine or meperidine, to an oral extended-release opioid, such as oxycodone or oxymorphone? (Start with 50% of an equianalgesic dose)	47.5	39.5	43.5
A patient is experiencing back pain and is being treated with a transdermal opioid product. After a fall at home, he would like to soak in a hot tub to relieve some of the muscle soreness. What is your advice? (Do not soak in the hot tub since heat can affect the absorption of the opioid.)	47.2	44.4	45.8
How should prescribers reassess patients maintained on ER/LA opioid analgesics during follow-up visits? (Perform a comprehensive physical examination at each visit.-False)	46.8	42.4	44.6
Patients considered opioid-tolerant are those (Who are taking 25 mcg/hour transdermal fentanyl for at least 7 days)	35.2	36.7	35.9
Federal regulations stipulate which of the following when writing a prescription for an ER/LA opioid? (There are specific federal limits to quantities of ER/LA opioids dispensed via a prescription.-False)	30.9	25.1	27.9
Which of the following are important factors to consider when selecting an initial dose of an ER/LA opioid analgesic? (The patient's family history of mental illness-No)	29.2	29.6	29.4

QUESTIONS/ITEMS AND CORRECT ANSWERS	PRESCRIBER SURVEY		
	RECRUITMENT METHOD		OVERALL
	% OF PRESCRIBERS RECRUITED THROUGH CE PROVIDERS THAT ANSWERED CORRECTLY % (N=301)	% OF PRESCRIBERS RECRUITED THROUGH IMS THAT ANSWERED CORRECTLY (N=311)	% OF ALL PRESCRIBERS THAT ANSWERED CORRECTLY (N=612)
How should prescribers reassess patients maintained on ER/LA opioid analgesics during follow-up visits? (Systematically perform drug screening for all patients.- False)	18.6	21.5	20.1

APPENDIX 9 LONG-TERM EVALUATION SURVEY QUESTIONS

INDIVIDUAL BLUEPRINT MESSAGE QUESTION/ITEMS AND CORRECT ANSWERS ORDERED HIGH TO LOW SCORE FOR THE LTE SURVEY

Table 1 Individual Blueprint Message Question/Items and Correct Answers Ordered High to Low Score for the LTE Survey

QUESTION/ITEMS AND CORRECT ANSWERS	% of All Prescribers that Answered Correctly (N=328)
Which of the following can potentiate the risk of a serious overdose or death when taken with an ER/LA opioid analgesic? (Illegal drugs-YES)	100
Which of the following can potentiate the risk of a serious overdose or death when taken with an ER/LA opioid analgesic? (Sedative hypnotics-YES)	99.7
Which of the following can potentiate the risk of a serious overdose or death when taken with an ER/LA opioid analgesic? (Alcohol -YES)	99.7
Central nervous system depressants, such as benzodiazepines, can have a potentiating effect on the sedation and respiratory depression caused by opioids. (TRUE)	99.4
Which of the following are risk factors for opioid abuse? Select all that apply. (A personal history of past or current alcohol or drug abuse.)	98.8
Case Scenario Elliot: Which of the following would be useful in further assessing possible abuse? Select all that apply. (Check the state Prescription Monitoring Program database for Elliot's prescription history (where available).)	98.8
How should prescribers monitor patient adherence to the treatment plan, especially with regard to misuse and abuse? Select all that apply. (Utilize state Prescription Drug Monitoring Programs)	98.2
How should prescribers monitor patient adherence to the treatment plan, especially with regard to misuse and abuse? Select all that apply. (Periodically re-evaluate therapy)	98.2
Case Scenario Lynette: Lynette reports that she keeps her medications at home in her purse or desk drawer, which is unlocked. On further questioning about her household, she mentions that her neighbor's teenage son has been helping her with her cat boxes for the last four months. Which of the following would be the most appropriate step(s)? Select all that apply. (Recommend storing medication in a safe and secure place away from children, family members, and visitors.)	98.2
Case Scenario Warren: Which of the following would be important steps prior to starting Warren on a trial of ER/LA opioid analgesic medication? Select all that apply. (Complete a comprehensive pain history and physical examination)	97.6
How should prescribers monitor patient adherence to the treatment plan, especially with regard to misuse and abuse? Select all that apply. (Document any "drug seeking" behavior)	97.3
Case Scenario Danielle: With this patient without clinical evidence of addictive illness, interim management at each office visit would include: (Pain control and functional improvement evaluation)	97.3
After thorough clinical evaluation, it is appropriate for prescribers to refer a patient at high risk for drug abuse to a pain management specialist. (TRUE)	97.3
Which of the following can potentiate the risk of a serious overdose or death when taken with an ER/LA opioid analgesic? (Anxiolytics-YES)	96.6

QUESTION/ITEMS AND CORRECT ANSWERS	% of All Prescribers that Answered Correctly (N=328)
How should prescribers monitor patient adherence to the treatment plan, especially with regard to misuse and abuse? Select all that apply. (Use urine drug testing for both screening and confirmatory tests)	96.3
Case Scenario Danielle: With this patient without clinical evidence of addictive illness, interim management at each office visit would include: (Asking about changes in medications or the patient's medical condition)	96.3
Case Scenario Nancy: In managing Nancy's treatment, you decide to rotate her medication to oxymorphone ER. The equianalgesic table indicates that the equianalgesic dose for oral oxycodone 25 mg/per day (current opioid) is 12.5 mg per day oral oxymorphone ER (new opioid). When you initiate the oxymorphone ER, which of the following instructions do you need to give Nancy? Select all that apply. (Don't drink alcohol while taking the oxymorphone ER)	95.7
Case Scenario Elliot: Which of the following factors in Elliot's history raise your assessment of his risk for opioid abuse and misuse? Select all that apply. (Request for specific drugs)	95.7
Case Scenario Elliot: Which of the following would be useful in further assessing possible abuse? Select all that apply. (Use a risk assessment tool, such as the ORT (Opioid Risk Tool) to find out about mood swings, use of illegal substances, or history of legal problems.)	95.7
When initiating an ER/LA opioid analgesic in a patient who is currently taking a sedative, reduce the dose of the opioid and/or sedative. (TRUE)	95.7
Case Scenario Lynette: Lynette reports that she keeps her medications at home in her purse or desk drawer, which is unlocked. On further questioning about her household, she mentions that her neighbor's teenage son has been helping her with her cat boxes for the last four months. Which of the following would be the most appropriate step(s)? Select all that apply. (Stress the safety concerns when ER/LA opioid analgesics are taken by someone for whom they are not prescribed)	95.1
Fatal respiratory depression may occur with the highest risk at initiation and when the dose is increased. (TRUE)	95.1
Case Scenario Fred: Fred is an 89-year-old obese man with severe lumbar disc degeneration treated for over 10 years with daily acetaminophen/oxycodone 5/325 mg every 6 hours. He has significantly increased back and leg pain after sliding off his chair onto the floor. The pain keeps him awake at night and now he wants "something that works better". You complete a thorough physical examination and abuse risk evaluation. You decide to start Fred on a trial of a daily ER/LA opioid analgesic. Which of the following statements are appropriate patient education and counseling information for you to give him(select all that apply): (Discuss risks of long-term opioid use including constipation and Fred or his caregivers should let you know if he has any bowel issues)	94.8
Concomitant drugs that act as inhibitors or inducers of various cytochrome P450 enzymes can result in higher or lower than expected blood levels of some opioids. (TRUE)	94.8
Case Scenario Lynette: Which of the following steps are most appropriate? Select all that apply. (Ask where she keeps her medications and how she secures them)	94.5

QUESTION/ITEMS AND CORRECT ANSWERS	% of All Prescribers that Answered Correctly (N=328)
Case Scenario Fred: Fred is an 89-year-old obese man with severe lumbar disc degeneration treated for over 10 years with daily acetaminophen/oxycodone 5/325 mg every 6 hours. He has significantly increased back and leg pain after sliding off his chair onto the floor. The pain keeps him awake at night and now he wants “something that works better”. You complete a thorough physical examination and abuse risk evaluation. You decide to start Fred on a trial of a daily ER/LA opioid analgesic. Which of the following statements are appropriate patient education and counseling information for you to give him(select all that apply): (The treatment goal: Control the pain so he can sleep at night and walk with assistance during the day; evaluate with physical examination and information from wife and family)	94.2
How should prescribers monitor patient adherence to the treatment plan, especially with regard to misuse and abuse? Select all that apply. (Perform medication reconciliation by counting leftover drug supplies)	93
Case Scenario Danielle: With this patient without clinical evidence of addictive illness, interim management at each office visit would include (select all that apply): (Assessment of the continued need for ER/LA opioid analgesics)	92.4
ER/LA opioid analgesic transdermal patches may be cut prior to use. (FALSE)	92.1
Case Scenario Elliot: You find out that Elliot has received 9 prescriptions for opioids from 4 different physicians, using 5 pharmacies in the past 3 months; some insurance paid for, some he paid for with cash. The urine drug screen is positive for THC, hydromorphone, and oxycodone metabolites. The best option would be to (select all that apply): (Not write a prescription today, as he lied about prescribers and drug use. His possible untreated addiction or abuse prevents you from addressing his pain. Refer to a pain management physician with addiction expertise.)	91.2
A patient should be told not to cut an extended release tablet in half to reduce the dose. (TRUE)	91.2
Case Scenario Elliot: Which of the following would be useful in further assessing possible abuse? Select all that apply. (Ask Elliot to provide a urine sample for drug screen.)	90.9
A patient with a history of substance abuse must not be prescribed an ER/LA opioid analgesic. (FALSE)	89.3
Case Scenario Elliot: Which of the following would be useful in further assessing possible abuse? Select all that apply. (Ask for the contact information for his primary care physician.)	88.7
Which of the following are risk factors for opioid abuse? Select all that apply. (A family history of illicit drug use or alcohol abuse.)	88.4
Case Scenario Warren: Which of the following would be important steps prior to starting Warren on a trial of ER/LA opioid analgesic medication? Select all that apply. (Obtain a signed Patient Prescriber Agreement for opioids)	88.4
Monoamine oxidase inhibitors (MAOIs) are the preferred antidepressants for use with ER/LA opioid analgesics. (FALSE)	87.8
For methadone, the peak of respiratory depression can occur later and can persist longer than the analgesic effects. (TRUE)	87.2

QUESTION/ITEMS AND CORRECT ANSWERS	% of All Prescribers that Answered Correctly (N=328)
Case Scenario Danielle: With this patient without clinical evidence of addictive illness, interim management at each office visit would include: (Checking the state Prescription Monitoring Program database for prescription history (where available))	86.3
Case Scenario Danielle: Danielle's urine drug screen comes back strongly positive for cocaine metabolites and negative for hydrocodone metabolites. When confronted, she admits to using cocaine, but says it was several weeks ago and requests another screen on the spot, which gives the same results. Finding only cocaine metabolites in the urine drug screen of two separate samples, without metabolites of the prescribed opioid suggests which of the following? Select the one best response. (Diversion of prescribed opioid)	85.7
Which of the following are risk factors for opioid abuse? Select all that apply. (A personal history of psychiatric disorders)	85.4
For which of the following conditions are ER/LA opioid analgesics indicated? Select all that apply. (Chronic non-cancer pain)	85.4
Case Scenario Elliot: Which of the following would be useful in further assessing possible abuse? Select all that apply. (Ask Elliot about his family's use of drugs and alcohol.)	85.4
Case Scenario Nancy: In managing Nancy's treatment, you decide to rotate her medication to oxymorphone ER. The equianalgesic table indicates that the equianalgesic dose for oral oxycodone 25 mg/per day (current opioid) is 12.5 mg per day oral oxymorphone ER (new opioid). When you initiate the oxymorphone ER, which of the following instructions do you need to give Nancy? Select all that apply. (Take oxymorphone ER tablets whole with enough water to swallow them.)	84.5
Some ER opioid formulations may rapidly release opioid (dose dump) when taken with alcohol. (TRUE)	81.4
Case Scenario Lynette: Which of the following steps are most appropriate? Select all that apply. (Collect a sample for urine drug screen)	79.9
Which of the following should prescribers do when initiating a patient on ER/LA opioid analgesics? Select all that apply. (Titrate doses based on efficacy and tolerability as indicated in the product label.)	77.7
Which of the following should prescribers do when initiating a patient on ER/LA opioid analgesics? Select all that apply. (Consider a rescue medication for break-through pain)	76.5
Patients who are not opioid tolerant can initiate opioid therapy with any type of ER/LA opioid analgesic. (FALSE)	74.7
Conversion of patients to or from methadone using equianalgesic tables can result in overdose and death. (TRUE)	74.1
Patients considered opioid-tolerant are those (select all that apply): (Who are taking at least 60 mg oral morphine/day or an equianalgesic dose of another opioid for one week or longer)	73.2
Which of the following can potentiate the risk of a serious overdose or death when taken with an ER/LA opioid analgesic? (Caffeine-NO)	72.6

QUESTION/ITEMS AND CORRECT ANSWERS	% of All Prescribers that Answered Correctly (N=328)
Case Scenario Warren: Which of the following would be important steps prior to starting Warren on a trial of ER/LA opioid analgesic medication? Select all that apply. (Obtain a comprehensive urine drug screen.)	71.6
Dispose of transdermal patches by cutting into small pieces and throwing in the trash. (FALSE)	69.8
Case Scenario Nancy: Which of the following opioids should be avoided for her pain management? Select all that apply. (Dolophine® (methadone hydrochloride))	67.4
Case Scenario Roberta: Which of the following would be the most appropriate step? Select the one best response. (Tell her you will not prescribe ER/LA opioid analgesics for her.)	62.2
Case Scenario Nancy: In managing Nancy's treatment, you decide to rotate her medication to oxymorphone ER. The equianalgesic table indicates that the equianalgesic dose for oral oxycodone 25 mg/per day (current opioid) is 12.5 mg per day oral oxymorphone ER (new opioid). The most prudent course of action is (select the one best response): (Reduce the starting dose of oxymorphone ER (new opioid) by 25% to 50%.)	58.5
Case Scenario Elliot: Which of the following factors in Elliot's history raise your assessment of his risk for opioid abuse and misuse? Select all that apply. (Cigarette smoking)	54
What should be done if a patient treated with a transdermal opioid develops a high fever? Select the one best response. (Monitor the patient closely for opioid side effects and reduce the dose of the patch if necessary)	51.5
Case Scenario Elliot: Which of the following factors in Elliot's history raise your assessment of his risk for opioid abuse and misuse? Select all that apply. (27 years old)	49.4
Case Scenario Elliot: Which of the following factors in Elliot's history raise your assessment of his risk for opioid abuse and misuse? Select all that apply. (Male gender)	42.1
Patients considered opioid-tolerant are those (select all that apply): (Who are using 25 mcg/hour transdermal fentanyl for at least 7 days.)	40.2
Case Scenario Nancy: Which of the following opioids should be avoided for her pain management? Select all that apply. (Butrans® (buprenorphine transdermal system))	34.1
Case Scenario Nancy: You decide to give Nancy a 5-day trial of immediate-release oxycodone, 5 mg every 6 hours and 1 extra 5 mg dose at bedtime (25 mg/day total). During that time, her pain was not well controlled and she frequently had breakthrough pain. She says she does not like taking a lot of pills. Starting which of the following would be appropriate (select all that apply): (Avinza® (morphine sulfate ER), 45 mg once a day)	28
Case Scenario Nancy: You decide to give Nancy a 5-day trial of immediate-release oxycodone, 5 mg every 6 hours and 1 extra 5 mg dose at bedtime (25 mg/day total). During that time, her pain was not well controlled and she frequently had breakthrough pain. She says she does not like taking a lot of pills. Starting which of the following would be appropriate (select all that apply): (Nucynta® ER (tapentadol), 50 mg twice a day.)	27.4

APPENDIX 10 RADARS[®] SYSTEM SUPPLEMENT

RADARS® System Programs Supplement

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General Description of RADARS® System

The Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System is a nationwide postmarketing surveillance system that collects product- and geographically-specific data on misuse, abuse, and diversion of prescription drugs. The RADARS System is comprised of the following core programs, each run independently by their respective principal investigators: Poison Center Program, Opioid Treatment Program, Survey of Key Informants' Patients Program, Drug Diversion Program, College Survey Program, StreetRx Program, and Web Monitoring Program.

Drugs affecting the central nervous system form a unique group of products for surveillance because they are often misused, abused, and diverted. These medications include opioid analgesics, stimulants, sedative-hypnotics, muscle relaxants, and anticonvulsants, among others. Misuse, abuse, and diversion of these products are difficult to monitor because the offender often attempts to conceal their use of the drug. The phases of drug abuse and addiction include opportunity and initial use, which may develop into chronic use, physical dependence as well as addiction in some cases. The RADARS System utilizes a mosaic strategy to detect misuse, abuse, and diversion at all phases of the spectrum of abuse and ultimate addiction. Data from the seven programs are interpreted together to provide a more complete picture of a drug's misuse, abuse, and diversion.

The list of drugs covered by the RADARS System includes the major opioids and stimulants, as well as other prescription medications and illicit drugs:

1. Opioid medications
 - a. Buprenorphine
 - b. Fentanyl
 - c. Hydrocodone
 - d. Hydromorphone
 - e. Methadone
 - f. Morphine
 - g. Oxycodone
 - h. Oxymorphone
 - i. Sufentanil
 - j. Tapentadol
 - k. Tramadol
2. Stimulants
 - a. Methylphenidate
 - b. Mixed amphetamines

Selected opioids are not included (butorphanol, codeine, nalbuphine, pentazocine).

The RADARS System is owned and operated by Rocky Mountain Poison & Drug Center, a department of the Denver Health and Hospital Authority – the public hospital for City and County of Denver, Colorado. The RADARS System is organized as a series of methodologically independent programs that report to the central site, Rocky Mountain Poison & Drug Center. The RADARS System is advised by a Scientific Advisory Board that is comprised of the Principal

Investigator of each Program as well as national experts in law enforcement, substance abuse, statistical analysis, and epidemiology. Current members of the advisory board:

- John J. Burke, President, Pharmaceutical Diversion Education, Inc.
- Theodore J. Cicero, PhD, Professor of Psychiatry, Anatomy and Neurobiology and Vice Chairman for Research, Department of Psychiatry, Washington University in St. Louis
- Richard C. Dart, MD, PhD, Executive Director of the RADARS System and Director of the Rocky Mountain Poison & Drug Center, Denver Health and Hospital Authority
- Nabarun Dasgupta, MPH, PhD, Chief Product Officer, Epidemico, Inc.
- Herbert D. Kleber, MD, Professor of Psychiatry and Director of the Division on Substance Abuse, Columbia University College of Physicians and Surgeons
- Steven P. Kurtz, PhD, Professor and Director, Center for Applied Research on Substance Use and Health Disparities, Nova Southeastern University
- Mark W. Parrino, MPA, President, American Association for the Treatment of Opioid Dependence
- Sidney H. Schnoll, MD, PhD, Vice President, Pharmaceutical Risk Management Services, PinneyAssociates
- George E. Woody, MD, Professor of Psychiatry, Perelman School of Medicine, University of Pennsylvania.

The RADARS System is supported by subscriptions from pharmaceutical manufacturers for surveillance, research, and reporting services. The RADARS System retains exclusive ownership of all surveillance data, databases, and systems. By contract, a subscriber does not have access to the database. A subscriber may use RADARS System reports in the development in scientific publications, but these materials must be submitted for review by the RADARS System for content accuracy before publication.

Overview of Quality Control Procedures

The aggregation of data from the individual surveillance programs comprises the central database from which standard RADARS System analyses are performed. These processes are subject to stringent document development and change control procedures including:

- Standard Operating Procedures (SOPs) for all programs
- Quality control steps including data entry verification, data validation, data verification, and final report verification
- Database controls including validation, database backup and disaster recovery processes, and audit trails
- Electronic systems controls including security and data transmission
- Corrective action processes
- Quality audits and monitoring, including database quality audits, monitoring visits at Program sites, internal audits, and contractor audits
- Training program and documentation for all RADARS System staff
- Central database compliance with 21 CFR part 11

Data Management and Statistical Analysis of RADARS System Data

The goal is to represent rates of misuse, abuse, and diversion throughout the United States. RADARS System Programs do not try to estimate prevalence, but instead show trends in misuse, abuse, and diversion by drug and region over time.

Each principal investigator retains control of the data from their program. Specific data fields from each program are uploaded to the central database housed at Rocky Mountain Poison & Drug Center. In each of the programs, the numerator represents the number of mentions of the defined case reported to that program. The specific definition of a case for each program is provided in the Supplement Tables 1 - 7.

Using the numerators from each program, rates are calculated using a variety of denominators depending on the question to be answered. For example, a population rate of misuse, abuse, and diversion is calculated using data from the United States Census Bureau. The denominator for each program is generated by using the sum of the population residing within ZIP codes covered by each program. While geographical coverage in each of the programs has varied slightly over the study period, these variations have been accounted for by generating rates using 3-digit ZIP codes to limit the denominator to covered areas in all analyses. Analysis can be performed to the level of 3-digit ZIP code and individual product or formulation.

To adjust for drug utilization, rates of misuse, abuse, and diversion can be calculated using data from IMS Government Solutions, Inc., a subsidiary of IMS Health, Inc. Measures of drug utilization include unique recipients of dispensed drugs (URDD), prescriptions dispensed, dosage units dispensed, and milligrams dispensed. The denominator used to represent drug utilization is determined by the purpose of the analysis or research question. In some instances, rates are generated by using more than one measure of drug utilization as they provide different information. For instance, if the purpose is to understand abuse based upon the number of people who have a prescription, then URDD would be an appropriate denominator. If the purpose is to understand abuse based upon the availability of a drug's dosage units dispensed (e.g. patches), then dosage units dispensed would be an appropriate denominator. As with the population rates, the denominator for each program is generated by using the sum of the drug utilization measure for only the 3-digit ZIP codes covered by each program.

Many variables can be assessed including the effects of a specific drug formulation, route of abuse, source of drug used for abuse, street cost of drug, outcome of the event, concomitantly abused drugs, and many others.

Data from RADARS System Programs have been published and compared to other sources. Selected validation analyses and other publications:

Common to all RADARS System Programs

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Poison Center Program

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in the United States using both population and drug availability rates.

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Table S1. Poison Center Program

The Poison Center Program records the specific prescription opioids and stimulants involved in poison center cases.

Principal investigator	Richard C. Dart, MD, PhD Executive Director of the RADARS System and Director of the Rocky Mountain Poison & Drug Center, Denver Health and Hospital Authority Professor, University of Colorado School of Medicine
Respondents	Participating poison centers including urban, suburban, and rural regions
Period of operation	2003 to date
Definition of case	Intentional Abuse: An exposure resulting from the intentional improper or incorrect use of a substance where the person was likely attempting to gain a high, euphoric effect, or some other psychotropic effect Intentional Misuse: An exposure resulting from the intentional improper or incorrect use for reasons other than the pursuit of a psychotropic effect
Population studied	General population seeking health care advice following an exposure to a drug
Coverage in 2015	Figure S2: 50 of the 55 poison centers in the United States, which includes 877 of the approximately 900 3-digit ZIP codes in the United States and corresponds to 94.3% of the United States population
Number of cases	
2015–Q4	7,882 Intentional Exposure* cases involving 8,640 mentions of an opioid analgesic 1,147 Intentional Abuse Exposure** cases involving 1,273 mentions of an opioid analgesic
2003–2015	353,148 Intentional Exposure cases involving 387,268 mention of an opioid analgesic 57,988 Intentional Abuse Exposure cases involving 64,494 mentions of an opioid analgesic
Data collection	Each contact with a poison center is managed by a specially trained nurse, pharmacist or health care worker. Most personnel have passed a national certifying exam. If the patient goes to a health care facility, nearly all cases are monitored for outcome. Case data (demographics, exposure characteristics, substances involved, exposure reason, medical outcome, etc.) are systematically collected using a nationally standardized electronic health record. The RADARS System routinely collects the full de-identified case medical record, including case notes, for any report of prescription opioid or stimulant exposure. The reason code for each exposure is determined and categorized, allowing for distinction between intentional and unintentional exposures as well as those determined to be adverse reactions. This determination allows for sub-analyses of cases meeting the definition of ‘intentional abuse’.

	Poison center data collected through the RADARS System allows for an overall measure of exposures reported and intentional abuse, as well as sub-analyses based upon age, reason, product involved, route of exposure, or medical outcome including death.
Limitations	The Poison Center Program relies on spontaneous reports; therefore, the number of cases is underreported. Although poison centers use specific procedures to elicit an accurate history, drug identification is often based on the history and may be inaccurate particularly in confused or comatose patients.

*Intentional Exposure: Exposure resulting from a purposeful action. National Poison Data System (NPDS) Coding Users' Manual v 3.1 © American Association of Poison Control Centers. 2014: p 67. https://aapcc.s3.amazonaws.com/pdfs/member-resources/NPDS_Coding_Users_Manual_v3.1_07May2014.pdf accessed July 26, 2014. Accessible to AAPCC members only.

**Intentional Abuse Exposure: An exposure resulting from the intentional improper or incorrect use of a substance where the patient was likely attempting to gain a high, euphoric effect or some other psychotropic effect, including recreational use of a substance for any effect. National Poison Data System (NPDS) Coding Users' Manual v 3.1 © American Association of Poison Control Centers. 2014: p 69. https://aapcc.s3.amazonaws.com/pdfs/member-resources/NPDS_Coding_Users_Manual_v3.1_07May2014.pdf accessed July 26, 2014. Accessible to AAPCC members only.

Table S2. Drug Diversion Program

The Drug Diversion Program collects case information on the illicit acquisition or distribution of prescription opioids and stimulants from law enforcement agencies investigating drug diversion.

Principal investigators	Steven P. Kurtz, PhD Professor and Director, Center for Applied Research on Substance Use and Health Disparities, Nova Southeastern University
Definition of case	Investigation that results in a written complaint or report
Respondents	Drug diversion investigators represent 245 agencies (municipal police departments, multi-jurisdictional drug task forces, county sheriffs' departments, regulatory agencies such as state medical and pharmacy boards, state police agencies, prosecutors' offices, and departments of health)
Period of operation	2002 to date
Population studied	Individuals officially investigated for illicit acquisition and/or distribution of prescription drugs (e.g. street dealing, doctor shopping, prescription forgery, theft)
Coverage in 2015	Figure S3. At least one participating agency in 49 states and the District of Columbia. The number of respondents varies slightly by quarter. There were 200 responding agencies for 4 th quarter, which corresponds to 37.8% of the United States population.
Number of cases	
2015–Q4	2,459 cases of diversion, 1,732 cases of opioid analgesic diversion
2002–2015	199,204 cases of diversion, 164,451 cases opioid analgesic diversion
Data collection	Each agency completes a standardized quarterly questionnaire that reports the number of newly opened and documented diversion cases (illicit acquisition or distribution of a prescription drug) within their jurisdiction. Case data include specific drug, brand, and dosage size information. The actual drug product is often available for identification by investigators. A separate questionnaire inquires about the street prices of various prescription medications in the same quarter, based on investigator knowledge of street purchases. When necessary, repeated contacts are made with investigators to verify information.
Limitations	Not all parts of the United States have prescription drug diversion agencies. Operational details and emphases of diversion agencies vary according to the needs of the community and local drug activity. Reporting agencies are unlikely to detect all instances of prescription drug diversion in a given jurisdiction, indicating potential for under-reporting.

Table S3. Opioid Treatment Program

The Opioid Treatment Program records the specific prescription opioids and stimulants endorsed by persons entering treatment for substance dependence or addiction.

Principal Investigators	<p>Mark W. Parrino, MPA President, American Association for the Treatment of Opioid Dependence</p> <p>Andrew S. Rosenblum, PhD Executive Director and Director of Institute for Treatment and Services Research, National Development & Research Institutes, Inc.</p>
Respondents	Patients entering participating federally approved opioid agonist treatment programs who reported abusing prescription opioids or heroin in the past 30 days.
Period of operation	2005 to date
Definition of case	A person endorsing abuse of any prescription opioid in the previous 30 days
Population studied	Patients with opioid dependence disorder for at least one year
Coverage in 2015	Figure S4. 278 3-digit ZIP codes in the United States were covered, which corresponds to 46.7% of the United States population.
Number of respondents	
2015–Q4	1,566 respondents, 4,191 endorsements of past month abuse of an opioid analgesic
2005–2015	76,770 respondents, 217,448 endorsements of past month abuse of an opioid analgesic
Data collection	<p>Each patient entering treatment at a participating facility is offered the opportunity to complete anonymously a standardized self-administered questionnaire that solicits information on specific prescription drugs “used to get high” in the past 30 days. Approximately 90% of patients entering treatment complete the survey.</p> <p>Data provided includes demographics, substance abuse treatment history, primary drugs of abuse, primary source of drug, history of pain, use of illicit substances, and injection of prescription drugs. Participants receive modest compensation for their participation in the study.</p> <p>The program is comprised primarily of treatment programs that use medication-assisted treatment.</p>
Limitations	Limitations include self-reporting, inability to confirm product identification, and survey selection bias. However data suggest that this is an experienced population and self-reported product identification is generally more accurate than inexperienced users.

Table S4. Survey of Key Informants' Patients Program

The Survey of Key Informants' Patients Program records the specific prescription opioids and stimulants endorsed by persons entering treatment for substance dependence or addiction.

Principal Investigator	Theodore J. Cicero, PhD Professor of Psychiatry, Anatomy and Neurobiology and Vice Chairman for Research, Department of Psychiatry, Washington University in St. Louis
Respondents	Persons seeking treatment for substance dependence or addiction who report abusing prescription opioids or heroin in the past 30 days
Period of operation	2008 to date
Definition of case	A person endorsing abuse of any prescription opioid or heroin in the previous 30 days
Population studied	Patients with substance use disorder
Coverage in 2015	Figure S5. Patients' home address included 409 3-digit ZIP codes in the US, which corresponds to 50.9% of the United States population.
Number of respondents	
2015–Q4	671 respondents involving 3,508 endorsements of past month abuse of an opioid analgesic
2008–2015	18,377 respondents involving 96,898 endorsements of past month abuse of an opioid analgesic
Data collection	<p>Each patient entering treatment at a participating facility is offered the opportunity to complete anonymously a standardized self-administered questionnaire that solicits information on specific prescription drugs “used to get high” in the past 30 days. An average of 85% of patients complete the survey. Participants receive modest compensation for their participation in the study.</p> <p>Data provided includes demographics, substance abuse treatment history, primary drugs of abuse, primary source of drug, history of pain, use of illicit substances, and injection of prescription drugs. The questionnaire is identical to the RADARS System Opioid Treatment Program.</p> <p>The program is comprised primarily of private treatment programs that do not use medication-assisted treatment.</p>
Limitations	Limitations include self-reporting, inability to confirm product identification, and survey selection bias. However data suggest that this is an experienced population and self-reported product identification is generally more accurate than inexperienced users.

Table S5. College Survey Program

The College Survey Program records the specific prescription opioids and stimulants and other drugs that self-identified undergraduate students endorse for nonmedical use.

Principal Investigator	Richard C. Dart, MD, PhD Executive Director of the RADARS® System and Director of the Rocky Mountain Poison & Drug Center, Denver Health and Hospital Authority Professor, University of Colorado School of Medicine
Respondents	Self-identified undergraduate students who are enrolled in a 2-year college, 4-year college, online course, or technical school in the United States at least part time
Period of operation	2008 to date
Definition of case	Respondent endorsing nonmedical use of a prescription opioid. Nonmedical use is defined as “any prescription drug taken without a doctor’s prescription or for a reason other than what was recommended by <i>your</i> prescribing doctor”.
Population studied	Undergraduate college students
Coverage in 2015	Figure S6. Responses were received from 730 3-digit ZIP codes, which corresponds to 94.6% of the United States population.
Number of respondents	
2015–Q4	1,850 respondents involving 1,385 endorsements of past 3 month abuse of an opioid analgesic
2008–2015	38,865 respondents involving 19,284 endorsements of past 3 month abuse of an opioid analgesic
Data collection	<p>An online questionnaire is deployed three times per year (May, August and December). To ensure representation throughout the United States, the country is divided into 4 quadrants as defined by the United States Census (West, Midwest, Northeast, and South). The targeted sample is typically achieved in approximately 10 days through the use of an online panel company. Participants receive modest compensation for their participation in the study.</p> <p>The confidential questionnaire collects data on respondent demographics, use of illicit drugs, non-medical use of prescription drugs, reasons for use, sources of drugs, routes of use, chronic and acute pain, and the Drug Abuse Screening Test (DAST-10). The DAST-10 is a brief, validated instrument for identifying individuals who abuse psychoactive drugs and yields a quantitative index score related to drug use and misuse.</p>
Limitations	The College Survey Program is limited by biases of self-reporting, inability to confirm product identification, and self-selection bias.

Table S6. StreetRx Program

The StreetRx Program determines the “black market” or “street price” of prescription drugs using crowdsourcing principles.

Principal Investigator	Nabarun Dasgupta, MPH, PhD Chief Product Officer, Epidemico, Inc.
Respondents	Individuals that purchased prescription opioid or stimulants in an illicit transaction
Period of operation	2011 to date
Definition of case	Entry of a price paid or that they heard was paid for a drug purchased on the street
Population studied	General population with internet access who report knowledge of the purchase of a prescription drug through illicit channels
Coverage in 2015	Figure S7. Individuals may respond from any part of the United States.
Number of respondents	
2015–Q4	8,104 price entries for an opioid analgesic
2010–2015	56,371 price entries for an opioid analgesic
Data collection	<p>The program utilizes a crowdsourcing website (www.StreetRx.com) which is accessible to anyone with an internet connection. Site users anonymously submit prices that they paid or heard were paid for specific drug products, specifying the drug formulation, dose, and the city or state in which the transaction occurred.</p> <p>Site visitors can query and view submitted prices at the city level by using a map interface. Additionally, links to information on drug treatment, overdose prevention, harm reduction, safe disposal, and pain management are also provided.</p>
Limitations	The crowdsourcing methodology utilized in the StreetRx Program is limited by spontaneous self-reporting and inability to confirm submitted data.

Table S7. Web Monitoring Program

The Web Monitoring Program provides a complimentary qualitative measure of prescription drug misuse, abuse, and associated consequences reported via the internet. The data from this program lend context and depth to the counts and rates generated in the other RADARS System Programs.

Principal Investigator	Jody L. Green, PhD, CCRP Director of Research Administration, Rocky Mountain Poison & Drug Center, Denver Health and Hospital Authority
Respondents	Individuals who post on the internet about prescription drugs of interest.
Period of operation	The period of operation is from September 2013 to date. However, this program has the unique ability to collect historical data back to 2006.
Definition of case	A single communication entered by one user at a specific time point. A post may contain one or many specific mentions of a drug.
Population studied	General population with internet access who post about prescription drugs of interest to public social media websites, blogs, and forums.
Coverage in 2015	Posts are captured from across the United States.
Number of posts identified	
2015–Q4	330,487 posts
2013–2015	2,380,724 posts
Number of posts analyzed	
2015–Q4	3,712 posts
2013–2015	17,847 posts
Data collection	<p>A real-time surveillance system that collects and organizes posts about prescription drugs on social media websites, blogs, and forums. A commercially available web monitoring platform is utilized to search and organize posts. This software collects posts from over 150 million websites worldwide (e.g. forums, blogs). Specific search-string criteria (including branded products, misspellings, and slang words), time period, and region are entered into the web monitoring platform and all posts matching these criteria are returned.</p> <p>Posts are reviewed by a team of trained coders to characterize the salient themes and to identify posts relating to misuse, abuse, addiction, overdose, and death. Other thematic codes of interest include route of administration and source of drug acquisition.</p>
Limitations	Limitations of this program include spontaneous reporting and the inability to confirm reports. There are also inherent limitations with qualitative data in that incidence or rates cannot be calculated. The anonymity of the worldwide web may permit false identities and false statements, none of which can be confidently resolved.

Figure S1. RADARS System Mosaic Surveillance Strategy for Prescription Drug Abuse

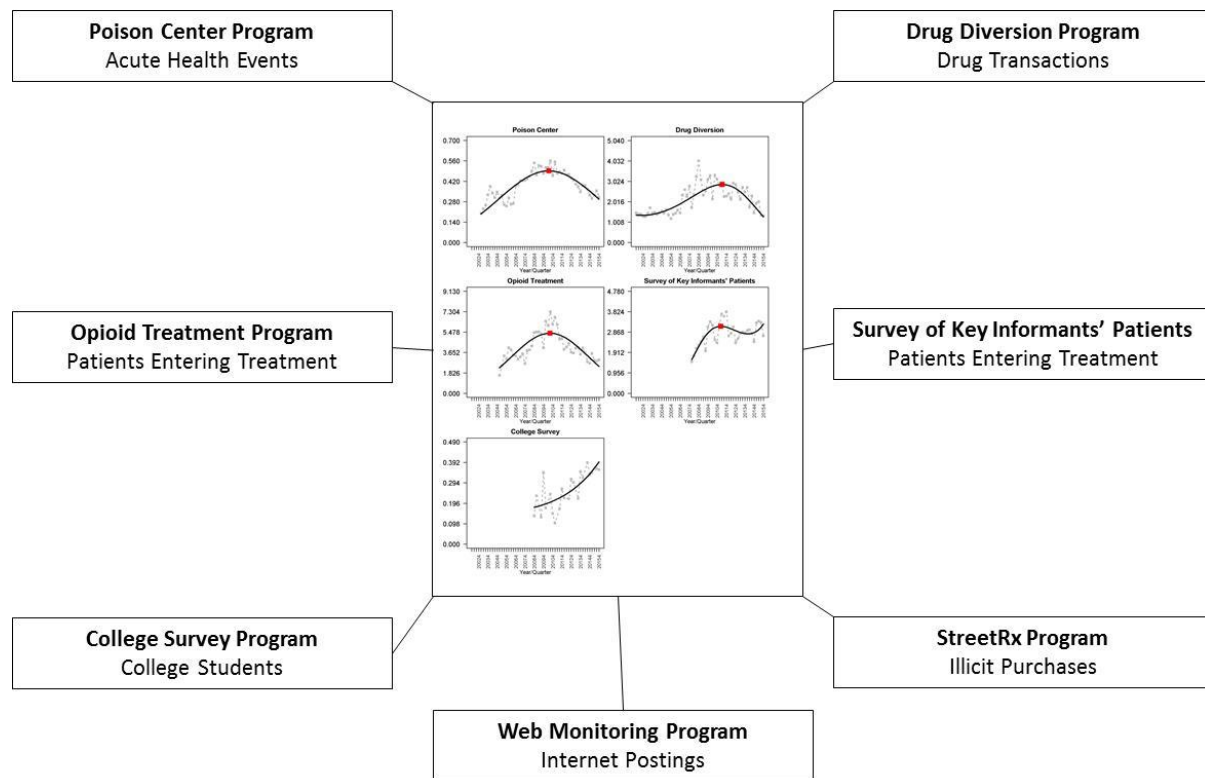
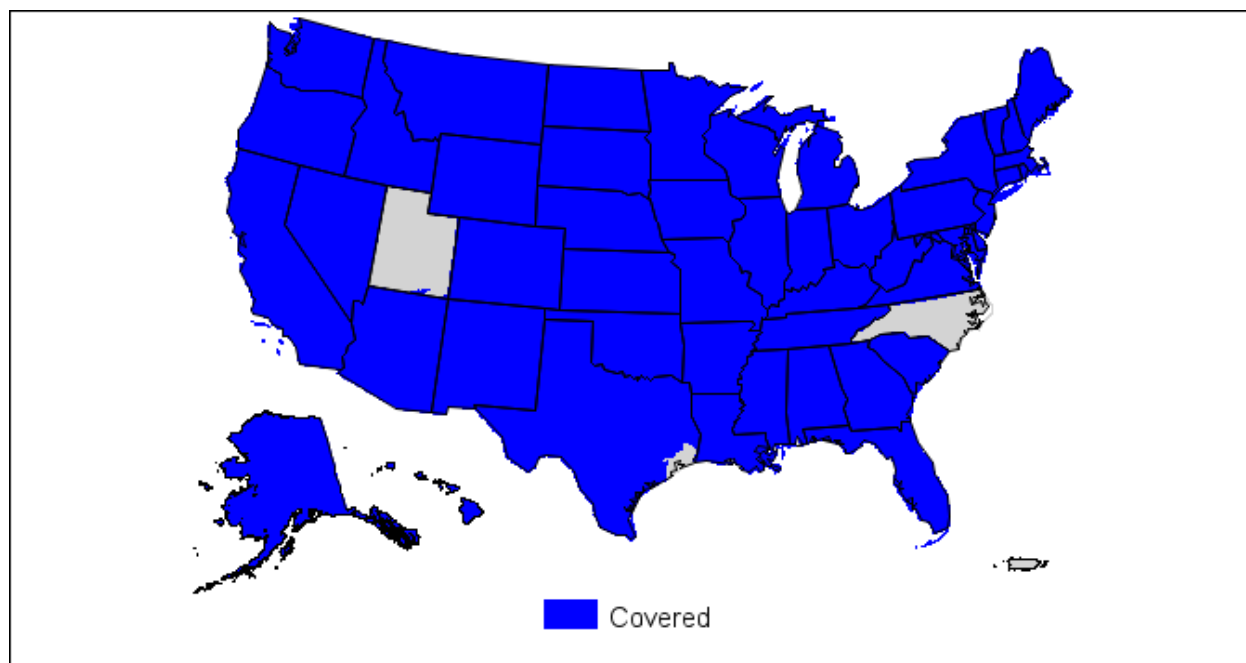
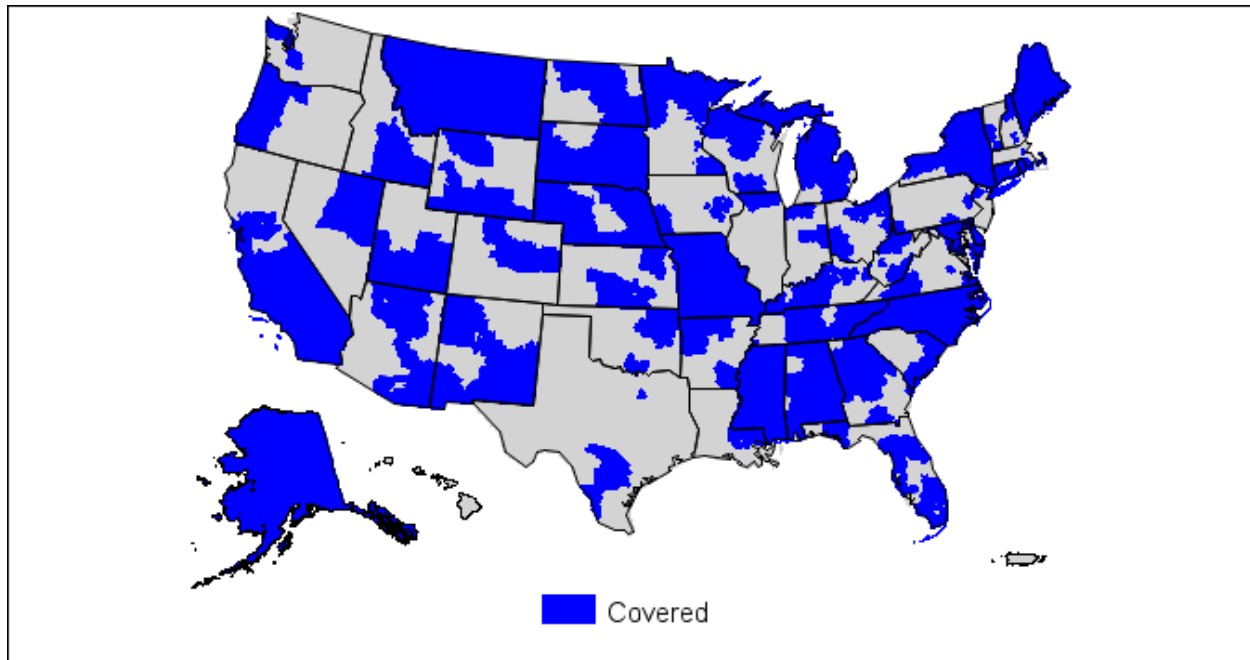


Figure S2. RADARS System Poison Center Program Service Areas, 2015



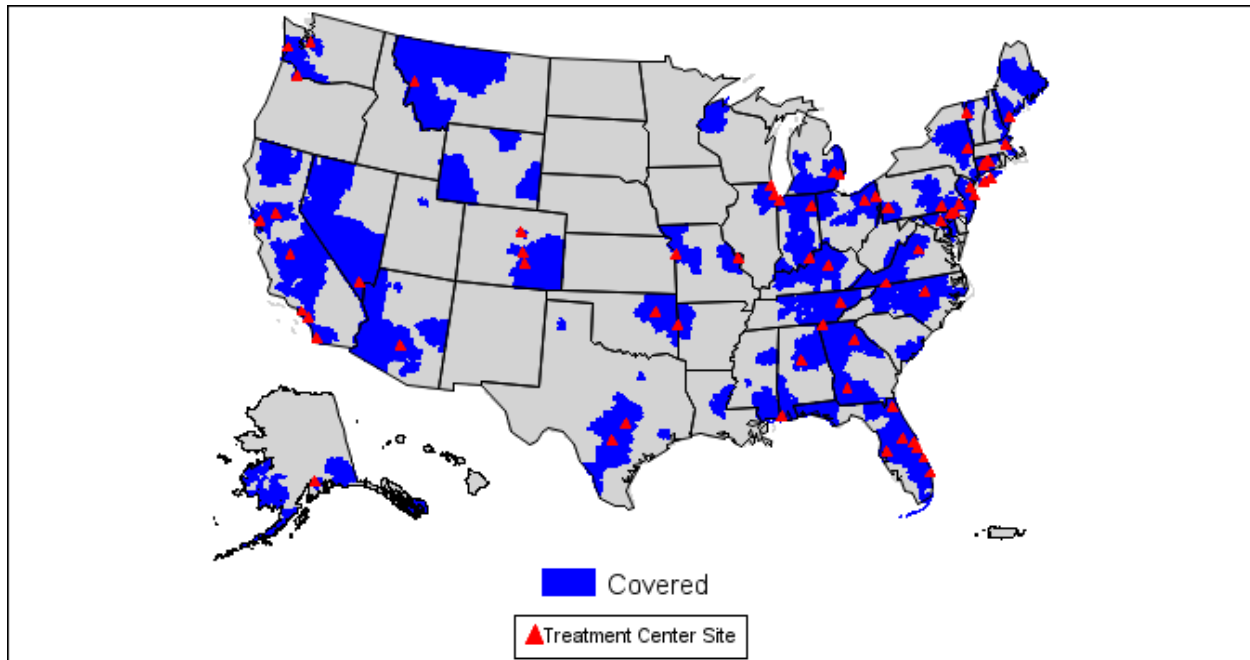
The covered regions indicate the state-designated service area of poison centers that participated in the Poison Center Program for 2015.

Figure S3. Jurisdictions of Agencies Participating in RADARS System Drug Diversion Program, 2015



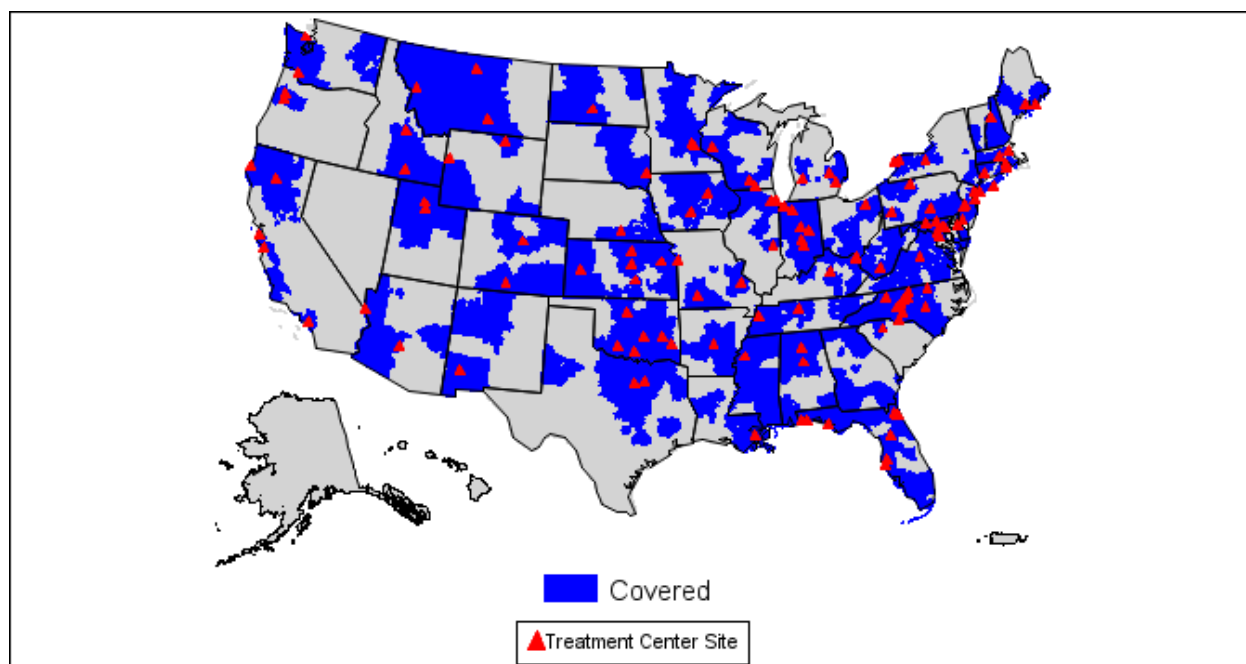
The covered regions show the geographical area covered by the jurisdiction of participating law enforcement agencies in 2015.

Figure S4. RADARS System Opioid Treatment Program Participation, 2015



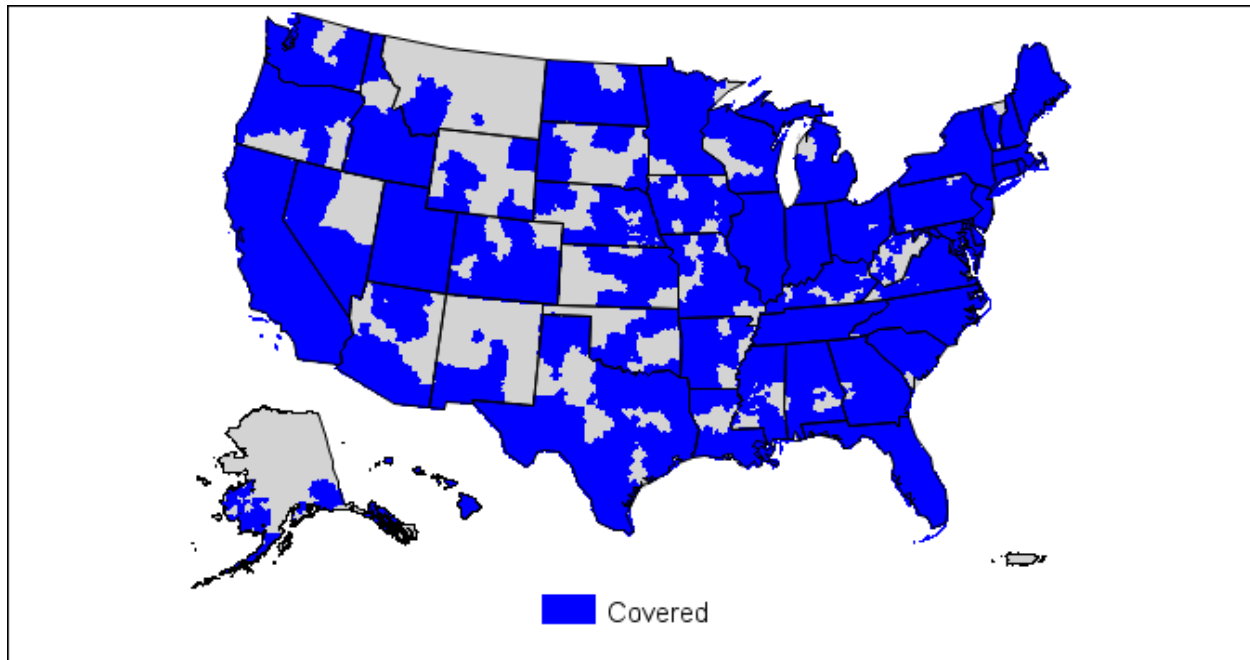
The covered areas indicate the 3-digit ZIP code of the home address of patients completing a questionnaire in the Opioid Treatment Program in 2015.

Figure S5. RADARS System Survey of Key Informants' Patients Program Participation, 2015



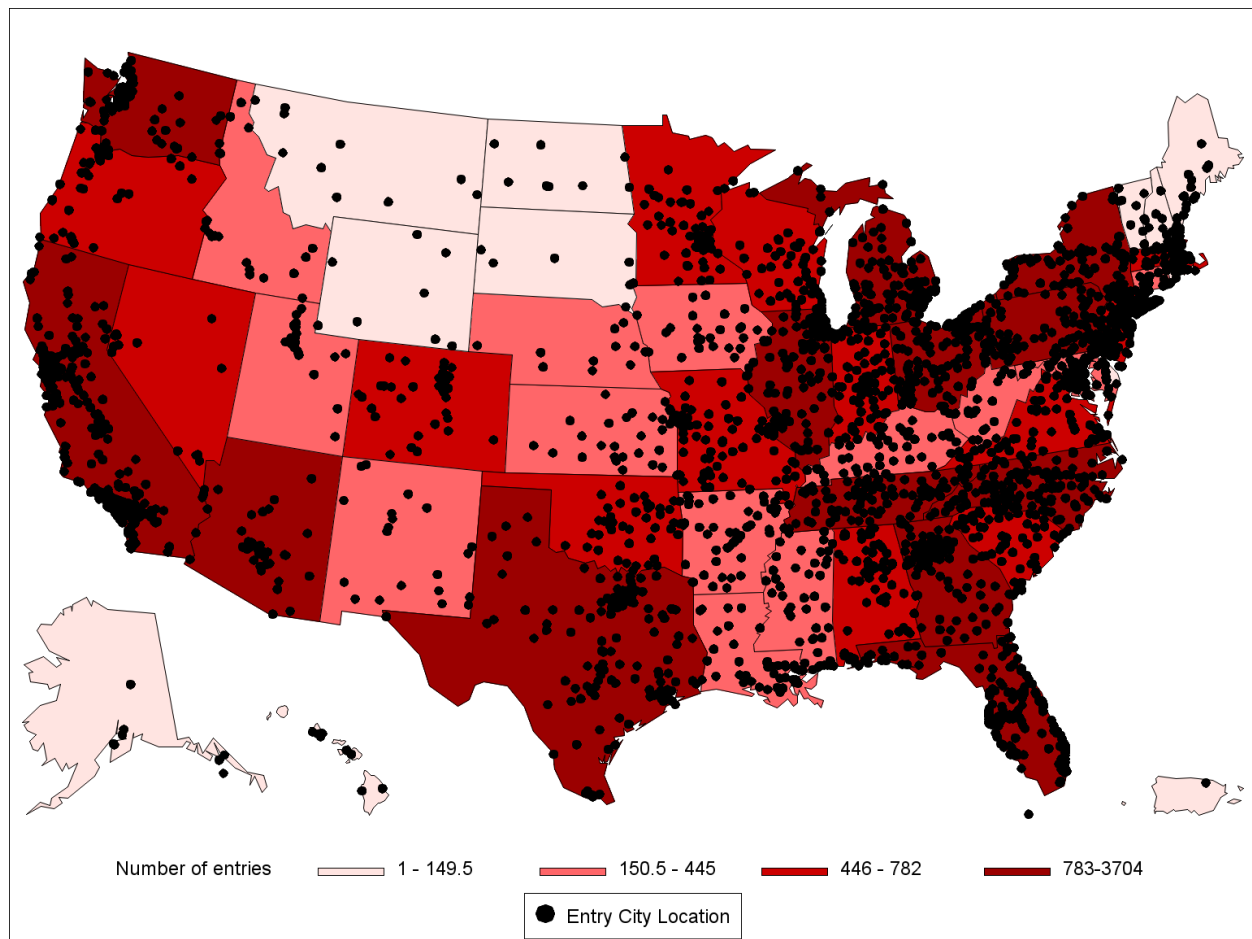
The covered areas indicate the 3-digit ZIP code of the home address of patients completing a questionnaire in the Survey of Key Informants' Patients Program in 2015.

Figure S6. RADARS System College Survey Program Participation, 2015



The map represents each 3-digit ZIP code that at least one respondent identified as their place of residence at the time of the survey.

Figure S7. RADARS System StreetRx Program Participation, 2015



The map represents the number of price entries by state in 2015. Each asterisk designates a specific city for a response. Users are required to enter the state where the transaction occurred, but entry of the specific city or 3-digit ZIP code is voluntary.

APPENDIX 11 RADARS[®] SYSTEM BIOGRAPHIES

RADARS® System Principal Investigators

Theodore J. Cicero, PhD

*Principal Investigator, Survey of Key Informants' Patients (SKIP) Program
Professor of Psychiatry, Anatomy and Neurobiology and Vice Chairman for Research,
Department of Psychiatry, Washington University in St. Louis*

Dr. Theodore J. Cicero received his PhD in Neuropharmacology from Purdue University in 1969 and began his career at Washington University School of Medicine in 1968 as a post-doctoral fellow where he rose to Professor of Psychiatry, Anatomy and Neurobiology in 1978. Cicero serves as Vice Chairman for Research in the department of Psychiatry and was appointed Vice Chancellor for Research for Washington University in 1996, serving until 2006. Dr. Cicero is a life fellow of the American College of Neuropsychopharmacology, past president and Treasurer of the College on Problems of Drug Dependence.

He has been a field editor for the Journal of Pharmacology and Experimental Therapeutics, as well as serving on the editorial boards and as an expert reviewer for numerous other scientific publications, including PAIN, Pharmacoepidemiology and Drug Safety, Pain Medicine, Journal of Substance Abuse Treatment and JAMA Psychiatry. Cicero has written more than 210 publications related to the neurobiological substrates of substance abuse and the epidemiology of substance abuse in humans entering treatment for addiction on opioids. He also has active grants from the National Institute on Drug Abuse.

In addition to his university and scientific positions, Cicero has also served on the Board of Scientific Counselors of the National Institute for Drug Abuse and was an expert advisor to the World Health Organization Substance Abuse Advisory Group. He is also a past chairperson of the Food and Drug Administration Drug Abuse Advisory panel (1985 – 1993).

Richard C. Dart, MD, PhD

Principal Investigator, Poison Center Program

Principal Investigator, College Survey Program

Executive Director of the RADARS® System and Director of the Rocky Mountain Poison & Drug Center – Denver Health and Hospital Authority

Professor, University of Colorado School of Medicine

Richard C. Dart, MD, PhD, is the Director of the Rocky Mountain Poison & Drug Center, Denver Health and Hospital Authority. He is the Executive Director of Research Abuse, Diversion, and Addiction-Related Surveillance (RADARS®) System. He is also Professor of Emergency Medicine at the University of Colorado School of Medicine. He is past-president of the American Association of Poison Control Centers (AAPCC) and is Fellow of the American College of Medical Toxicology (FACMT), American Academy of Clinical Toxicology (FAACT) and American College of Emergency Physicians (FACEP).

Raised in Michigan, Dr. Dart earned his bachelor's degree in biology at Albion College and his medical degree at Wayne State University in Detroit, Michigan. He completed residency training in emergency medicine at the University of Arizona and then completed a fellowship in Medical Toxicology as well as a doctorate of Pharmacology and Toxicology at the University of Arizona. He is board certified by the American Board of Emergency Medicine and the American Board of Medical Toxicology.

Dr. Dart has earned numerous awards for his teaching, research and leadership endeavors. He was the 2004 recipient of the American College of Medical Toxicology Matthew J. Ellenhorn Award for Excellence in Medical Toxicology. He was selected as an inaugural member of the Medical Toxicology Subboard of the American Board of Emergency Medicine. In 2002 he was recognized with a special citation from the Commissioner of the U.S. Food and Drug Administration for his work on snake antivenom. His research interests include the postmarketing surveillance of opioid analgesics, development of orphan antidotes (antivenoms, metal chelators and others), the stocking of antidotes, various aspects of OTC analgesic toxicity and their treatments, and adverse drug event reporting.

In 2000, Dr. Dart edited the first edition of *The 5-Minute Toxicology Consult* and is the editor *Medical Toxicology 3rd edition*, a well-known text for toxicologists. He has published more than 250 scientific publications and is frequently invited to lecture to health care and regulatory audiences. He is also a Deputy Editor of medical journal *Annals of Emergency Medicine*.

Nabarun Dasgupta, MPH, PhD

Principal Investigator, StreetRx Program

Chief Product Officer, Epidemico, Inc.

Dr. Nabarun Dasgupta is a quantitative epidemiologist involved in the study of the medical and nonmedical uses of prescription opioids and heroin. He is the Chief Product Officer at Epidemico, Inc. (www.epidemico.com), a public health informatics company. He has worked with diverse groups in public health (e.g., clinical practices, nonprofit organizations, state and local health departments, and the pharmaceutical industry) in reducing the adverse consequences of opioid use.

Dr. Dasgupta began his professional education at Princeton University, where he earned a Bachelor of Arts degree in molecular biology, and then a master of public health degree in the epidemiology of microbial diseases from Yale School of Medicine. He completed his doctoral degree in the Department of Epidemiology in pharmacoepidemiology, at the University of North Carolina Gillings School of Global Public Health, where he focused on definitional aspects of overdose death reporting and using prescription monitoring program data to evaluate dose-response relationships for overdose mortality between extended-release and immediate-release opioid analgesics.

Dr. Dasgupta's areas of research are in pharmacoepidemiology, opioid overdose, and consequences of injection drug use, as well as use of new digital media for drug safety and pharmacovigilance. He is also involved in designing and evaluating interventions for reducing the unintended consequences of prescription opioid use. Dr. Dasgupta is also co-founder of Project Lazarus (www.projectlazarus.org), a community-based pain management and overdose prevention nonprofit organization in Appalachian North Carolina.

Jody L. Green, PhD, CCRP

Principal Investigator, Web Monitoring Program

Director of Research Administration, Rocky Mountain Poison & Drug Center – Denver Health and Hospital Authority

Dr. Jody L. Green is currently the Director of Research Administration at the Denver Health Rocky Mountain Poison and Drug Center in Denver, Colorado. She is also the past-president of the Society of Clinical Research Associates (SoCRA). She received her doctorate in applied statistics and research methods from the University of Northern Colorado.

Dr. Green operates the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS®) System and is the principal investigator of the RADARS® System Web Monitoring Program, Global Toxicsurveillance Network (GTNet), and the National Survey of Non-Medical Use of Prescription Drugs Program among other national surveillance programs. Dr. Green has vast experience with National Poison Data System and contributed as a coauthor to the annual reports from 2006 to 2010. She is a member of the Prevention of Overdoses and Treatment Errors in Children Taskforce of the Centers for Disease Control and Prevention (CDC) which is an assembly of experts to develop strategies to keep children safe from unintentional medication overdoses. She also serves as an expert in surveillance methodology specifically for prescription and over-the-counter drug safety, as well as prescription drug abuse surveillance.

Dr. Green has obtained certification as a Certified Clinical Research Professional (CCRP). She has authored or co-authored over 40 manuscripts throughout her career. She has initiated and coordinated multiple efforts with the RADARS® System both domestically and internationally in an attempt to advance the monitoring of prescription drug misuse, abuse and diversion at a global level.

Steven P. Kurtz, PhD

Principal Investigator, Drug Diversion Program

Professor and Director of the Center for Applied Research on Substance Use and Health Disparities, Nova Southeastern University

Dr. Steven Kurtz was awarded his PhD in Sociology by Florida International University in 1999. Dr. Kurtz is Professor and Director of the Center for Applied Research on Substance Use and Health Disparities (ARSH) at Nova Southeastern University, where his research is primarily focused on illicit and prescription drug abuse, drug diversion, HIV risk behaviors, and related health and social problems among not-in-treatment populations.

Dr. Kurtz is Principal Investigator for the Drug Diversion Program of the RADARS® System prescription drug abuse and diversion surveillance system. He also serves as PI for a National Institute on Drug Abuse-funded clinical trial examining the efficacy of a novel substance abuse intervention for young adults. He has previously served as PI for a study of prescription drug diversion in South Florida, as well as PI or Co-I on a wide range of epidemiologic and intervention studies of substance using populations.

Dr. Kurtz is an appointed member of the Behavioral and Social Science Approaches to Preventing HIV/AIDS (BSPH) study section at the National Institutes of Health. He serves on the Scientific Advisory Board for the RADARS System, and as alternate member representing the South Florida Sentinel Site of NIDA's National Drug Early Warning System. Dr. Kurtz is a member of the Credentials Committee of the College on Problems of Drug Dependence and of the Review Board of the International AIDS Society and National Institute on Drug Abuse Joint Fellowship Programme.

Mark W. Parrino, MPA

Co-Principal Investigator, Opioid Treatment Program (OTP)

President, American Association for the Treatment of Opioid Dependence

Mr. Parrino has been involved in the delivery of health care and substance abuse treatment since 1974. He received both a Baccalaureate in Psychology (1974) and a Masters in Health Policy, Planning and Administration (1982) from New York University.

Mr. Parrino served as the Director of the Gramercy Park Medical Group, an outpatient methadone treatment program, from 1980 to 1994. He also served as President of the National Development and Research Institutes, Inc. (NDRI) and was the Chair of New York City's Health Systems Agency's Technical Advisory Group on Substance Abuse.

Mr. Parrino served as the Chair of the Center for Substance Abuse Treatment (CSAT) Consensus Panel for State Methadone Treatment Guidelines, the first Treatment Improvement Protocol (TIP) published for national distribution. Currently, Mr. Parrino is the President of the American Association for the Treatment of Opioid Dependence and continues to be responsible for the development and implementation of the Association's organizing initiatives. He is a consultant and educator to government, community and business groups concerning substance abuse treatment and policy. Mr. Parrino is a recipient of the Robert Wood Johnson Foundation Innovators Award for 2003.

Andrew S. Rosenblum, PhD

Co-Principal Investigator, Opioid Treatment Program (OTP)

Executive Director and Director of Institute for Treatment and Services Research, National Development & Research Institutes, Inc.

Dr. Andrew Rosenblum is NDRI's Executive Director as well as the Director of the Institute for Treatment and Services Research at NDRI. He also serves as the section editor of the journal *Substance Use and Misuse* and as a peer-reviewer for NIH-NIDA grant proposals. Dr. Rosenblum earned his Baccalaureate in Philosophy from Adelphi University and a Masters in Psychology from the New School for Social Research. Dr. Rosenblum completed his doctoral degree in Psychology at the Graduate Center at City University of New York.

Dr. Rosenblum's addiction-related research interests include development and evaluation of psychosocial interventions, eLearning and eTherapy applications, and prevalence studies. Most of his research activities have been funded by the NIH. Recent and current projects include a survey and a clinical trial of agonist medications in the criminal justice system, a clinical trial on the use of buprenorphine to treat chronic pain, a randomized clinical trial of self-help groups designed for consumers with co-occurring substance use and mental health disorders (Double Trouble in Recovery; DTR); a nationwide prevalence study of prescription opioid abuse, and web-based self-management interventions for chronic pain patients and PTSD symptomatic substance-misusing veterans. Dr. Rosenblum is also PI on a Health and Human Services grant designed to develop policy recommendations for emergency preparedness and response for opioid treatment programs and, is a Co-investigator (Dr. Alexander Bennett is PI) on a prospective longitudinal study that is examining factors contributing to overdose among young veterans.

APPENDIX 12 RADARS[®] SYSTEM BRIEFING BOOK

**Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and
Mitigation Strategy (REMS): RADARS[®] System Surveillance**

28 March 2016

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1. EXECUTIVE SUMMARY

The fifth assessment of the REMS is to conduct surveillance for abuse, misuse, overdose, addiction, and death and to evaluate if the REMS meets its surveillance goals, and if it does not, to modify it appropriately based on the metrics. Briefly, therefore, the overall surveillance objective is to evaluate trends before and after the shared REMS is implemented to assess changes in abuse, misuse, overdose, addiction, and death for different risk groups and settings. Specific aims 5.2-5.4 from the ER/LA REMS proposal are listed below along with select high-level results.

ASSESSMENT 5.2: Intentional exposures among adolescents and adults, including severity and deaths, using nationally-based poison control surveillance data. Using data from the RADARS System Poison Center Program:

- ER/LA REMS mean intentional abuse population rates fell from 0.123 in the pre-implementation period to 0.069 in the active period per 100,000 population, a 44.04% (-50.57%, -36.64%) decrease, while IR prescription opioid mean intentional abuse population rates fell from 0.276 to 0.191 per 100,000 population, a 30.89% (-36.40%, -24.90%) decrease over the same time period. These mean decreases were significantly different ($p=0.006$). Prescription stimulants mean intentional abuse population rates fell from 0.148 to 0.129 per 100,000 population, a 13.35% (-19.35%, -6.90%) decrease over the same time period. These mean decreases were significantly different ($p<0.001$).
- ER/LA REMS mean intentional abuse prescription rates fell from 0.064 in the pre-implementation period to 0.035 in the active period per 1,000 prescriptions, a 44.42% (-50.34%, -37.79%) decrease, while IR prescription opioid mean intentional abuse prescription rates fell from 0.018 to 0.013 per 1,000 prescriptions, a 24.99% (-30.45%, -19.10%) decrease over the same time period. These mean decreases were significantly different ($p<0.001$). Prescription stimulants population rates fell from 0.032 to 0.023 per 1,000 prescriptions, a 26.25% (-32.50%, -19.41%) decrease over the same time period. These mean decreases were significantly different ($p<0.001$).
- ER/LA REMS mean population based death rates fell from 0.004 in the pre-implementation period to 0.002 in the active period per 100,000 population, a 42.39% (-59.22%, -18.61%) decrease, while IR prescription opioid mean population based death rates fell from 0.012 to 0.010 per 100,000 prescriptions, a 17.66% (-31.11%, -1.57%) decrease over the same time period. These mean decreases were not significantly different ($p=0.072$). Prescription stimulants mean death population rates increased from 0.002 to 0.002 per 100,000 populations a 1.31% (-39.02%, 68.31%) increase over the same time period. These mean differences were not significantly different ($p=0.072$).
- ER/LA REMS mean prescription based death rates fell from 0.002 in pre-implementation period to 0.001 in the active period per 1,000 prescriptions, a 42.78% (-59.43%, -19.30%) decrease, while IR prescription opioid mean prescription based death rates fell from <0.001 to <0.001 per 1,000 prescriptions, a 10.62% (-25.63%, 7.42%) decrease over the

same time. The mean decreases were significantly different ($p=0.025$). Prescription stimulants mean prescription based death rates decreased from <0.001 to <0.001 per 1,000 prescriptions, a 13.77% (-48.75%, 45.10%) decrease over the same time period. These means decreases were not significantly different ($p=0.197$).

ASSESSMENT 5.3: Unintentional exposures among infants and children, including severity and deaths, using nationally-based poison control surveillance data. Using data from the RADARS System Poison Center Program:

- ER/LA REMS mean pediatric (under 6) poison center unintentional exposure population rates fell from 0.530 in the pre-implementation period to 0.420 in the active period per 100,000 population, a 20.76% (-32.37%, -7.16%) decrease, while IR prescription opioid mean pediatric unintentional exposures fell from 3.895 to 3.276 per 100,000 population, a 15.89% (-21.52%, -9.84%) decrease over the same time period. These mean differences were not significantly different ($p=0.499$). Prescription stimulants mean pediatric unintentional exposure population rates decreased from 5.511 to 5.453 per 100,000 population a 1.05% (-5.09%, 3.16%) decrease over the same time period. These mean decreases were significantly different ($p=0.008$).
- ER/LA REMS mean pediatric (under 6) poison center unintentional exposure prescription rates fell from 0.021 in the pre-implementation period to 0.016 in the active period per 1,000 prescriptions, a 22.39% (-33.09%, -9.97%) decrease, while IR prescription opioids mean pediatric unintentional exposures fell from 0.019 to 0.018 per 1,000 prescriptions, a 9.96% (-15.78%, -3.74%) decrease over the same time period. These mean differences were not significantly different ($p=0.074$). Prescription stimulants mean pediatric unintentional general prescription rates decreased from 0.092 to 0.076 per 1,000 prescriptions, a 16.94% (-22.79%, -10.65%) decrease over the same time. These mean decreases were not significantly different ($p=0.421$).

ASSESSMENT 5.4: Rates of individuals in substance abuse treatment programs abusing ER/LA REMS opioids, as well as source of acquiring the ER/LA REMS opioids, as compared to comparator IR opioids and benzodiazepines using the national surveillance systems among substance abuse treatment seekers. Using data from the RADARS System Treatment Center Programs Combined:

- ER/LA REMS mean past 30 day use to get high rates from the combined treatment center programs population rates fell from 1.987 in the pre-implementation period to 1.053 in the active period per 100,000 population, a 47.02% (-60.00%, -29.81%) decrease, while IR prescription mean opioid rates fell from 2.133 to 1.875 per 100,000 population, a 12.09% (-27.31%, 6.32%) decrease over the same time period. These mean differences were significantly different ($p=0.003$). Benzodiazepines are not collected by the RADARS System Treatment Center Programs.
- ER/LA REMS mean past 30 day use to get high rates from the combined treatment center prescription rates fell from 0.994 in the pre-implementation period to 0.534 in the active period per 1,000 prescriptions, a 46.31% (-59.60%, -28.64%) decrease, while mean IR prescription opioids fell from 0.135 to 0.132 per 1,000 prescriptions, a 2.27% (-18.78%,

17.60%) decrease over the same time period. These mean differences were significantly different ($p < 0.001$).

2. INTRODUCTION

In response to a growing number of reports of abuse, misuse, overdose, addiction, and death associated with extended-release (ER)/long-acting (LA) opioids, on February 6, 2009, the Food and Drug Administration (FDA) sent letters to manufacturers of certain opioid drug products indicating that these drugs would be required to have a Risk Evaluation and Mitigation Strategy (REMS) to ensure the benefits of the drugs continue to outweigh the risks. The specific goal of the REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA REMS opioid analgesics while maintaining patient access to pain medications. The affected drugs include branded and generic drug products, including:

- ER, oral dosage forms containing hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, or tapentadol;
- Fentanyl and buprenorphine-containing transdermal delivery systems; *and*
- Methadone tablets and solutions that are indicated for use as analgesics.

When used properly, such drugs can play an important role in the management of moderate to severe chronic and acute pain. However, serious outcomes such as those listed above may result when used improperly. This briefing document describes the surveillance of outcomes of interest in temporal relation to the ER/LA REMS. Outcomes of interest include:

- Emergency Department Visits from the RADARS System Poison Center Program
 - Under 20 years treated/evaluated and released (< 20 years)
 - Adult treated/evaluated and released (≥ 20 years)
- Abuse from the RADARS System Poison Center Program
 - Intentional abuse exposures
 - Adolescent intentional abuse exposures (13-19 years)
- Misuse from the RADARS System Poison Center Program
 - Misuse exposures
 - Adult unintentional exposures (≥ 20 years)
 - Child and adolescent unintentional exposures (6-19 years)
 - Pediatric unintentional exposures (≤ 5 years)
 - Pediatric unintentional general exposures (≤ 5 years)
 - Pediatric unintentional general exposures (≤ 5 years) resulting in a major medical outcome, hospitalization or death
 - Pediatric unintentional general exposures (≤ 5 years) treated/evaluated and released
 - Unintentional therapeutic errors
- Abuse from the RADARS System Treatment Center Programs Combined

- Past 30 day mentions of use to get high
- Deaths from the RADARS System Poison Center Program
 - Major medical outcomes, hospitalization or death
 - Deaths
- Abuse from the RADARS System College Survey Program
 - Past 90 day mentions of non-medical use

3. BACKGROUND

3.1. Description of Prescription Drug Abuse Epidemic in the United States (US)

Prescription drugs, including opioids, provide therapeutic value to millions of Americans. However, prescription drug abuse is the fastest growing drug problem in the US and has become a national epidemic. Overdoses and deaths involving non-medical prescription drug use, especially opioid analgesics, have risen dramatically over the last decade such that overdose death rates in the US have more than tripled since 1990 [1]. In 2012, an estimated 6.8 million Americans (2.6 percent of the population) reported using prescription drugs non-medically in the previous month [2]. Many factors contribute to this epidemic, including the increasing prevalence of chronic pain in an aging US population, wider acceptance of opioids for treatment of chronic pain, the misperception that these drugs are safe when used outside of medical practice, their relatively low cost, and the increase in potency of some agents.

3.2. Overview of ER/LA REMS Products

The following table lists the generic names, brand names (when applicable), and Sponsors for the ER/LA REMS products included in the REMS during the surveillance period included in this report [3].

Table 3.2.1 ER/LA REMS Generic and Branded Product Names (as of 5/2015)

Generic Name	Brand Name	Sponsor
Buprenorphine transdermal system	Butrans [®]	Purdue Pharma L.P.
Fentanyl transdermal system		Actavis Laboratories Inc.
Fentanyl transdermal system		Aveva Drug Delivery Systems, Inc.
Fentanyl transdermal system		Mallinckrodt
Fentanyl ER transdermal system		Mylan Technologies, Inc.
Fentanyl transdermal system		Noven Pharmaceuticals, Inc.
Fentanyl transdermal system		Par Pharmaceuticals Company, Inc.
Fentanyl transdermal system		Sandoz Inc.
Fentanyl transdermal system	Duragesic [®]	Janssen Pharmaceuticals,

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Advisory Committee
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Generic Name	Brand Name	Sponsor
		Inc.
Hydrocodone bitartrate ER capsules	Zohydro®	Zogenix, Inc.
Hydromorphone hydrochloride ER tablets	Exalgo®	Mallinckrodt
Hydromorphone hydrochloride ER tablets		Actavis Laboratories, Inc.
Methadone hydrochloride oral concentrate		Roxane Laboratories, Inc.
Methadone hydrochloride Intensol™ oral solution		Roxane Laboratories, Inc.
Methadone hydrochloride tablets		Mallinckrodt
Methadone hydrochloride tablets	Methadose®	Mallinckrodt
Methadone hydrochloride tablets		The PharmaNetwork, LLC
Methadone hydrochloride tablets		Sandoz, Inc.
Methadone hydrochloride tablets	Dolophine®	Roxane Laboratories, Inc.
Methadone hydrochloride tablets		Roxane Laboratories, Inc.
Methadone hydrochloride oral solution		Vistapharm, Inc.
Morphine sulfate ER capsules		Actavis Elizabeth, LLC
Morphine sulfate ER capsules		Actavis Laboratories, Inc.
Morphine sulfate ER capsules	Kadian®	Actavis Laboratories, Inc.
Morphine sulfate ER capsules		Par Pharmaceuticals Company, Inc.
Morphine sulfate ER capsules	Avinza®	Pfizer, Inc.
Morphine sulfate ER capsules		Ranbaxy
Morphine sulfate ER capsules		Upsher-Smith, Laboratories, Inc.
Morphine sulfate ER tablets	MS Contin®	Purdue Pharma L.P.
Morphine sulfate ER tablets		Mallinckrodt
Morphine sulfate ER tablets		Mylan Technologies, Inc.
Morphine sulfate ER tablets		Nesher Pharmaceuticals
Morphine sulfate ER tablets		Rhodes
Morphine sulfate ER tablets		Vintage Pharmaceuticals
*Morphine sulfate and naltrexone ER capsules	Embeda®	Pfizer, Inc.
Oxycodone hydrochloride ER tablets	OxyContin®	Purdue Pharma L.P.
*Oxycodone hydrochloride and naloxone hydrochloride ER tablets	Targiniq ER	Purdue Pharma L.P.
Oxycodone hydrochloride ER tablets		Impax
Oxycodone hydrochloride ER tablets		Actavis Laboratories Inc.
Oxycodone hydrochloride ER tablets		Par Pharmaceuticals Company, Inc.
Oxycodone hydrochloride ER tablets		Sandoz, Inc.
Oxycodone hydrochloride ER tablets		Ranbaxy Pharmaceuticals
Oxymorphone hydrochloride ER tablets		Actavis Elizabeth, Inc.
Oxymorphone hydrochloride ER tablets	Opana ER®	Endo Pharmaceuticals.

Generic Name	Brand Name	Sponsor
		Inc.
*Oxymorphone hydrochloride ER tablets		Endo Pharmaceuticals, Inc.
Oxymorphone hydrochloride ER tablets		Impax
Oxymorphone hydrochloride ER tablets		Mallinckrodt
Oxymorphone hydrochloride ER tablets		Roxane Laboratories
Tapentadol ER oral tablets	Nucynta ER®	Depomed

*Approved, but not marketed in study period.

4. METHODS

4.1. Objectives

The fifth assessment of the REMS is to conduct surveillance for abuse, misuse, overdose, addiction, and death and to evaluate if the REMS meets its surveillance goals, and if it does not, to modify it appropriately based on the metrics. Briefly, therefore, the overall surveillance objective is to evaluate trends before and after the implementation of the shared REMS to assess changes in abuse, misuse, overdose, addiction, and death for different risk groups and settings.

4.2. Study Design

The study design will be unique to each metric and data source. The surveillance metrics proposed are similar to the targets that the FDA outlined in its 2010 Final Report of the Metric Working Group. To consider the assessments proposed, it is helpful to review the surveillance data by what data are feasible to collect or obtain. ASSESSMENT 5 DATA SOURCES ARE:

- ASSESSMENT 5.2: Intentional exposures among adolescents and adults, including severity and deaths, using nationally-based poison control surveillance data.
- ASSESSMENT 5.3: Unintentional exposures among infants and children, including severity and deaths, using nationally-based poison control surveillance data.

4.3. Data Sources

4.3.1. RADARS System

The Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System provides post-marketing surveillance of prescription medication abuse, misuse, and diversion to pharmaceutical companies, regulatory agencies, and policy making organizations. The RADARS System is comprised of multiple programs which gather data from several unique populations along the spectrum of drug abuse.

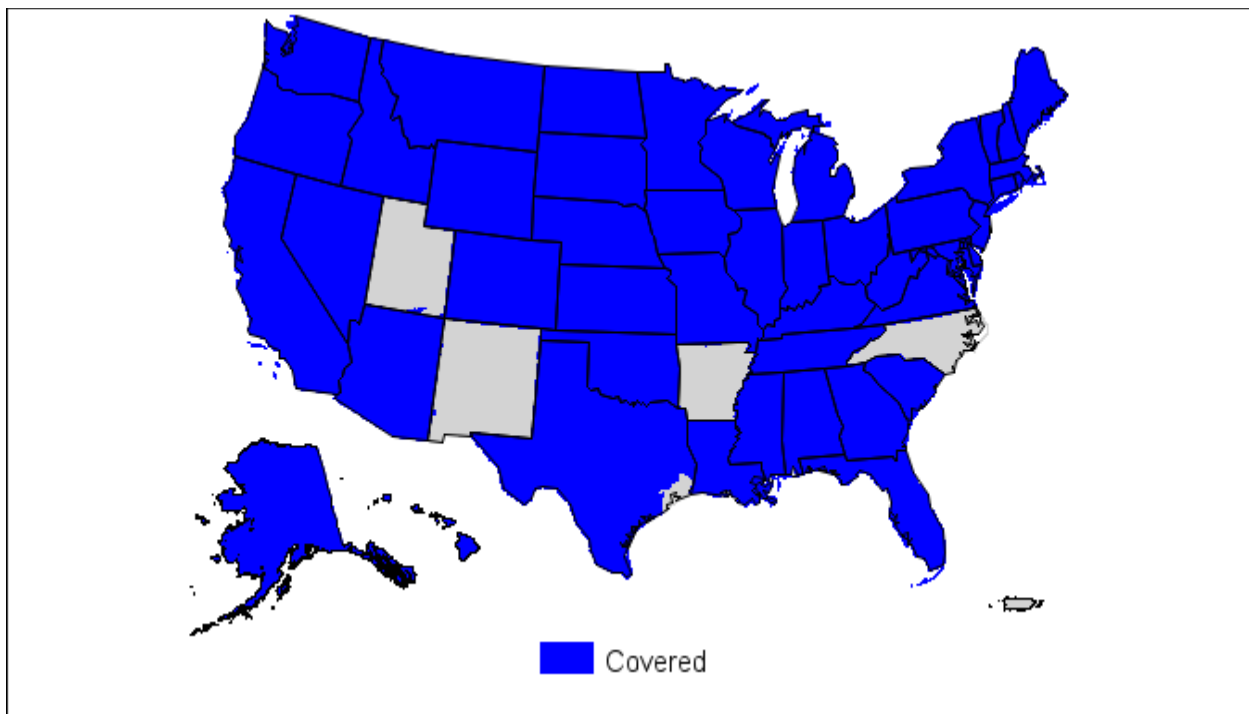
4.3.2. Poison Center Program

The RADARS System Poison Center Program obtains data from individuals within the general population and from healthcare providers who are seeking advice regarding potential toxic exposures, including prescription opioids. The objectives of the Poison Center Program are to

detect product-specific prescription drug abuse and misuse in near real-time and to identify geographic sites with disproportionately high rates of abuse and misuse. Poison center data collected through the RADARS System provide an estimate of change in intentional abuse, misuse, and deaths associated with these drugs. As of December 2014, the Poison Center Program gathered data from 48 regional US Poison Centers in 46 states, including urban, suburban, and rural regions (over 90% of the US population). Investigators at each participating poison center collect data using a nationally standardized electronic health record. In addition to obtaining exposure and substance data, the Poison Center Program collects demographic, clinical effects, treatment, and medical outcomes information. The Poison Center Program was initiated in 2002.

The Poison Center Program study protocol was last reviewed and received approval from the Colorado Multiple Institutional Review Board (COMIRB) on 08 January 2016. In addition, the study protocol was reviewed and approved by the institutional review board (IRB) of each participating poison center as deemed necessary by their IRB.

RADARS System Poison Center Program 2014 Coverage Map



4.3.3. Treatment Center Programs Combined

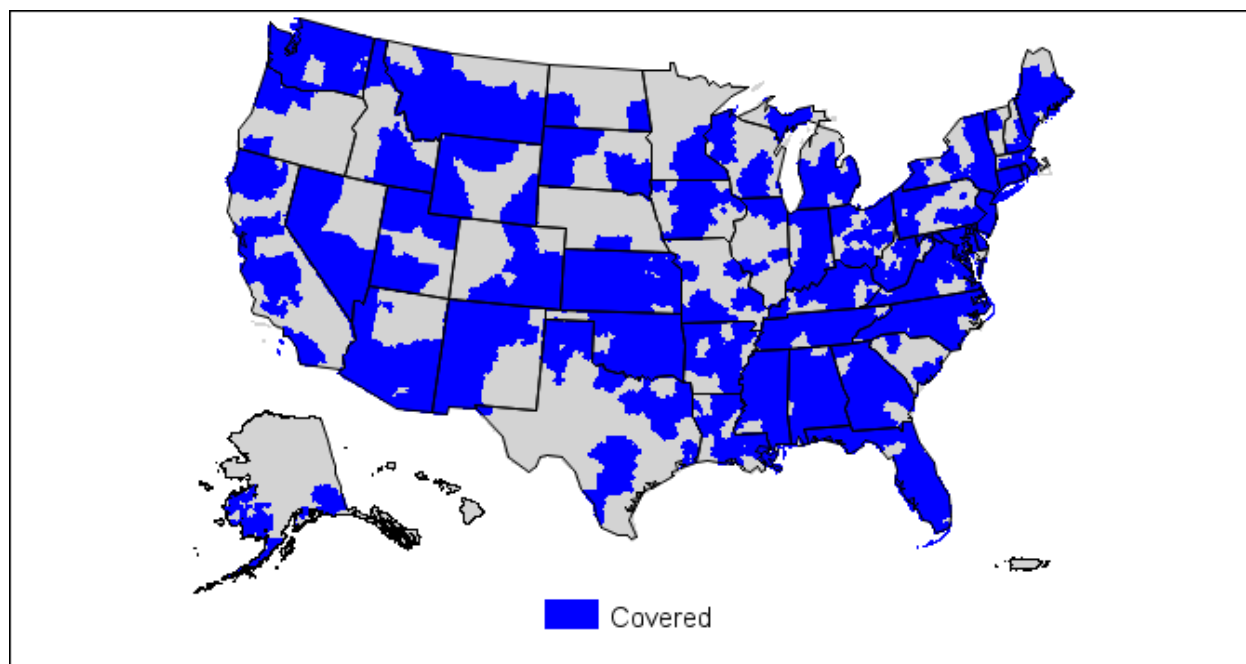
The Treatment Center Programs Combined provide data from two distinct RADARS System programs: Opioid Treatment Program and Survey of Key Informants' Patients Program. These two programs use the same core data collection form and complement each other by providing information from patients entering both private and public opioid addiction treatment programs. Patients enrolling in the study are voluntarily recruited and complete a self-administered

anonymous questionnaire within the first week of admission. The objectives of these programs are to estimate one-month prevalence and the injection rate of prescription and illicit opioid drugs among patients admitted to opioid treatment programs. In addition, they seek to determine the patient's drug of choice and the source of the primary drug.

As of December 2014, the Opioid Treatment Program includes 75 medication-assisted (methadone and buprenorphine) maintenance treatment programs in both urban and rural areas across 33 states. Formal data collection began in 2005. The Opioid Treatment Program study protocol was last reviewed and received expedited approval from the IRB of the Principal Investigator, National Development and Research Institutes Inc. on 21 March 2014.

As of December 2014, the Survey of Key Informants' Patients Program includes 186 substance abuse treatment programs covering 48 states. These primarily private treatment centers are balanced geographically with representation from urban, suburban, and rural centers. The Survey of Key Informants' Patients became a RADARS System program in 2008. The Survey of Key Informants' Patients Program study protocol was last reviewed and received expedited approval from the IRB of Washington University in St. Louis, the home institution of the Principal Investigator, on 15 April 2014.

RADARS System Treatment Center Programs Combined 2014 Coverage Map

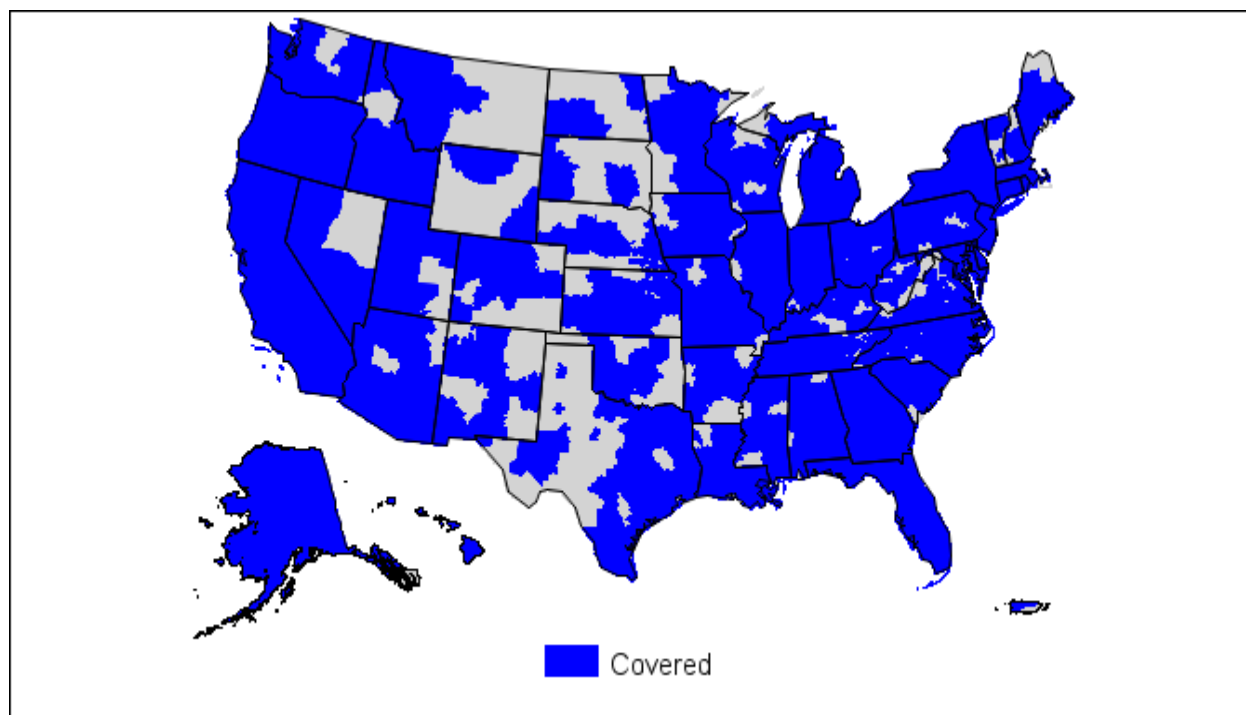


4.3.4. College Survey Program

The College Survey Program is an online questionnaire that collects data from self-identified students attending a 2- or 4-year college, university, or technical school at least part-time during the specified sampling period. Data on non-medical use (abuse) of specific prescription drugs are collected at the completion of the fall and spring academic semesters/quarters and at the end of

the summer. The objectives of the College Survey Program are to estimate the scope of non-medical prescription drug use among US college students, determine the drug source, and determine the route of drug administration among these students. A target of 2000 surveys is completed three times per year with enrollment stratified into the four US Census-regions to ensure nationwide distribution of respondents. A nationwide panel company is utilized to identify and target ideal responders. Students are sent an invitation to participate in the study and they receive credits upon completion of the survey. The survey inquires about the non-medical use of prescription drugs by capturing product specific endorsements. Data are national, timely, and drug specific. The College Survey Program was launched in 2008. The College Survey Program study protocol was last reviewed and approved by COMIRB on 23 October 2015.

RADARS System College Survey Program 2014 Coverage Map



4.3.5. IMS Government Solutions, Inc., a subsidiary of IMS Health, Inc., Prescription and Dosing Unit Data

IMS Government Solutions, Inc., a subsidiary of IMS Health, Inc., (IMS Health) has been obtaining data on prescription dispensing since 2001. Timely product and geographically specific data are obtained from a sample of roughly 80% of retail pharmacies in the US. IMS Health uses a complex proprietary projection methodology to extrapolate from the observed data to the universe of all retail prescriptions in the US. The proposed study will use estimates from IMS Health for total prescriptions dispensed and total dosing units dispensed at the 3-digit ZIP code level for all ER/LA REMS opioids and comparator groups. For a given year-quarter the totals of prescriptions and dosing units in the 3-digit ZIP codes covered by the RADARS System Programs will be computed and these numbers used as the denominators when calculating

product availability rates. Rates will be scaled per 1,000 prescriptions or per 100,000 dosing units dispensed.

4.3.6. US Census Population Data

Three-digit ZIP code population data from the 2000 and 2010 US decennial Censuses will be utilized to compute rates of abuse, misuse, and death. For a given year-quarter the total population in the 3-digit ZIP codes covered by the RADARS System Programs will be extrapolated and this number used as the denominator when calculating population rates. Age specific populations were calculated for pediatric, child, adolescent, and adult rates. All rates will be scaled per 100,000 population.

4.4. Data Management

4.4.1. Poison Center Program Data Management

Participating poison centers have a standard protocol for the management of all cases. The specialists who manage the calls obtain details of the exposure from the caller or the health care provider, and populate standardized fields in the call log database. Investigators at each participating poison center have been trained to use a standardized pre-formatted database to extract all exposure cases regarding the drugs of interest. Each data set includes the standardized fields common to all poison centers with all identifying information removed. Each site coordinator reviews each case and removes all patient identifiers prior to electronic transfer to the RADARS System. To ensure confidentiality, each database is encrypted before the data transfer occurs.

RADARS System staff review these databases for inconsistencies. If inconsistencies are found, the site is notified and asked to rectify the queries. Each case is then reviewed to determine the accuracy of the reason code used. Exposure cases are composed of two main categories: *unintentional/other* (resulting from unforeseen or unplanned events, adverse reactions, other, and unknown reasons), and *intentional exposures* (which include suicide, intentional misuse, abuse, intentional unknown, and withdrawal cases). All data are uploaded into a SQL database for summarization and analysis.

4.4.2. Treatment Center Programs Combined Data Management

4.4.2.1. Opioid Treatment Program

Participating opioid treatment centers fax completed surveys to the data coordination group on a designated day of the week. Optical character recognition software is used to identify the data within the fax image and all data are exported into an SPSS database. Database quality assurance includes form review and data review within the data recognition software and data edit checking using SPSS. SPSS edit checking is done by flagging inconsistent responses (e.g., letters appearing in ZIP code or duplicate cases in the data). Incoming surveys are manually logged into an Excel spreadsheet to represent the number of surveys faxed from each study site each week. These data are matched against the aggregate count of subjects within site generated by SPSS. The final quarterly SPSS database is then submitted to the RADARS System.

4.4.2.2. Survey of Key Informants' Patients Program

Each completed questionnaire is logged in the participating Key Informants' site binder, indicating date received. These questionnaires are then submitted to the data coordination group for data entry. All data entry is double-checked and verified for accuracy and quality assurance. Electronic data edit checks are performed to identify inconsistent responses. Quarterly databases are then submitted to the RADARS System.

4.4.3. College Survey Program Data Management

For each survey launch, the data are downloaded as an SPSS file from a secure hosting site once a sample of approximately 2,000 respondents has been obtained. These data are then stored in their raw format on the RADARS System secure server. After the raw data file has been downloaded, the data are then cleaned using validated SAS® software routines, and based on specified inclusion/exclusion criteria, certain respondents are eliminated.

4.5. Design

RADARS System surveillance data obtained quarterly from July 2010 through December 2014 will be utilized to assess changes over time in rates of abuse, misuse, overdose, addiction, and death.

4.6. Population

The Poison Center Program obtains data from the general population of the US, the Treatment Center Programs Combined obtain data from those entering substance treatment, and the College Survey Program samples from self-identified students attending a 2- or 4- year college, university, or technical school.

4.7. Outcome Variables

Outcome variables include measures of abuse, misuse, major medical outcomes, hospitalization or death, events, death, unintentional therapeutic errors, pediatric unintentional general exposures, and adolescent abuse. Each outcome is described in the sections below. Table 4.7.1 summarizes the outcomes measured in each of the RADARS System Programs.

Table 4.7.1 ER/LA REMS Outcomes by RADARS System Program

	RADARS System Program		
	Poison Center Program	Treatment Center Programs Combined	College Survey Program
Under 20 Years Treated/Evaluated and Released (< 20 years)	X		
Adult Treated/Evaluated and Released (≥ 20 years)	X		
Abuse	X	X	X
Adolescent Intentional Abuse	X		

	RADARS System Program		
	Poison Center Program	Treatment Center Programs Combined	College Survey Program
(13-19 years)			
Misuse	X		
Adult Unintentional Exposures (≥ 20 years)	X		
Child and Adolescent Unintentional Exposures (6-19 years)	X		
Pediatric Unintentional Exposures (≤ 5 years)	X		
Pediatric Unintentional General Exposures (≤ 5 years)	X		
Pediatric Unintentional General Exposures (≤ 5 years) resulting in a Major Medical Outcome, Hospitalization or Death	X		
Pediatric Unintentional General Exposures (≤ 5 years) Treated/Evaluated and Released	X		
Unintentional Therapeutic Errors	X		
Major Medical Outcome, Hospitalization or Death	X		
Death	X		

4.7.1. Treated/Evaluated, and Released

In the Poison Center Program this group will include any exposures with a level of healthcare coded as treated/evaluated and released.

4.7.2. Abuse

Measures of abuse will be captured in all three RADARS System Programs included in this analysis: Poison Center Program, Treatment Center Programs Combined, and College Survey Program. In the Poison Center Program, an intentional abuse case is defined as: “An exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high euphoric effect or some other psychotropic effect” [4]. In the Treatment Center Programs Combined, abuse will be measured as survey respondent endorsing the use of an opioid “to get high” in the past 30 days. Lastly, in the College Survey Program, abuse will be defined as the endorsement of the non-medical use of a drug in the last three months.

4.7.3. Misuse

Our working definition of misuse is: the intentional use of a prescription drug in a way other than prescribed or directed by a healthcare provider or the use of an over-the-counter drug in other ways than directed, including: patients intentionally using an over-the-counter or a prescription drug for a different condition than the drug is directed or prescribed for, patients intentionally

taking more drug or at a different dosing interval than prescribed, and individuals intentionally using a drug not prescribed for them, though for therapeutic purposes. Misuse will be captured in the Poison Center Program and be defined as those cases with a reason for exposure of intentional misuse, unintentional general and unintentional therapeutic error. In the Poison Center Program, intentional misuse is defined as: “an exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of psychotropic effect” [4]. Definitions of unintentional general and unintentional therapeutic errors and exposures appear below.

4.7.4. Unintentional Exposures

Unintentional Exposures will be captured in the Poison Center Program. In the Poison Center Program, unintentional exposures are defined as: “Exposure resulting from an unforeseen or unplanned event” [4].

4.7.5. Unintentional Therapeutic Errors

Unintentional Therapeutic Errors will be captured in the Poison Center Program. In the Poison Center Program, unintentional therapeutic errors are defined as: “An unintentional deviation from a proper therapeutic regiment that results in the wrong dose, incorrect route of administration, administration to the wrong person, or administration of the wrong substance” [4].

4.7.6. Pediatric Unintentional General Exposures

Pediatric Unintentional General Exposures will be captured in the Poison Center Program and are defined as those cases in children under 6 with a reason code of unintentional general which consists primarily of accidental unsupervised ingestions such as a toddler getting into a grandparent’s prescription medicine.

4.7.7. Pediatric Unintentional General Exposures Resulting in a Major Medical Outcome, Hospitalization, or Death

Pediatric Unintentional General Exposures will be captured in the Poison Center Program and are defined as those cases in children under 6 with a reason code of unintentional general and an exposure resulting in a major medical outcome or death defined as a Major Medical Outcome, Hospitalization, or Death. In addition those with a level of healthcare coded as: admitted to critical care, admitted to non-critical care, or admitted to psychiatric care facility will be included.

4.7.8. Pediatric Unintentional General Exposures Treated/Evaluated and Released

Pediatric Unintentional General Exposures will be captured in the Poison Center Program and are defined as those cases in children under 6 with a reason code of unintentional general and level of healthcare coded as treated/evaluated and released.

4.7.9. Adolescent Abuse

Adolescent Abuse will be captured in the Poison Center Program and is defined as cases 13-19 years old or with an age code of teen that have a reason for exposure of intentional abuse. This is a subset of all intentional abuse cases noted above.

4.7.10. Major Medical Outcome, Hospitalization, or Death

In the Poison Center Program any exposure resulting in a major medical outcome, hospitalization, or death will be included.

4.7.11. Death

Death is recorded in the Poison Center Program medical outcome field and is based upon case follow-up.

4.8. Comparators

Two comparator groups were analyzed: IR prescription opioids and prescription stimulants.

4.8.1. Immediate-Release (IR) Prescription Opioids

Rates of abuse, misuse, and death for ER/LA REMS opioids will be compared to corresponding rates for prescription IR opioids. This control group will include IR formulations of fentanyl, hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, and tapentadol. IR formulations for injection will be excluded.

4.8.2. Prescription Stimulants

Although the ER/LA REMS is specifically targeted to ER/LA REMS opioids, some overlap of the education effect may be realized for IR opioids as well. For this reason ER/LA REMS opioid rates will also be compared to rates for prescription stimulants when collected. Prescription stimulants will consist of methylphenidates and prescription amphetamines. Prescription stimulants are not collected in the Treatment Center Programs Combined and thus will be excluded for analyses of this program only.

4.9. Denominators

Three denominators that will be considered are population, number of prescriptions dispensed, and number of dosing units dispensed. The population denominator will be considered primary.

4.10. Analysis

Poisson regression will be used to compare changes in rates of abuse, misuse, and death and other outcomes over time within the ER/LA REMS opioid group to changes in rates among the comparator groups.

Time will be divided into three periods: Pre-Implementation (third quarter 2010 through second quarter 2012), Transition (third quarter 2012 through second quarter 2013), and Active Period (third quarter 2013 through fourth quarter 2014). The Transition Period corresponds to the release of the class-wide medication guide, while the Active Period corresponds to the time

period when both the medication guide and prescriber education were implemented. Mean outcome rates will be compared across the three periods.

Drug products will be categorized as an ER/LA REMS opioid or comparators: IR opioids or stimulants. The total number of mentions of one or more ER/LA REMS opioid or comparator in the 3-digit ZIP codes covered by the RADARS System each quarter will be computed and used as the dependent variable in the Poisson regression models. The denominator of the rates will enter the Poisson model as an offset variable. A drug group specific variance structure will be fit, thus allowing for different variances in the ER/LA REMS opioid group versus the comparators.

For the means model, the Poisson regression model will include fixed effects for the period by drug group effect which will be used to determine if:

1. There are changes in the Pre-Implementation to Transition Period means.
2. There are changes in the Pre-Implementation to Active Period means.
3. There are changes in the Transition to Active Period means
4. The Transition Period to Pre-Implementation changes in means in the ER/LA REMS group differs from the changes in means for the comparator groups.
5. The Active Period to Transition changes in means in the ER/LA REMS group differs from the changes in means for the comparator groups.
6. The Active Period to Pre-Implementation changes in means in the ER/LA REMS group differs from the changes in means for the comparator groups.

5. RESULTS

5.1. Overall Results

5.1.1. Emergency Department Visits from the RADARS System Poison Center Program

Figure 5.1.1.1 through Figure 5.1.1.3 display the pre-implementation to active period percent change in population, prescription dispensed, and dosing unit mean rates for exposures treated/evaluated and released and 95% confidence intervals for ER/LA REMS opioids and comparator drugs.

Figure 5.1.1.1
 The RADARS System Poison Center Program
Treated/Evaluated and Released
Percent Change from Pre-Implementation to Active Period Average Population Adjusted
Rates
 From Third Quarter 2010 to Fourth Quarter 2014

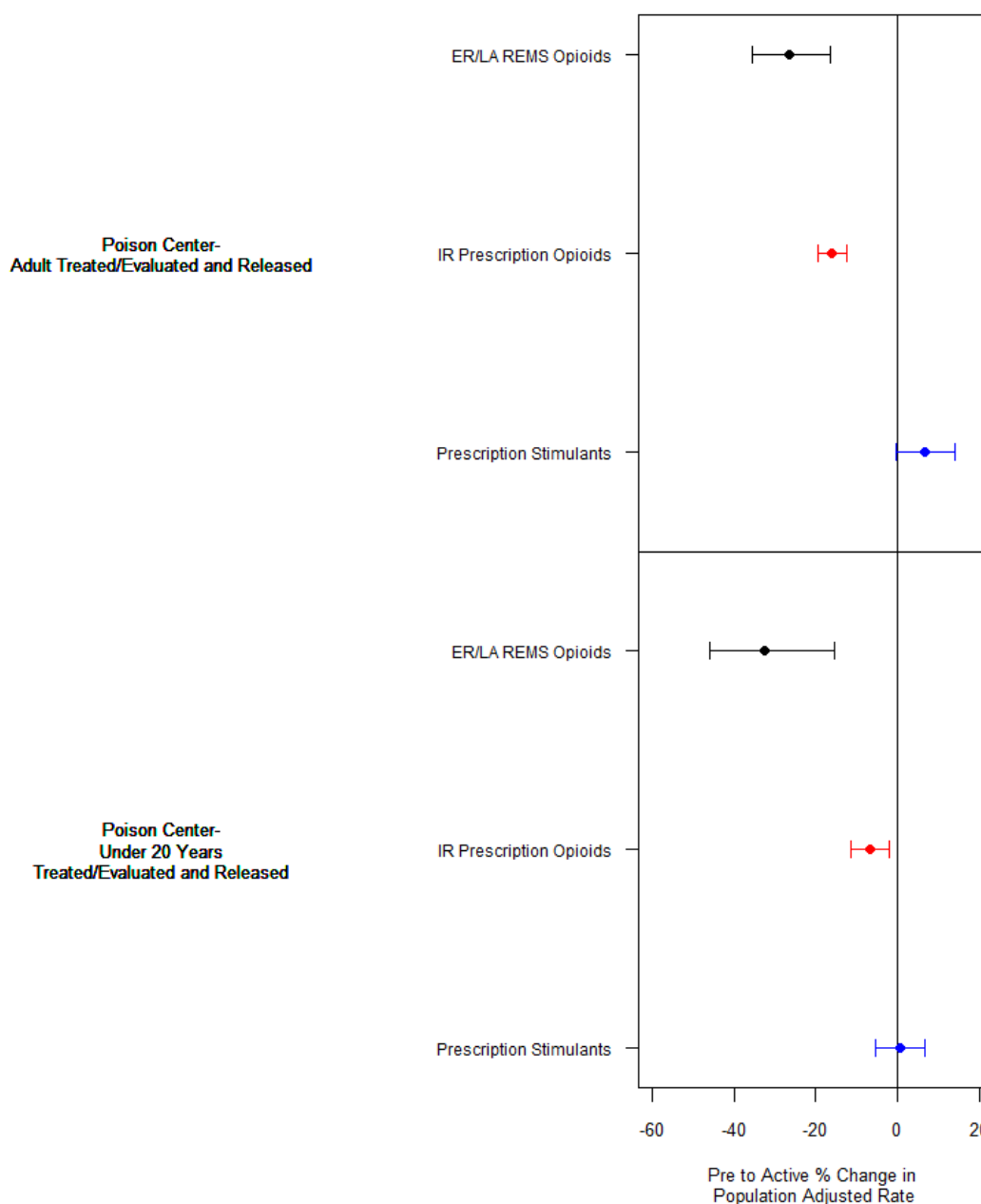


Figure 5.1.1.2
 The RADARS System Poison Center Program
Treated/Evaluated and Released
Percent Change from Pre-Implementation to Active Period Average Prescription Adjusted Rates
 From Third Quarter 2010 to Fourth Quarter 2014

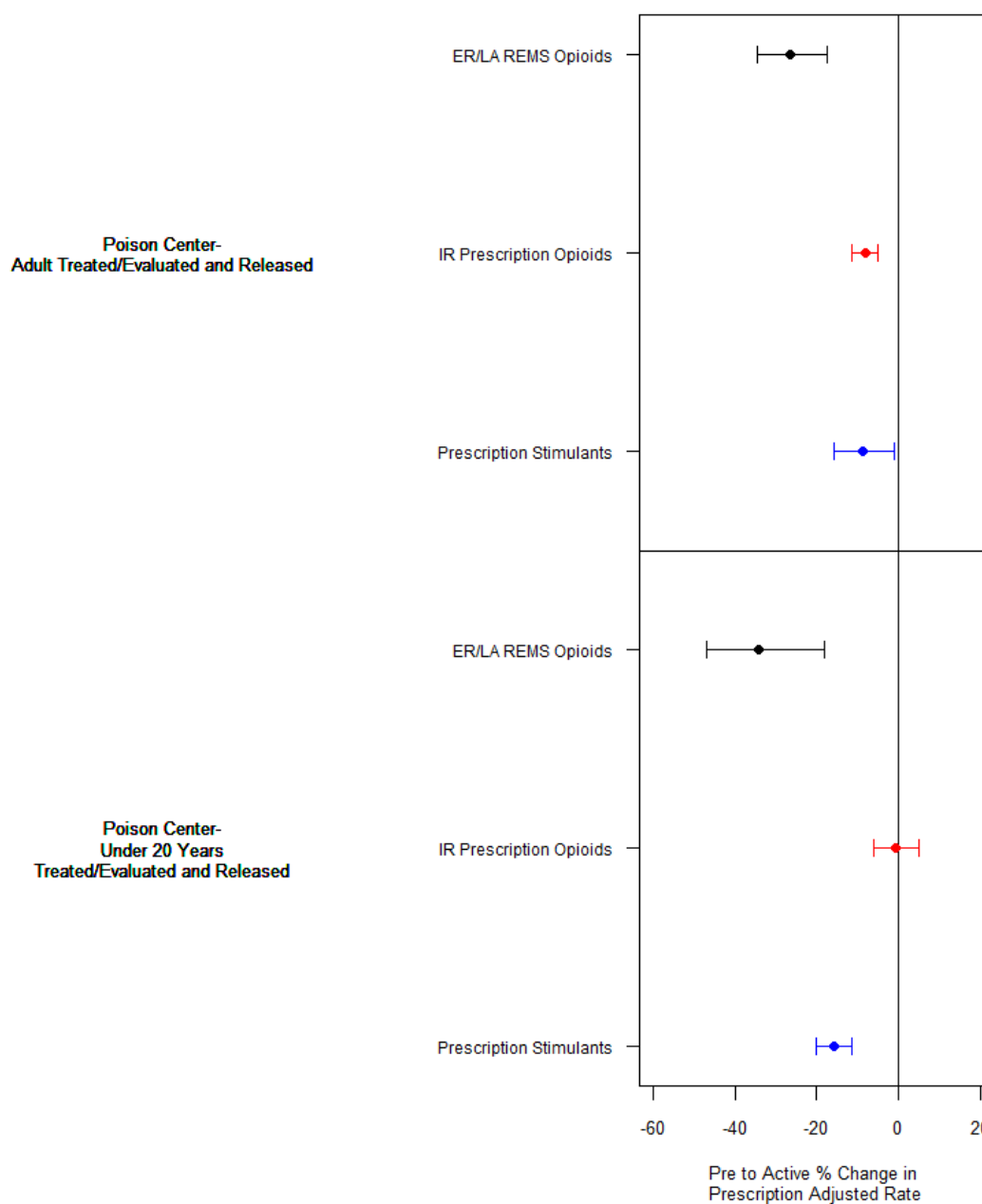
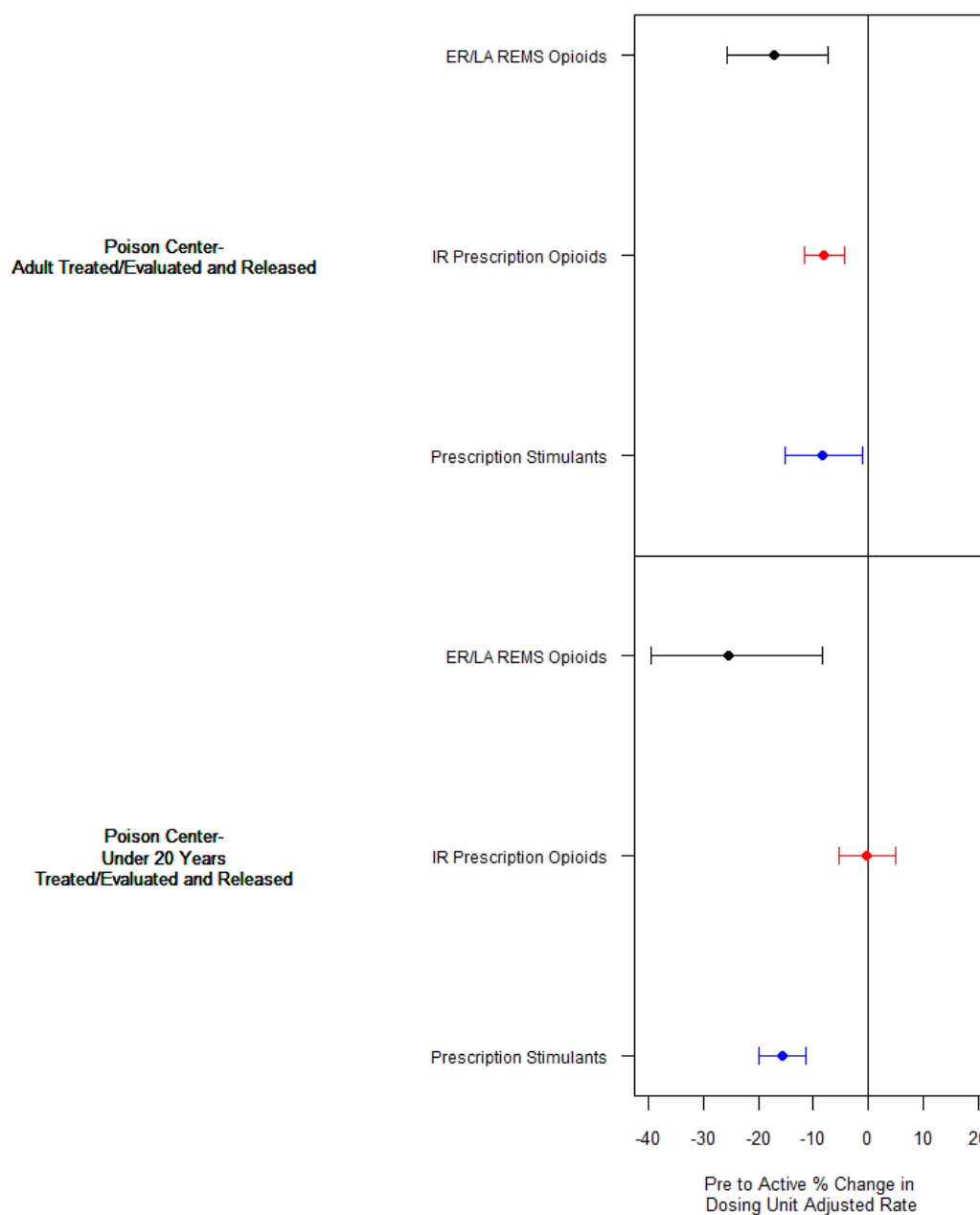


Figure 5.1.1.3
 The RADARS System Poison Center Program
Treated/Evaluated and Released
Percent Change from Pre-Implementation to Active Period Average Dosing Unit Adjusted Rates
 From Third Quarter 2010 to Fourth Quarter 2014



5.1.2. Abuse from the RADARS System Poison Center Program

Figure 5.1.2.1 through Figure 5.1.2.3 display the pre-implementation active period percent change in population, prescription dispensed, and dosing unit mean rates for intentional abuse exposures and 95% confidence intervals for ER/LA REMS opioids and comparator drugs.

Figure 5.1.2.1
 The RADARS System Poison Center Program
Intentional Abuse
Percent Change from Pre-Implementation to Active Period Average Population Adjusted Rates
 From Third Quarter 2010 to Fourth Quarter 2014

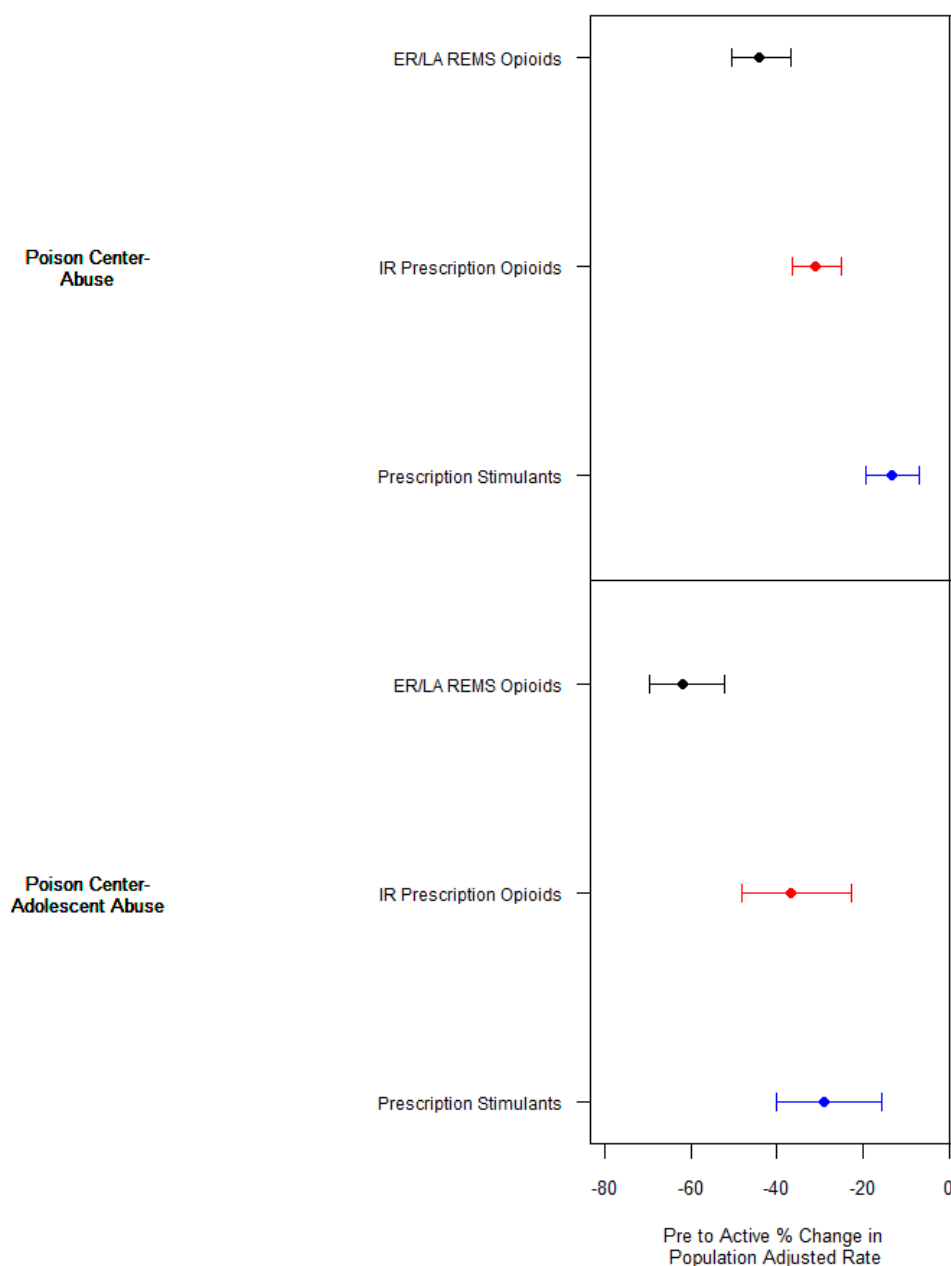


Figure 5.1.2.2
 The RADARS System Poison Center Program
Intentional Abuse
Percent Change from Pre-Implementation to Active Period Average Prescription Adjusted Rates
 From Third Quarter 2010 to Fourth Quarter 2014

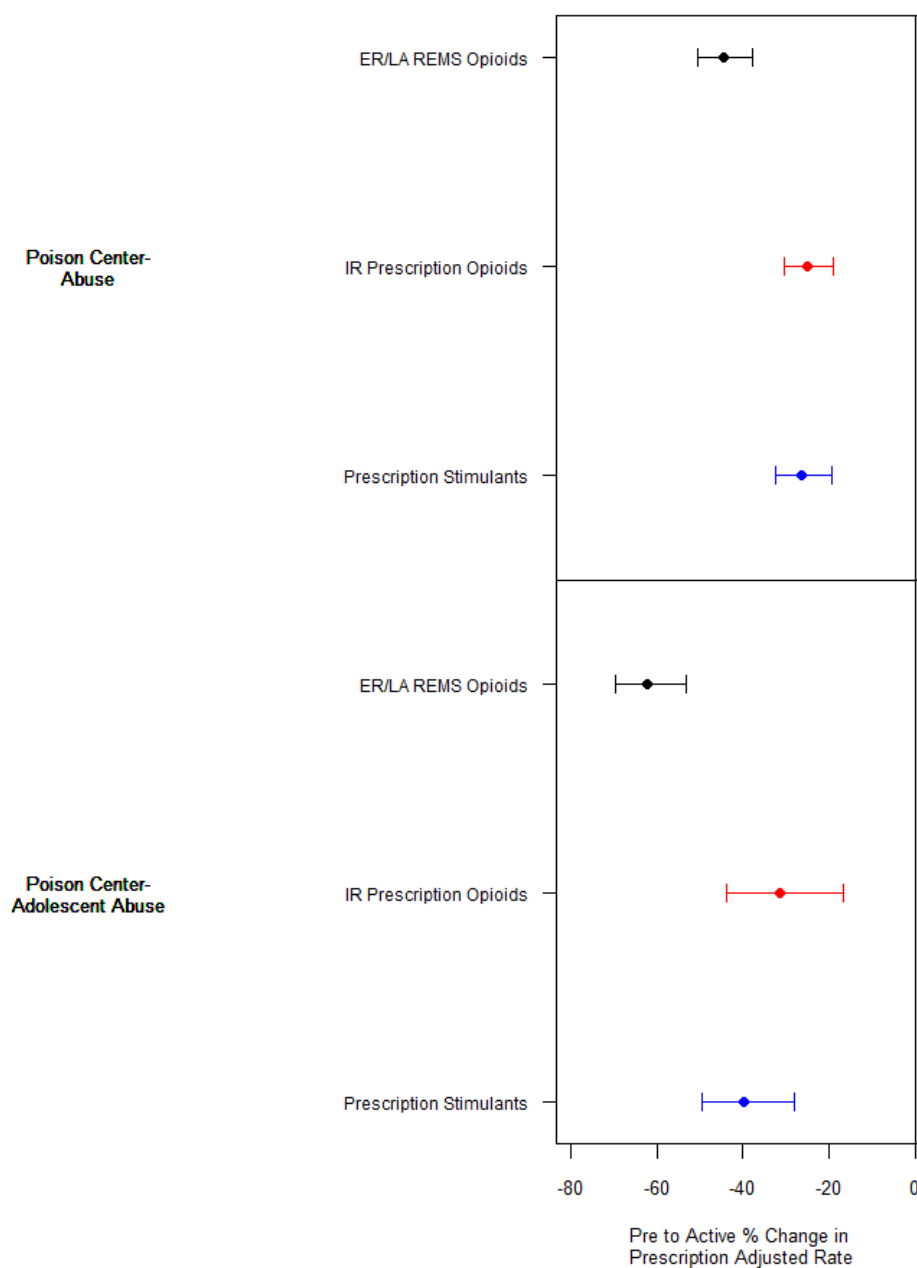
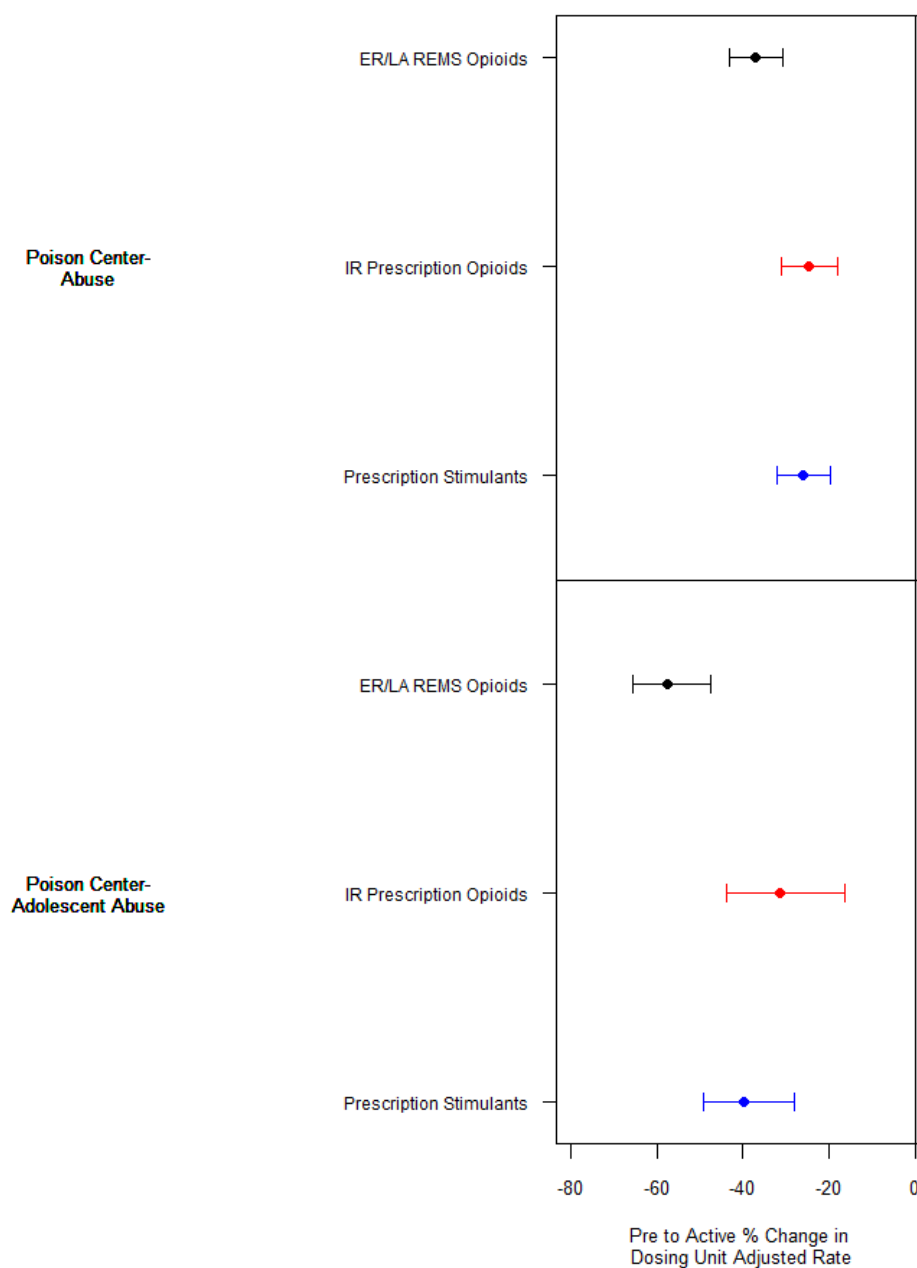


Figure 5.1.2.3
 The RADARS System Poison Center Program
Intentional Abuse
Percent Change from Pre-Implementation to Active Period Average Dosing Unit Adjusted Rates
 From Third Quarter 2010 to Fourth Quarter 2014



5.1.3. Misuse from the RADARS System Poison Center Program

[Figure 5.1.3.1](#) through [Figure 5.1.3.3](#) display the pre-implementation to active period percent change in population, prescription dispensed, and dosing unit mean rates for misuse exposures and 95% confidence intervals for ER/LA REMS opioids and comparator drugs.

Figure 5.1.3.1
 The RADARS System Poison Center Program
Misuse
Percent Change from Pre-Implementation to Active Period Average Population Adjusted Rates
 From Third Quarter 2010 to Fourth Quarter 2014

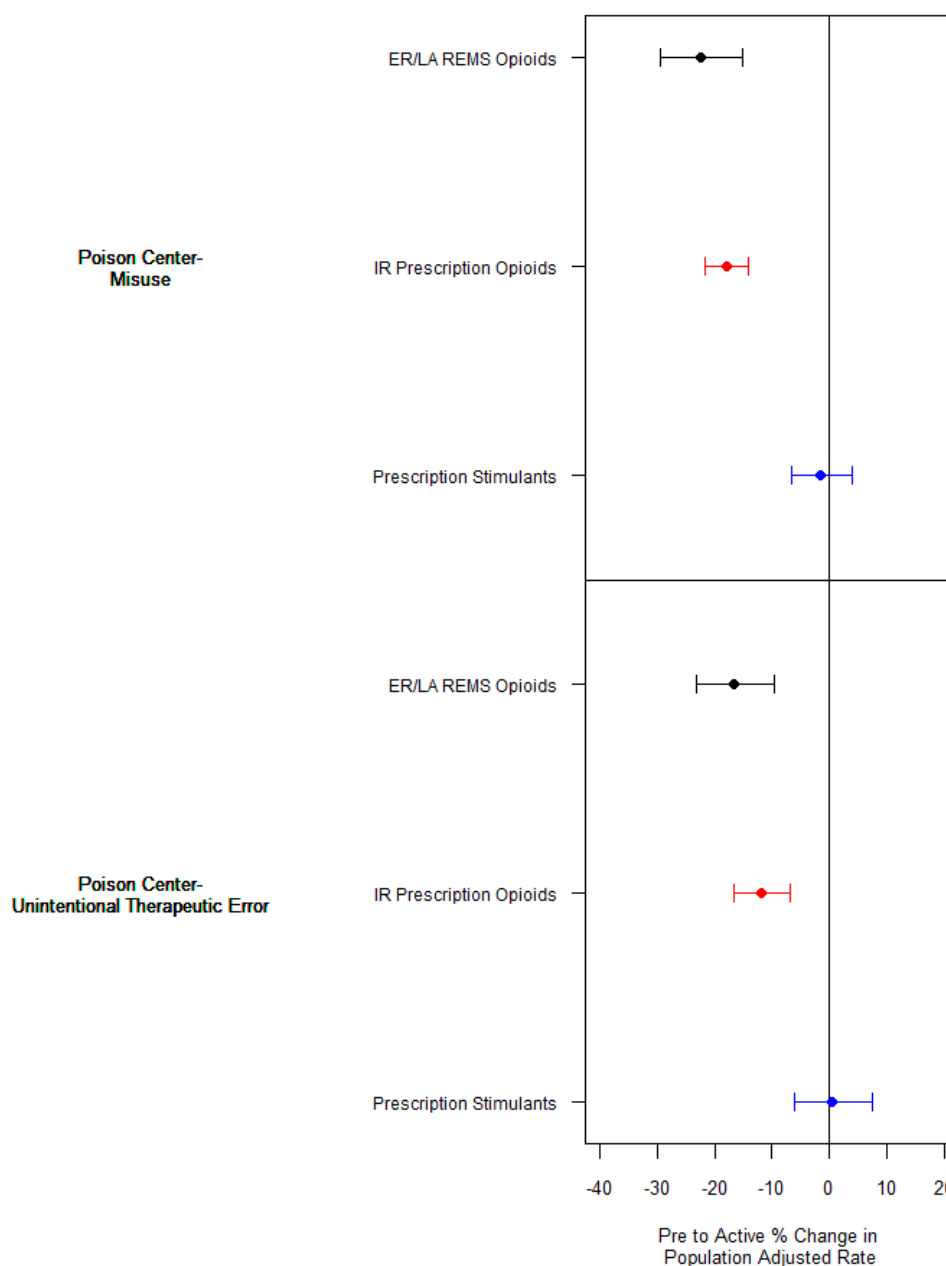


Figure 5.1.3.2
 The RADARS System Poison Center Program
Misuse
Percent Change from Pre-Implementation to Active Period Average Prescription Adjusted Rates
 From Third Quarter 2010 to Fourth Quarter 2014

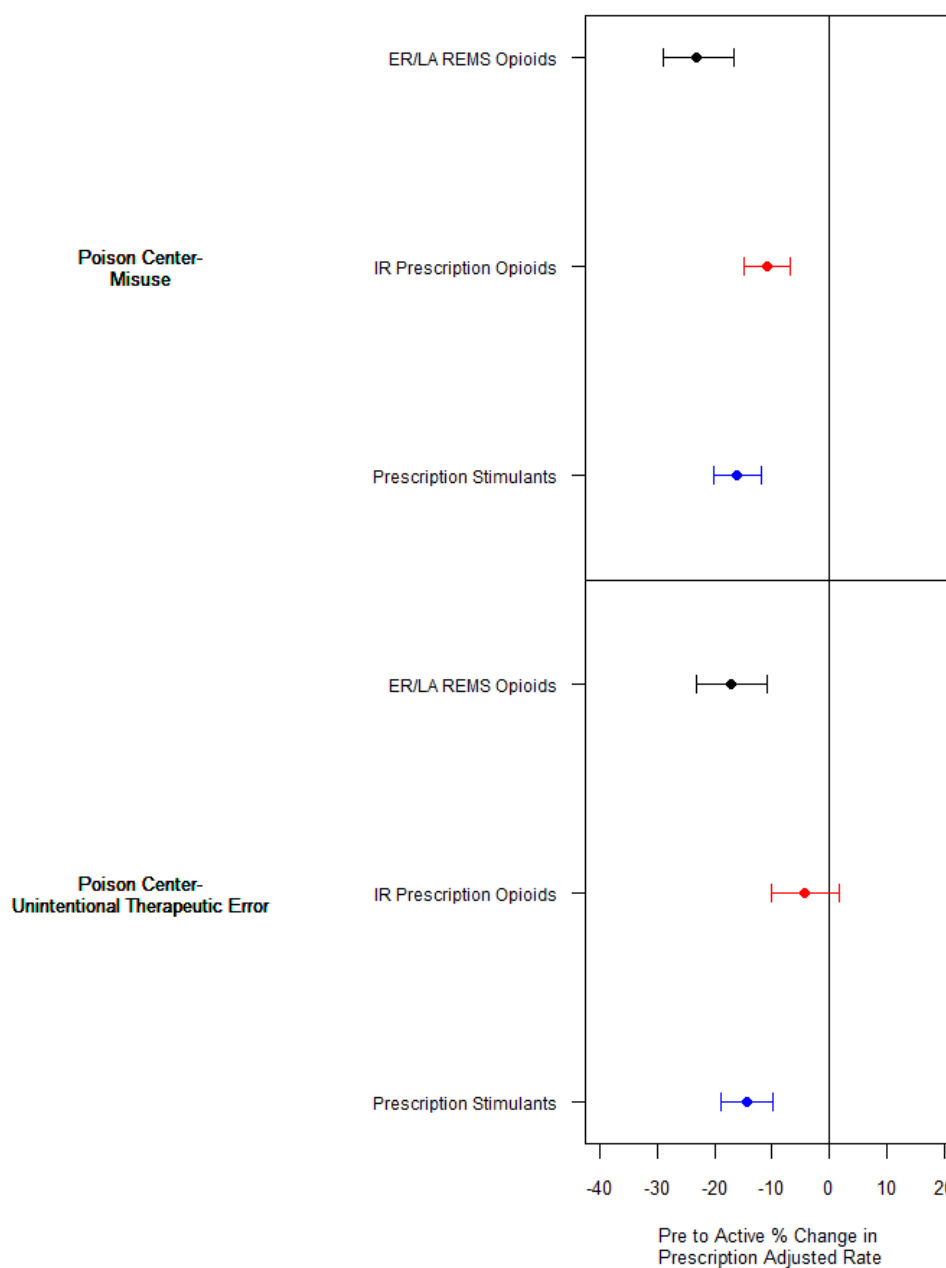
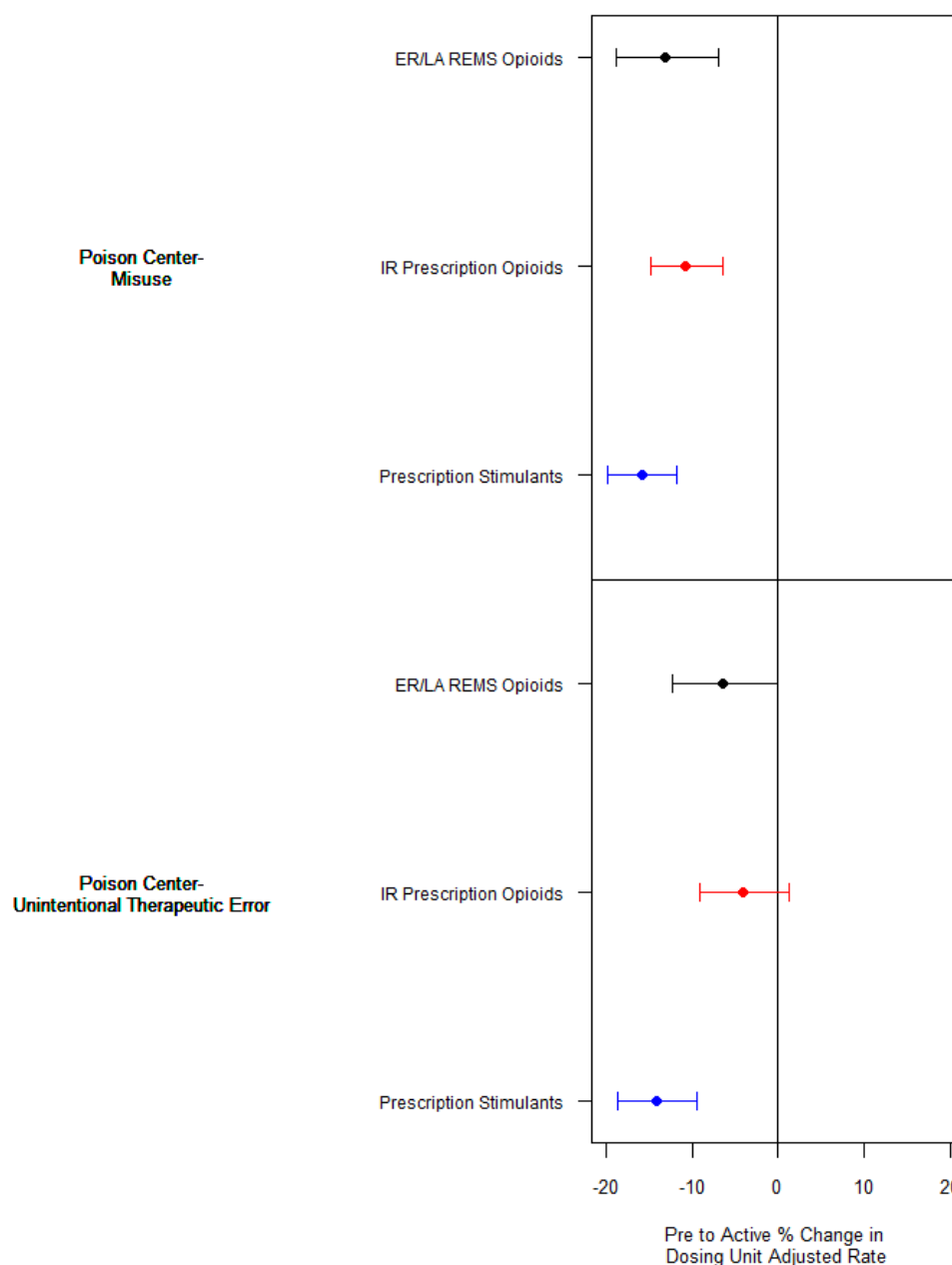


Figure 5.1.3.3
 The RADARS System Poison Center Program
Misuse
Percent Change from Pre-Implementation to Active Period Average Dosing Unit Adjusted Rates
 From Third Quarter 2010 to Fourth Quarter 2014



5.1.4. Unintentional Exposures from the RADARS System Poison Center Program

[Figure 5.1.4.1](#) through [Figure 5.1.4.3](#) display the pre-implementation to active period percent change in population, prescription dispensed, and dosing unit mean rates for unintentional exposures and 95% confidence intervals for ER/LA REMS opioids and comparator drugs.

Figure 5.1.4.1
 The RADARS System Poison Center Program
Unintentional Exposures
Percent Change from Pre-Implementation to Active Period Average Population Adjusted Rates
 From Third Quarter 2010 to Fourth Quarter 2014

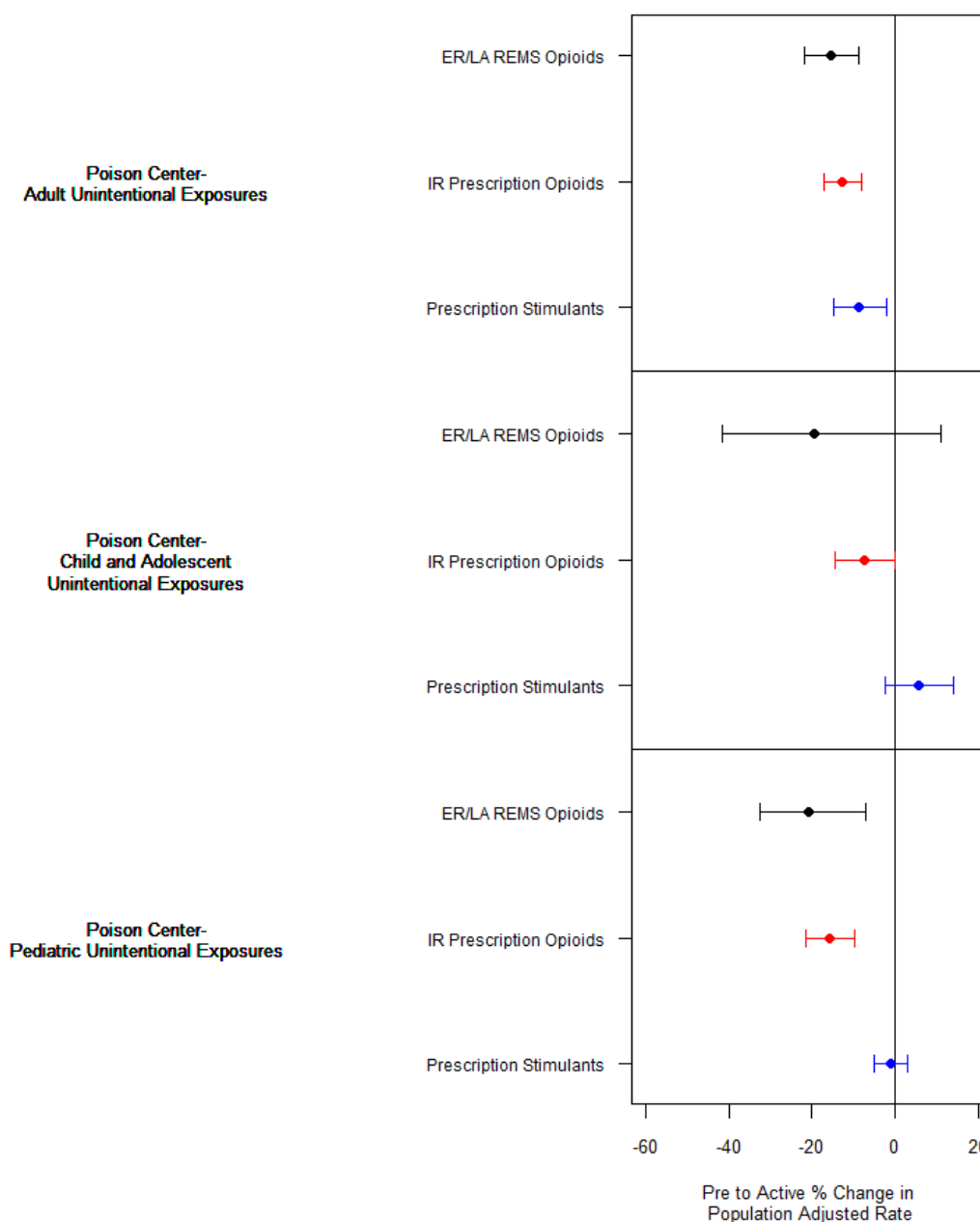


Figure 5.1.4.2
 The RADARS System Poison Center Program
Unintentional Exposures
Percent Change from Pre-Implementation to Active Period Average Prescription Adjusted Rates
 From Third Quarter 2010 to Fourth Quarter 2014

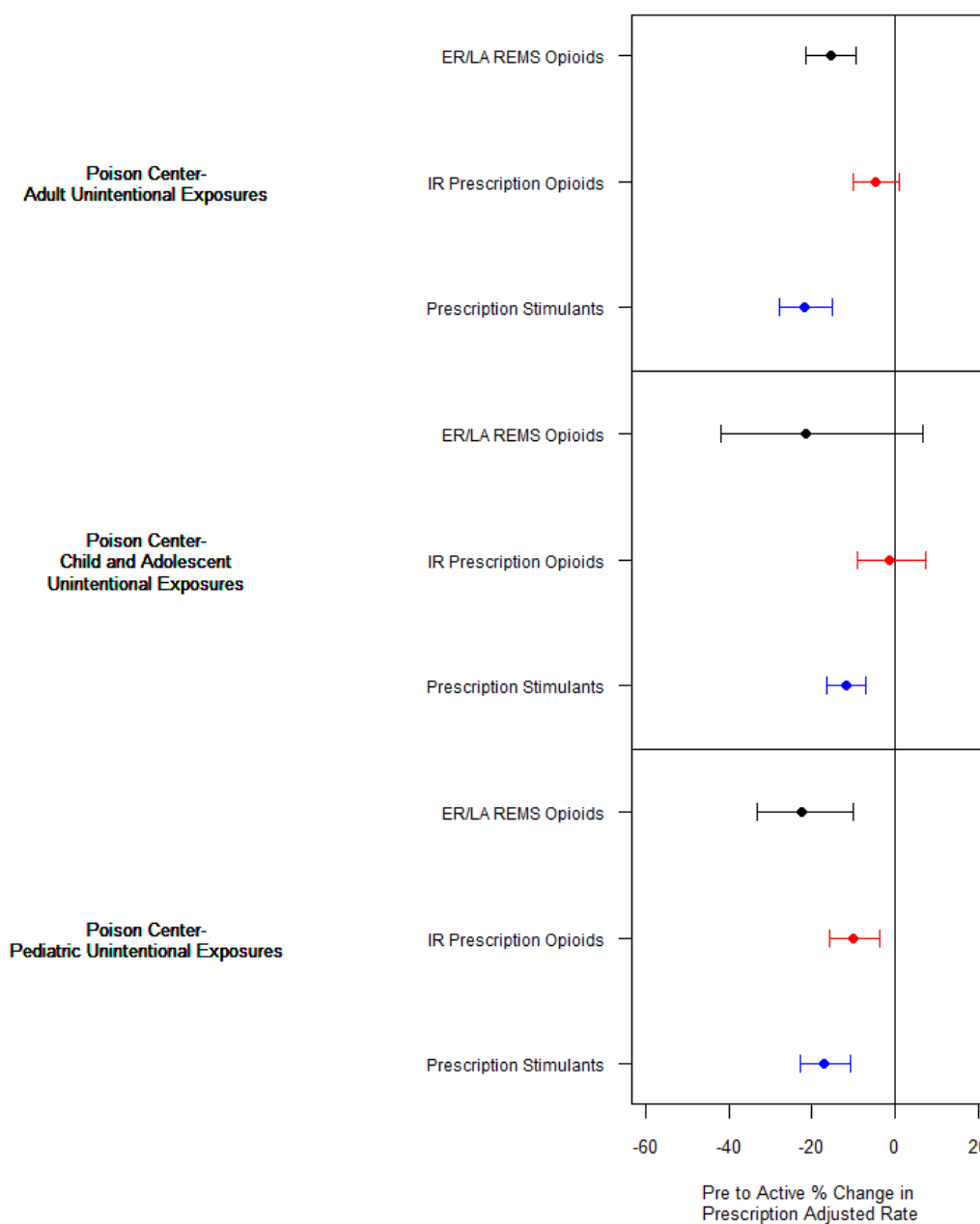
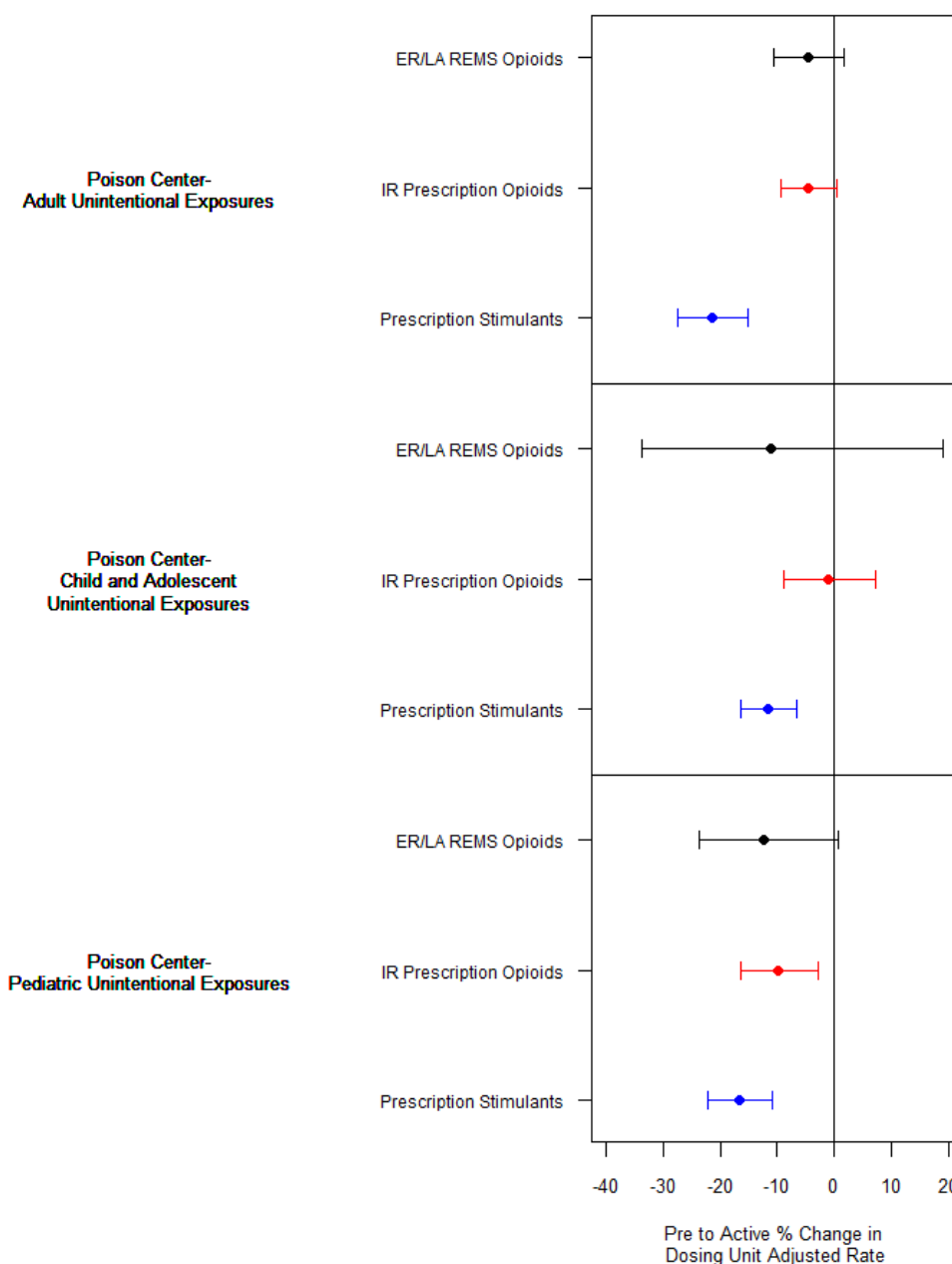


Figure 5.1.4.3
 The RADARS System Poison Center Program
Unintentional Exposures
Percent Change from Pre-Implementation to Active Period Average Dosing Unit Adjusted Rates
 From Third Quarter 2010 to Fourth Quarter 2014



5.1.5. Pediatric Unintentional General Exposures from the RADARS System Poison Center Program

[Figure 5.1.5.1](#) through [Figure 5.1.5.3](#) display the pre-implementation to active period percent change in population, prescription dispensed, and dosing unit mean rates for pediatric unintentional general exposures and 95% confidence intervals for ER/LA REMS opioids and comparator drugs.

Figure 5.1.5.1

The RADARS System Poison Center Program
Pediatric Unintentional General Exposures
Percent Change from Pre-Implementation to Active Period Average Population Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

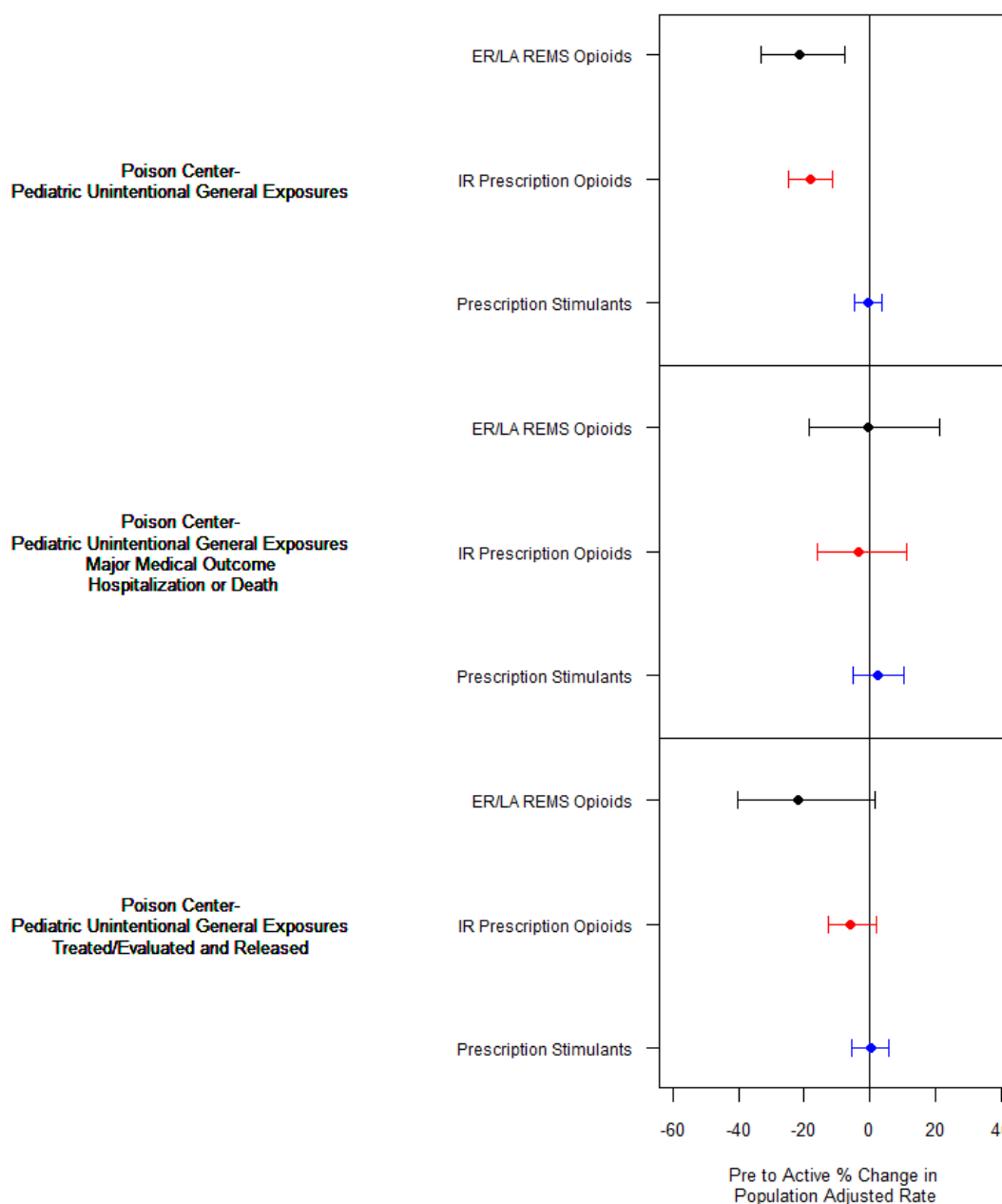


Figure 5.1.5.2
 The RADARS System Poison Center Program
Pediatric Unintentional General Exposures
Percent Change from Pre-Implementation to Active Period Average Prescription Adjusted Rates
 From Third Quarter 2010 to Fourth Quarter 2014

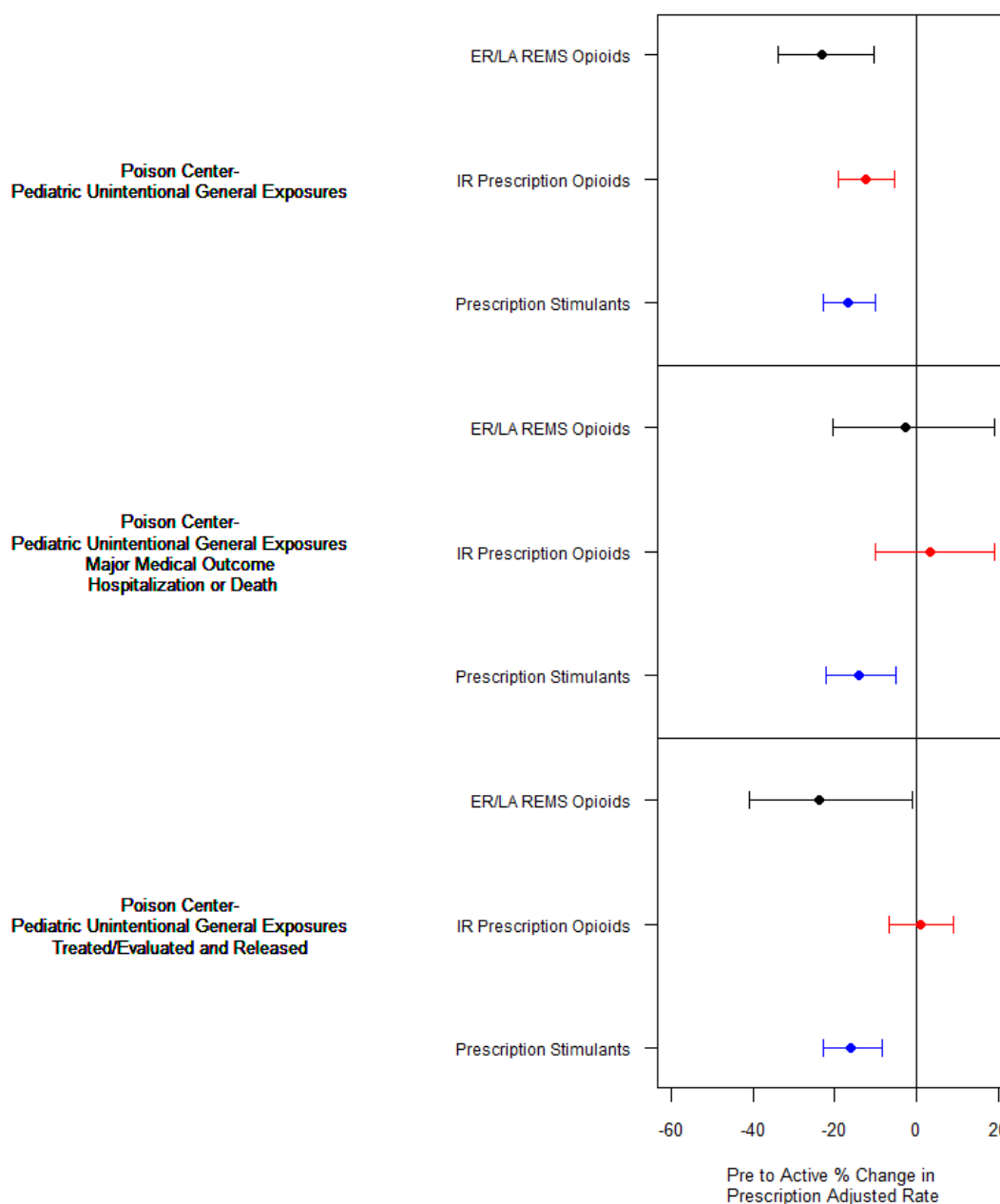
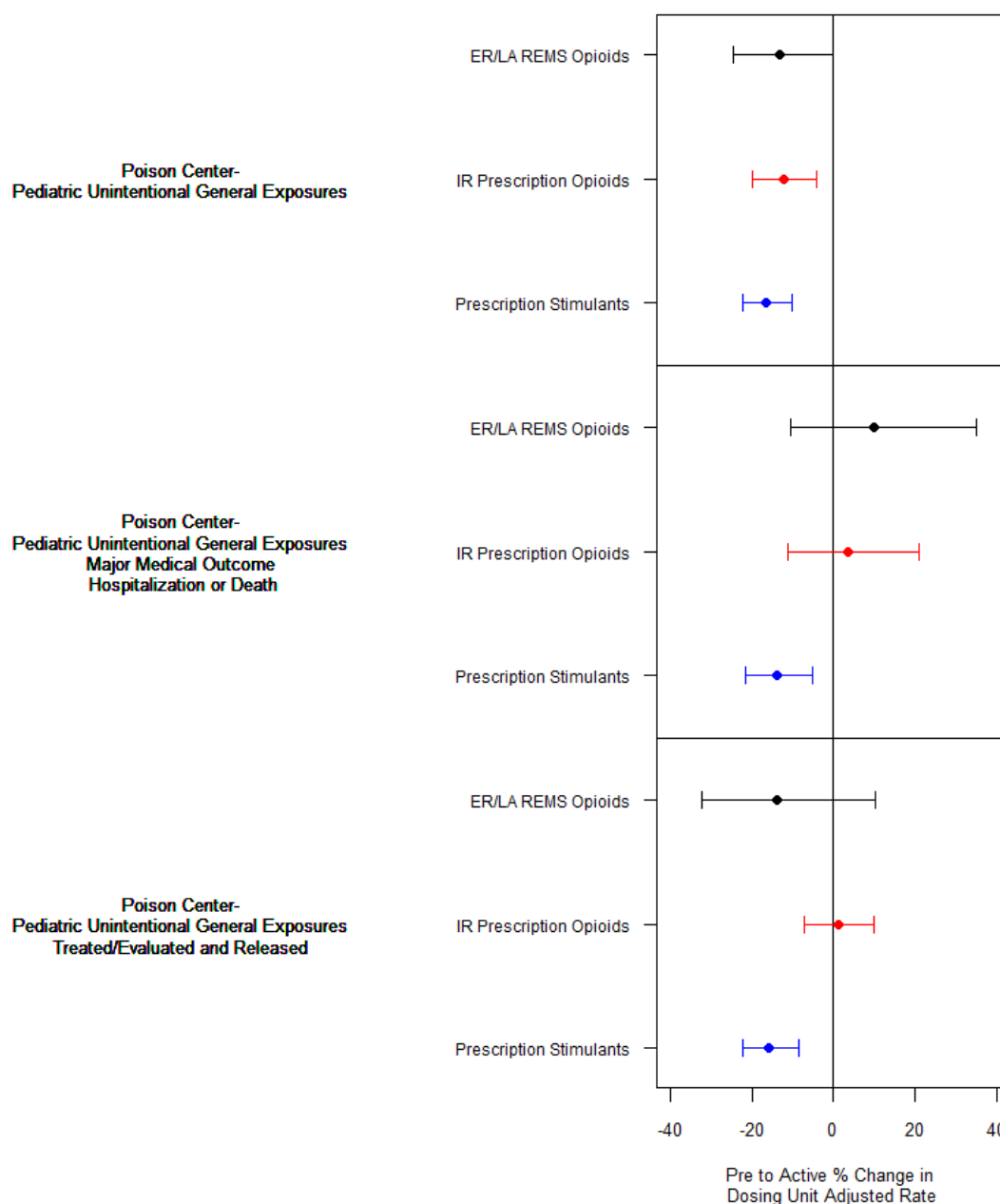


Figure 5.1.5.3
 The RADARS System Poison Center Program
Pediatric Unintentional General Exposures
Percent Change from Pre-Implementation to Active Period Average Dosing Unit Adjusted Rates
 From Third Quarter 2010 to Fourth Quarter 2014



5.1.6. Abuse from the RADARS System Treatment Center Programs Combined

[Figure 5.1.6.1](#) through [Figure 5.1.6.3](#) display the pre-implementation to active period percent change in population, prescription dispensed, and dosing unit mean past 30 day mentions of use to get high (abuse) mention rates and 95% confidence intervals for ER/LA REMS opioids and comparator drugs.

Figure 5.1.6.1

The RADARS System Treatment Center Programs Combined
Mean Past 30 Day Mentions
Percent Change from Pre-Implementation to Active Period Average Population Adjusted
Rates
From Third Quarter 2010 to Fourth Quarter 2014

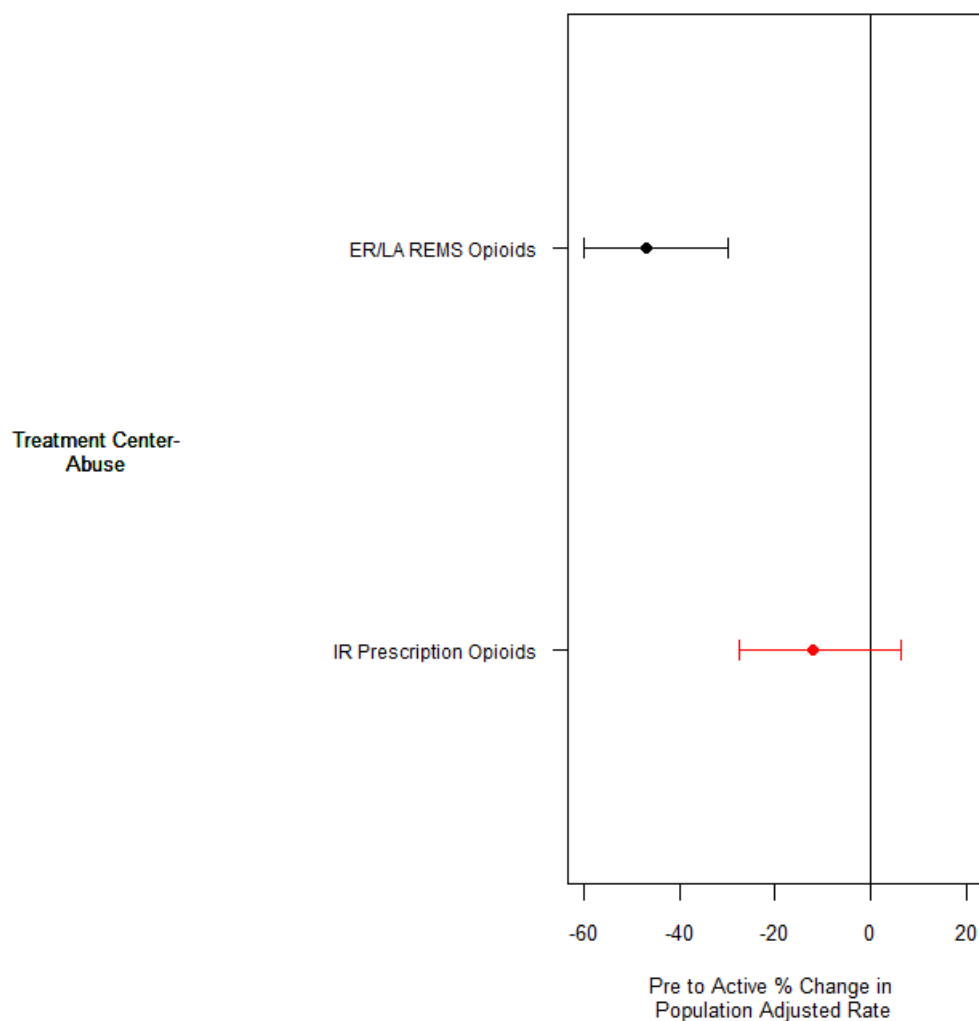


Figure 5.1.6.2

The RADARS System Treatment Center Programs Combined
Mean Past 30 Day Mentions
Percent Change from Pre-Implementation to Active Period Average Prescription Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

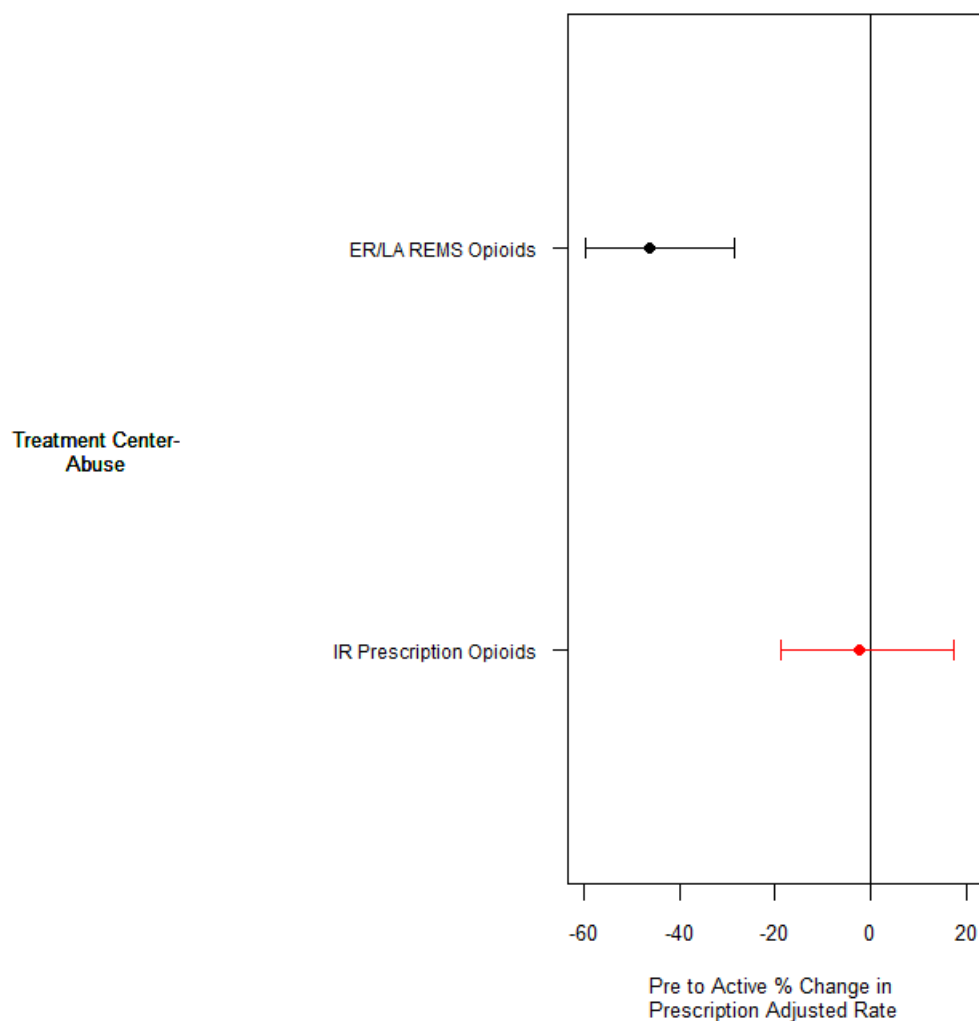
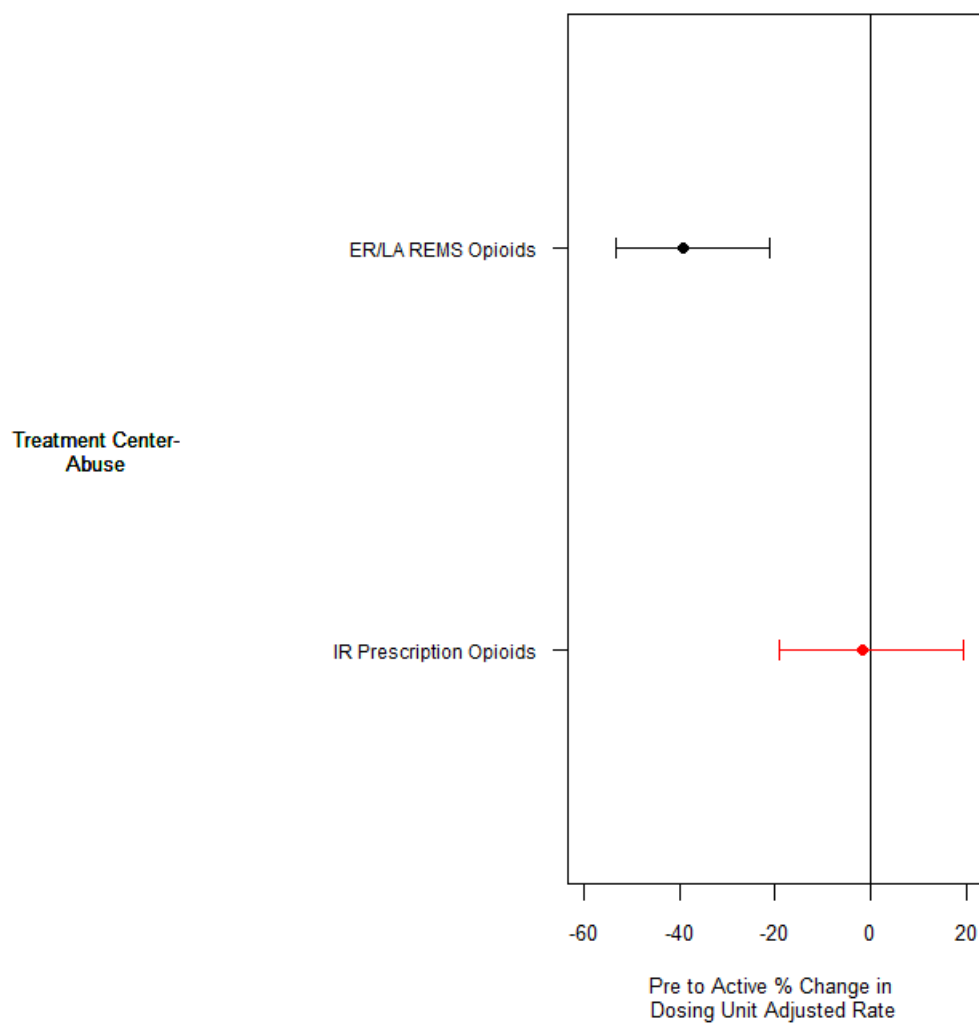


Figure 5.1.6.3

The RADARS System Treatment Center Programs Combined
Mean Past 30 Day Mentions
Percent Change from Pre-Implementation to Active Period Average Dosing Unit Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014



5.1.7. Deaths from the RADARS System Poison Center Program

Figure 5.1.7.1 through Figure 5.1.7.3 display pre-implementation to active period percent change in population, prescription dispensed, and dosing unit mean major medical outcome, hospitalization or death rates and 95% confidence intervals for ER/LA REMS opioids and comparator drugs.

Figure 5.1.7.1
 The RADARS System Poison Center Program
Major Medical Outcome, Hospitalization or Death
Percent Change from Pre-Implementation to Active Period Average Population Adjusted Rates
 From Third Quarter 2010 to Fourth Quarter 2014

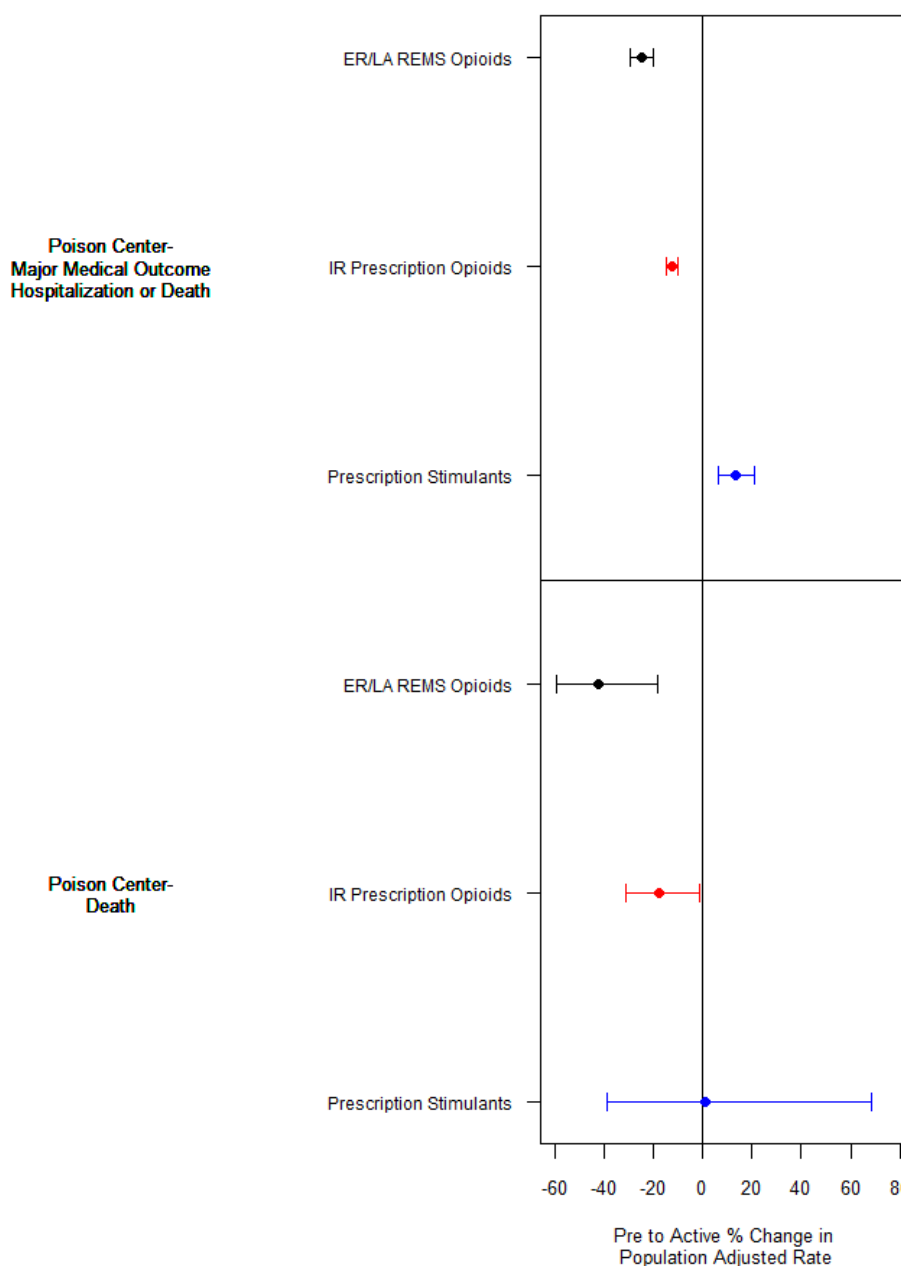


Figure 5.1.7.2

The RADARS System Poison Center Program
Major Medical Outcome, Hospitalization or Death
Percent Change from Pre-Implementation to Active Period Average Prescription Adjusted Rates
 From Third Quarter 2010 to Fourth Quarter 2014

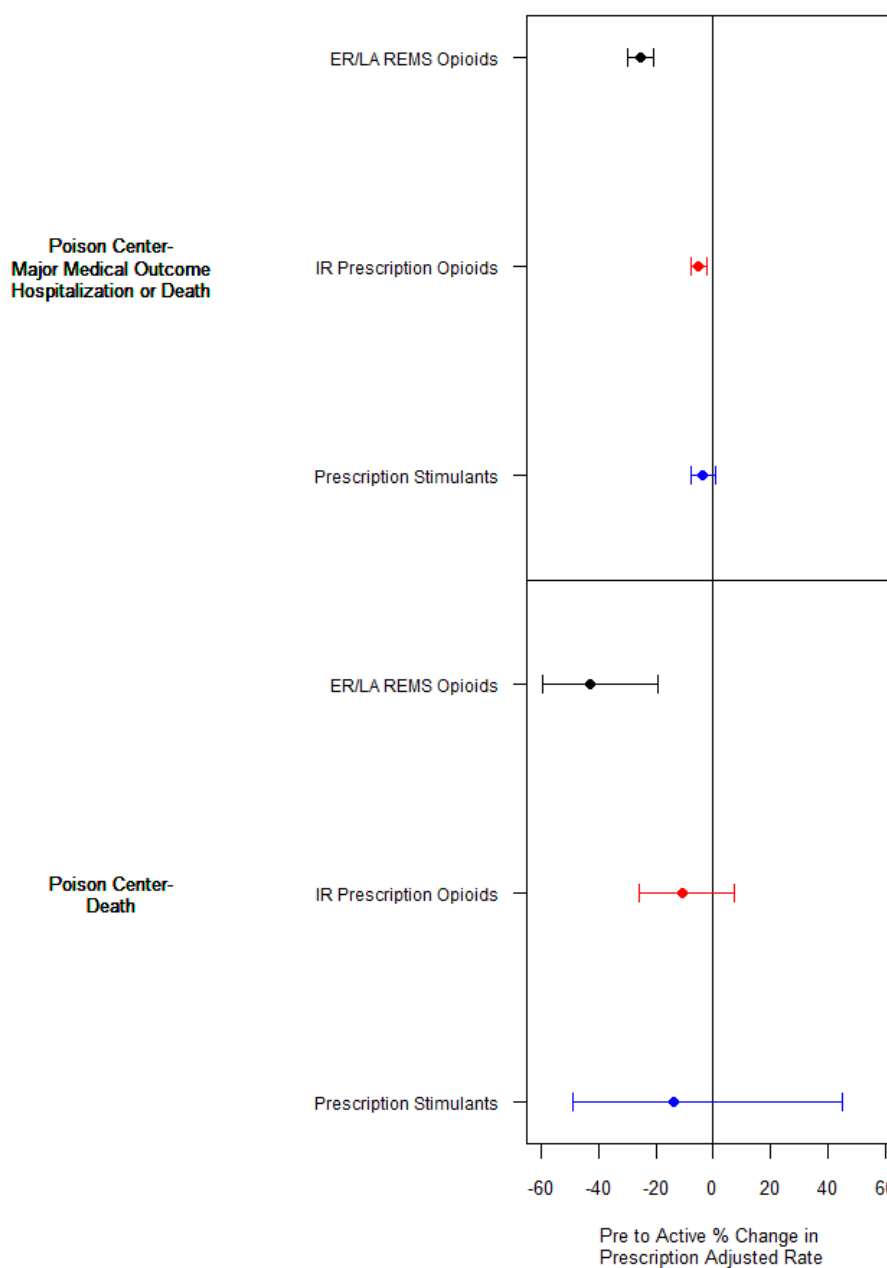
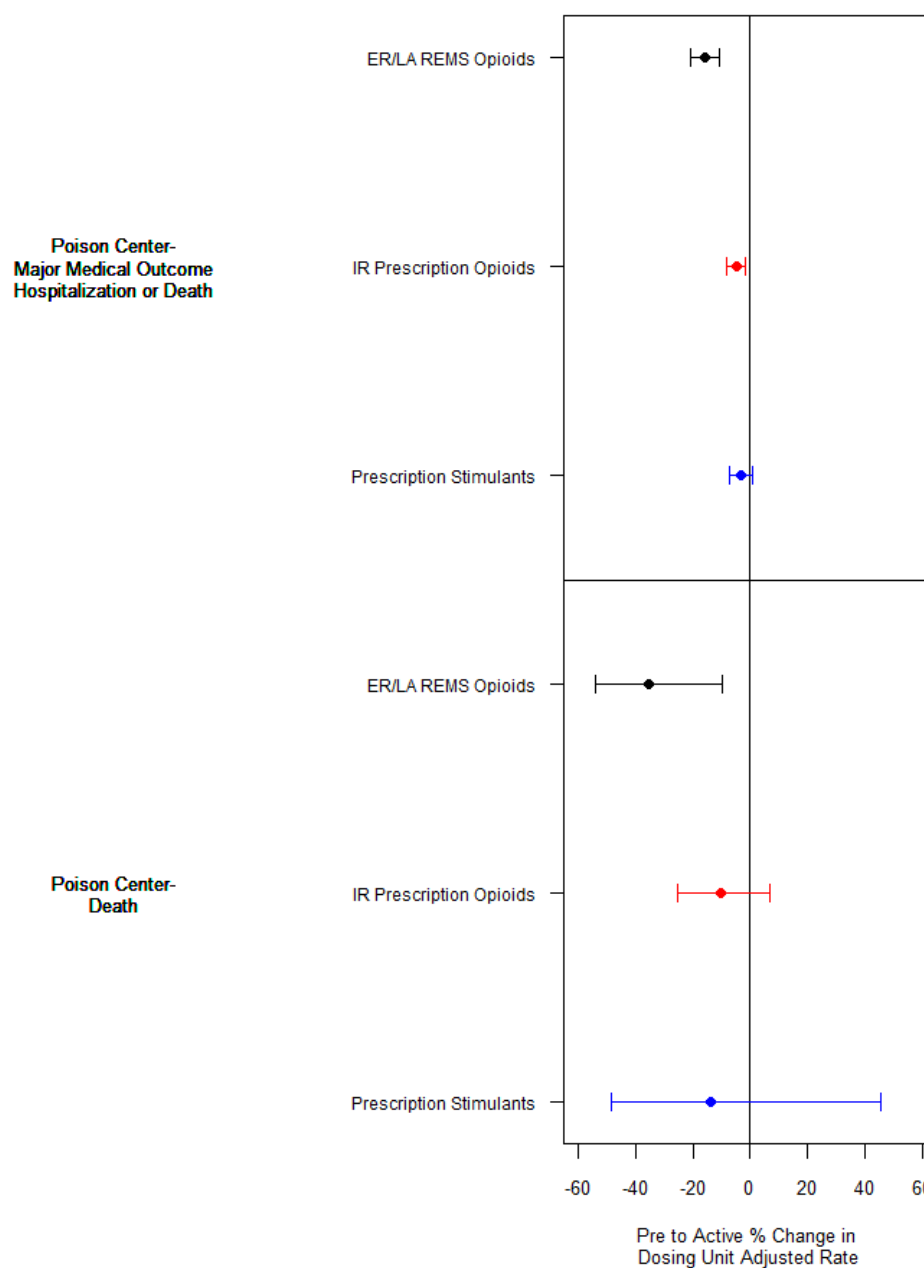


Figure 5.1.7.3
 The RADARS System Poison Center Program
Major Medical Outcome, Hospitalization or Death
Percent Change from Pre-Implementation to Active Period Average Dosing Unit Adjusted Rates
 From Third Quarter 2010 to Fourth Quarter 2014



5.1.8. Abuse from the RADARS System College Survey Program

Figure 5.1.8.1 through Figure 5.1.8.3 display the pre-implementation to active period percent change in population, prescription dispensed, and dosing unit mean past 90 day non-medical use (abuse) mention rates and 95% confidence intervals for ER/LA REMS opioids and comparator drugs.

Figure 5.1.8.1
The RADARS System College Survey Program
Mean Past 90 Day Abuse Mentions
Percent Change from Pre-Implementation to Active Period Average Population Adjusted
Rates
From Third Quarter 2010 to Fourth Quarter 2014

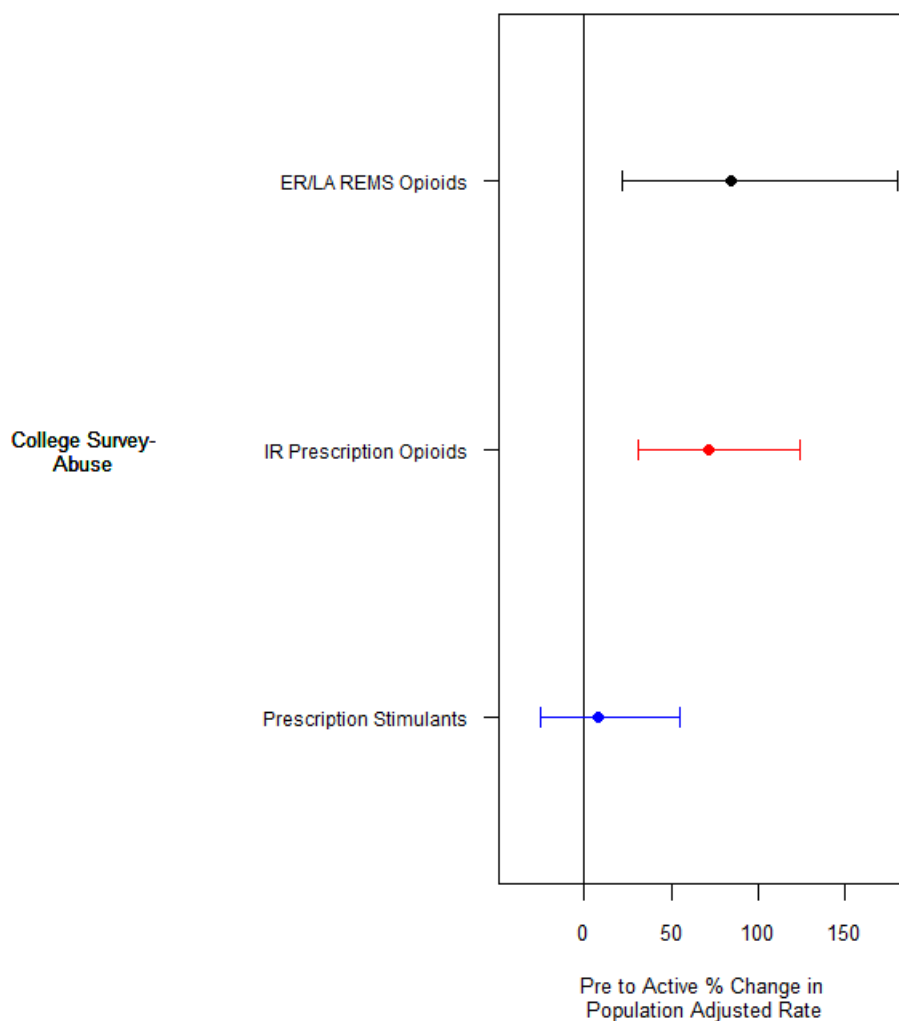


Figure 5.1.8.2
The RADARS System College Survey Program
Mean Past 90 Day Abuse Mentions
Percent Change from Pre-Implementation to Active Period Average Prescription Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

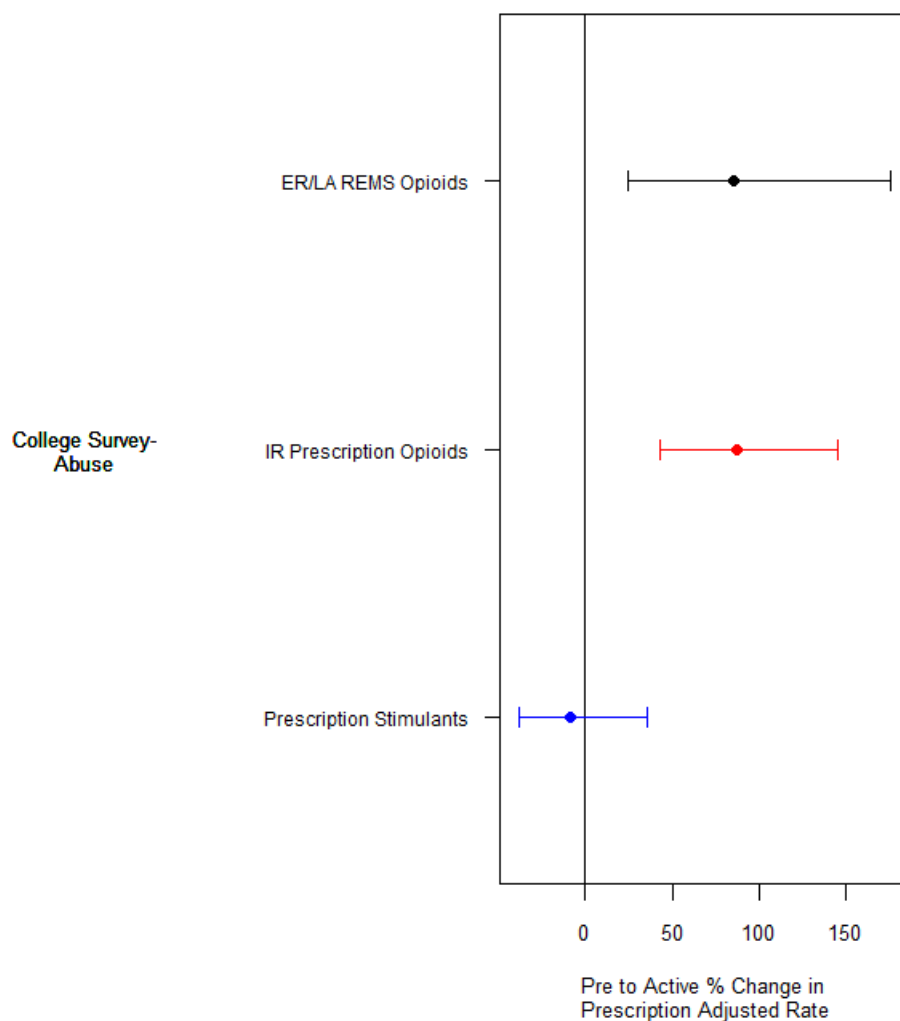
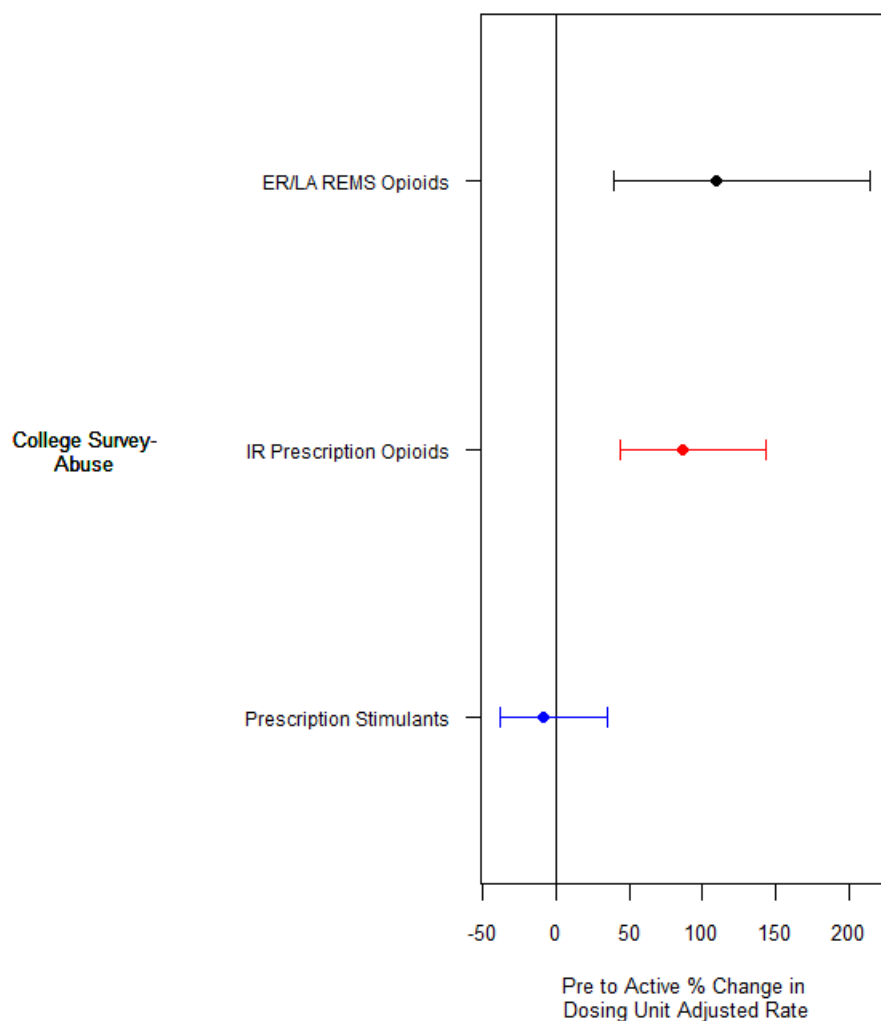


Figure 5.1.8.3
The RADARS System College Survey Program
Mean Past 90 Day Abuse Mentions
Percent Change from Pre-Implementation to Active Period Average Dosing Unit Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014



5.2. Emergency Department Visits from the RADARS System Poison Center Program

5.2.1. Under 20 Years Treated/Evaluated and Released from the RADARS System Poison Center Program

Figure 5.2.1.1 through Figure 5.2.1.3 show the observed and predicted population, prescription dispensed, and dosing unit mean under 20 years treated/ evaluated and released rates and 95% confidence intervals for ER/LA REMS opioids and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 5.2.1.1

The RADARS System Poison Center Program
Under 20 Years Treated/Evaluated and Released Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

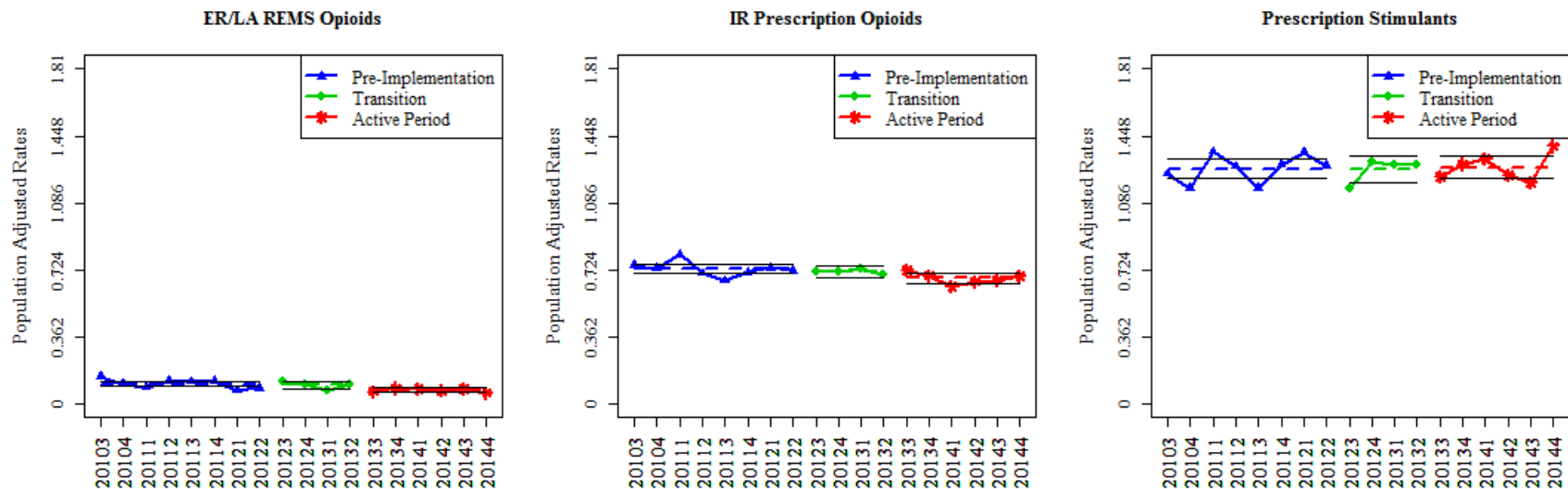


Table 5.2.1.1

The RADARS System Poison Center Program
Under 20 Years Treated/Evaluated and Released Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.107	Pre versus Transition	-6.26%(-25.62%,18.15%)	0.584	.
	Transition	0.100	Transition versus Active	-27.91%(-44.51%,-6.33%)	0.014	.
	Active	0.072	Pre versus Active	-32.42%(-45.99%,-15.44%)	<.001	.
IR Prescription Opioids	Pre	0.727	Pre versus Transition	-1.80%(-7.10%,3.80%)	0.522	0.702
	Transition	0.714	Transition versus Active	-5.10%(-10.50%,0.63%)	0.080	0.045
	Active	0.677	Pre versus Active	-6.80%(-11.30%,-2.08%)	0.005	0.006
Prescription Stimulants	Pre	1.270	Pre versus Transition	-0.38%(-7.01%,6.72%)	0.913	0.622
	Transition	1.265	Transition versus Active	0.99%(-5.99%,8.48%)	0.788	0.015
	Active	1.278	Pre versus Active	0.60%(-5.29%,6.86%)	0.846	<.001

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids under 20 years treated/ evaluated and released population rate decreased 6.26% between the Pre-Implementation and Transition time periods. This decrease is not statistically significant.

The mean IR prescription opioids under 20 years treated/ evaluated and released population rate decreased 1.80% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the under 20 years treated/ evaluated and released population rate is not statistically significant, indicating that the mean difference in under 20 years treated/ evaluated and released population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.702).

The mean prescription stimulants under 20 years treated/ evaluated and released population rate decreased 0.38% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the under 20 years treated/ evaluated and released population rate is not statistically significant, indicating that the mean difference in under 20 years treated/ evaluated and released population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.622).

The mean ER/LA REMS opioids under 20 years treated/ evaluated and released population rate decreased 27.91% between the Transition and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids under 20 years treated/ evaluated and released population rate decreased 5.10% between the Transition and Active Period time periods. The interaction of drug by time period for the under 20 years treated/ evaluated and released population rate is statistically significant, indicating that the mean difference in under 20 years treated/ evaluated and released population rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids ($p=0.045$).

The mean prescription stimulants under 20 years treated/ evaluated and released population rate increased 0.99% between the Transition and Active Period time periods. The interaction of drug by time period for the under 20 years treated/ evaluated and released population rate is statistically significant, indicating that the mean difference in under 20 years treated/ evaluated and released population rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p=0.015$).

The mean ER/LA REMS opioids under 20 years treated/ evaluated and released population rate decreased 32.42% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids under 20 years treated/ evaluated and released population rate decreased 6.80% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the under 20 years treated/ evaluated and released population rate is statistically significant, indicating that the mean difference in under 20 years treated/ evaluated and released population rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids ($p=0.006$).

The mean prescription stimulants under 20 years treated/ evaluated and released population rate increased 0.60% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the under 20 years treated/ evaluated and released population rate is statistically significant, indicating that the mean difference in under 20 years treated/ evaluated and released population rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p<.001$).

Figure 5.2.1.2

The RADARS System Poison Center Program
Under 20 Years Treated/Evaluated and Released Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

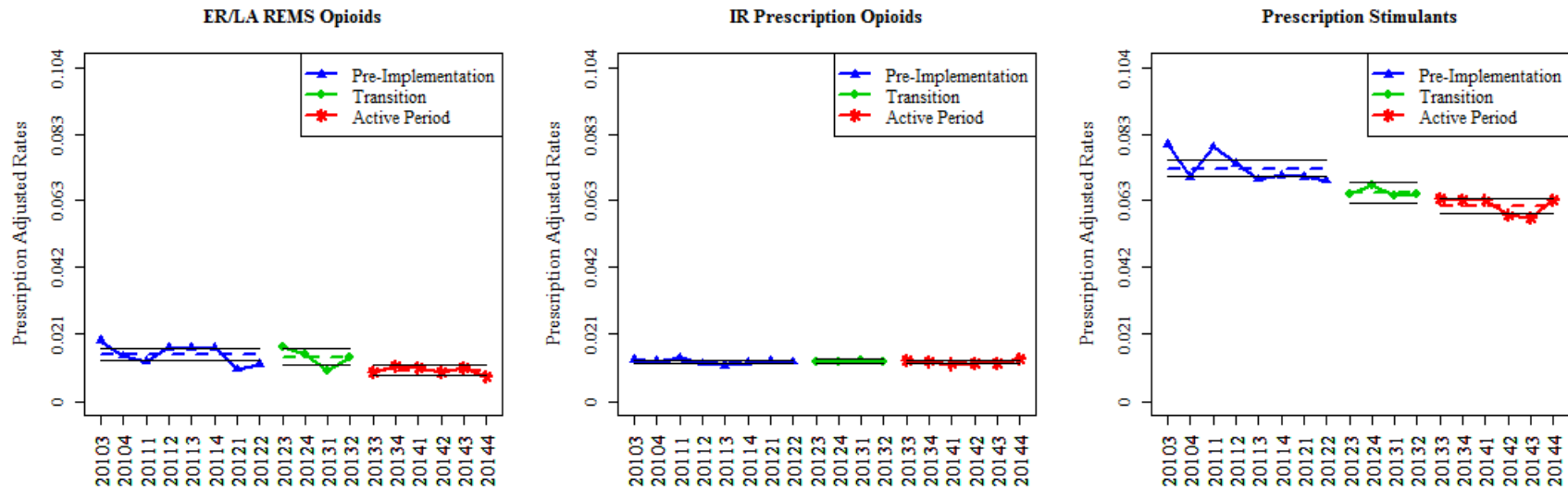


Table 5.2.1.2

The RADARS System Poison Center Program
Under 20 Years Treated/Evaluated and Released Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.015	Pre versus Transition	-6.89%(-25.59%,16.51%)	0.533	.
	Transition	0.014	Transition versus Active	-29.16%(-45.03%,-8.71%)	0.008	.
	Active	0.010	Pre versus Active	-34.04%(-46.92%,-18.04%)	<.001	.
IR Prescription Opioids	Pre	0.012	Pre versus Transition	0.58%(-5.38%,6.91%)	0.853	0.515
	Transition	0.013	Transition versus Active	-1.17%(-7.34%,5.41%)	0.721	0.013
	Active	0.012	Pre versus Active	-0.60%(-5.86%,4.97%)	0.830	<.001
Prescription Stimulants	Pre	0.073	Pre versus Transition	-10.07%(-15.34%,-4.47%)	<.001	0.769
	Transition	0.065	Transition versus Active	-6.44%(-12.13%,-0.37%)	0.038	0.037
	Active	0.061	Pre versus Active	-15.86%(-20.19%,-11.28%)	<.001	0.033

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids under 20 years treated/ evaluated and released prescriptions dispensed rate decreased 6.89% between the Pre-Implementation and Transition time periods. This decrease is not statistically significant.

The mean IR prescription opioids under 20 years treated/ evaluated and released prescriptions dispensed rate increased 0.58% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the under 20 years treated/ evaluated and released prescriptions dispensed rate is not statistically significant, indicating that the mean difference in under 20 years treated/ evaluated and released prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.515).

The mean prescription stimulants under 20 years treated/ evaluated and released prescriptions dispensed rate decreased 10.07% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the under 20 years treated/ evaluated and released prescriptions dispensed rate is not statistically significant, indicating that the mean difference in under 20 years treated/ evaluated and released prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.769).

The mean ER/LA REMS opioids under 20 years treated/ evaluated and released prescriptions

dispensed rate decreased 29.16% between the Transition and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids under 20 years treated/ evaluated and released prescriptions dispensed rate decreased 1.17% between the Transition and Active Period time periods. The interaction of drug by time period for the under 20 years treated/ evaluated and released prescriptions dispensed rate is statistically significant, indicating that the mean difference in under 20 years treated/ evaluated and released prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids ($p=0.013$).

The mean prescription stimulants under 20 years treated/ evaluated and released prescriptions dispensed rate decreased 6.44% between the Transition and Active Period time periods. The interaction of drug by time period for the under 20 years treated/ evaluated and released prescriptions dispensed rate is statistically significant, indicating that the mean difference in under 20 years treated/ evaluated and released prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p=0.037$).

The mean ER/LA REMS opioids under 20 years treated/ evaluated and released prescriptions dispensed rate decreased 34.04% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids under 20 years treated/ evaluated and released prescriptions dispensed rate decreased 0.60% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the under 20 years treated/ evaluated and released prescriptions dispensed rate is statistically significant, indicating that the mean difference in under 20 years treated/ evaluated and released prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids ($p<.001$).

The mean prescription stimulants under 20 years treated/ evaluated and released prescriptions dispensed rate decreased 15.86% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the under 20 years treated/ evaluated and released prescriptions dispensed rate is statistically significant, indicating that the mean difference in under 20 years treated/ evaluated and released prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p=0.033$).

Figure 5.2.1.3

The RADARS System Poison Center Program
Under 20 Years Treated/Evaluated and Released Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

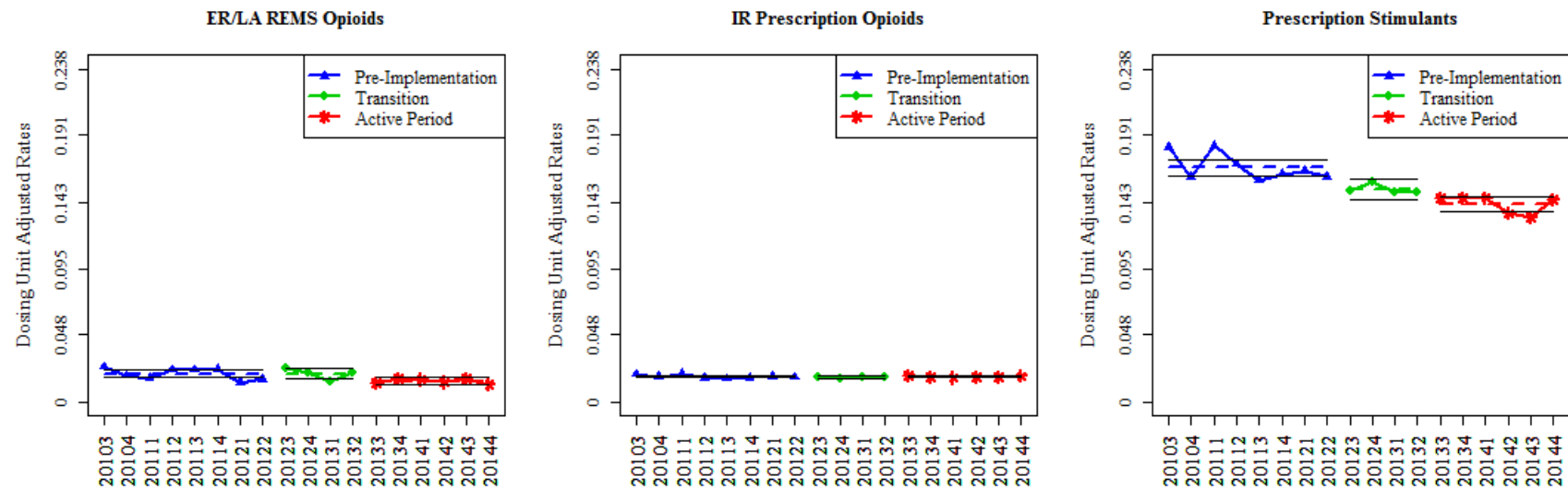


Table 5.2.1.3

The RADARS System Poison Center Program
Under 20 Years Treated/Evaluated and Released Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.020	Pre versus Transition	-0.88% (-19.88%, 22.61%)	0.935	.
	Transition	0.020	Transition versus Active	-24.82% (-40.90%, -4.37%)	0.020	.
	Active	0.015	Pre versus Active	-25.49% (-39.37%, -8.43%)	0.005	.
IR Prescription Opioids	Pre	0.018	Pre versus Transition	-2.16% (-7.68%, 3.70%)	0.462	0.909
	Transition	0.018	Transition versus Active	1.81% (-4.26%, 8.25%)	0.568	0.017
	Active	0.018	Pre versus Active	-0.39% (-5.42%, 4.91%)	0.883	0.007
Prescription Stimulants	Pre	0.168	Pre versus Transition	-9.37% (-14.44%, -4.00%)	<.001	0.426
	Transition	0.152	Transition versus Active	-6.89% (-12.30%, -1.14%)	0.019	0.091
	Active	0.142	Pre versus Active	-15.61% (-19.77%, -11.25%)	<.001	0.250

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids under 20 years treated/ evaluated and released dosing units rate decreased 0.88% between the Pre-Implementation and Transition time periods. This decrease is not statistically significant.

The mean IR prescription opioids under 20 years treated/ evaluated and released dosing units rate decreased 2.16% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the under 20 years treated/ evaluated and released dosing units rate is not statistically significant, indicating that the mean difference in under 20 years treated/ evaluated and released dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.909).

The mean prescription stimulants under 20 years treated/ evaluated and released dosing units rate decreased 9.37% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the under 20 years treated/ evaluated and released dosing units rate is not statistically significant, indicating that the mean difference in under 20 years treated/ evaluated and released dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.426).

The mean ER/LA REMS opioids under 20 years treated/ evaluated and released dosing units rate decreased 24.82% between the Transition and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids under 20 years treated/ evaluated and released dosing units rate increased 1.81% between the Transition and Active Period time periods. The interaction of drug by time period for the under 20 years treated/ evaluated and released dosing units rate is statistically significant, indicating that the mean difference in under 20 years treated/ evaluated and released dosing units rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids ($p=0.017$).

The mean prescription stimulants under 20 years treated/ evaluated and released dosing units rate decreased 6.89% between the Transition and Active Period time periods. The interaction of drug by time period for the under 20 years treated/ evaluated and released dosing units rate is not statistically significant, indicating that the mean difference in under 20 years treated/ evaluated and released dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.091$).

The mean ER/LA REMS opioids under 20 years treated/ evaluated and released dosing units rate decreased 25.49% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids under 20 years treated/ evaluated and released dosing units rate decreased 0.39% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the under 20 years treated/ evaluated and released dosing units rate is statistically significant, indicating that the mean difference in under 20 years treated/ evaluated and released dosing units rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids ($p=0.007$).

The mean prescription stimulants under 20 years treated/ evaluated and released dosing units rate decreased 15.61% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the under 20 years treated/ evaluated and released dosing units rate is not statistically significant, indicating that the mean difference in under 20 years treated/ evaluated and released dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.250$).

Figure 5.2.1.4 through Figure 5.2.1.6 display the mean under 20 years treated/evaluated and released rate percent change from the pre-implementation average population-, prescription dispensed-, and dosing unit- adjusted rates for ER/LA REMS opioids and comparator drugs.

Figure 5.2.1.4

The RADARS System Poison Center Program
Under 20 Years Treated/Evaluated and Released
Percent Change from Average Pre-Implementation Population Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

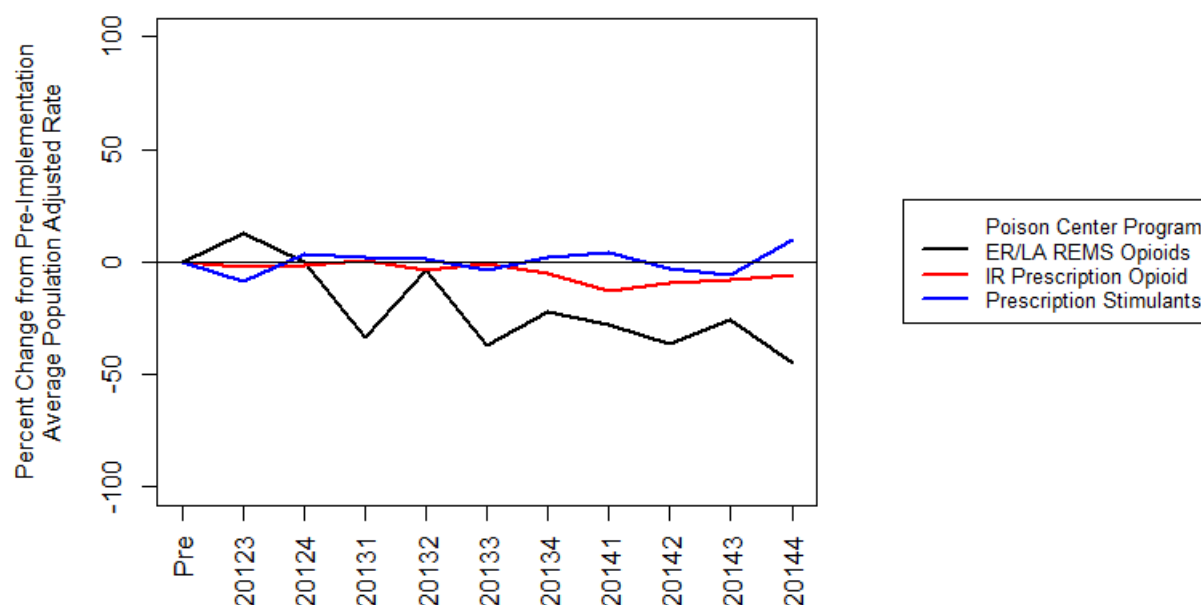


Figure 5.2.1.5

The RADARS System Poison Center Program
Under 20 Years Treated/Evaluated and Released
Percent Change from Average Pre-Implementation Prescription Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

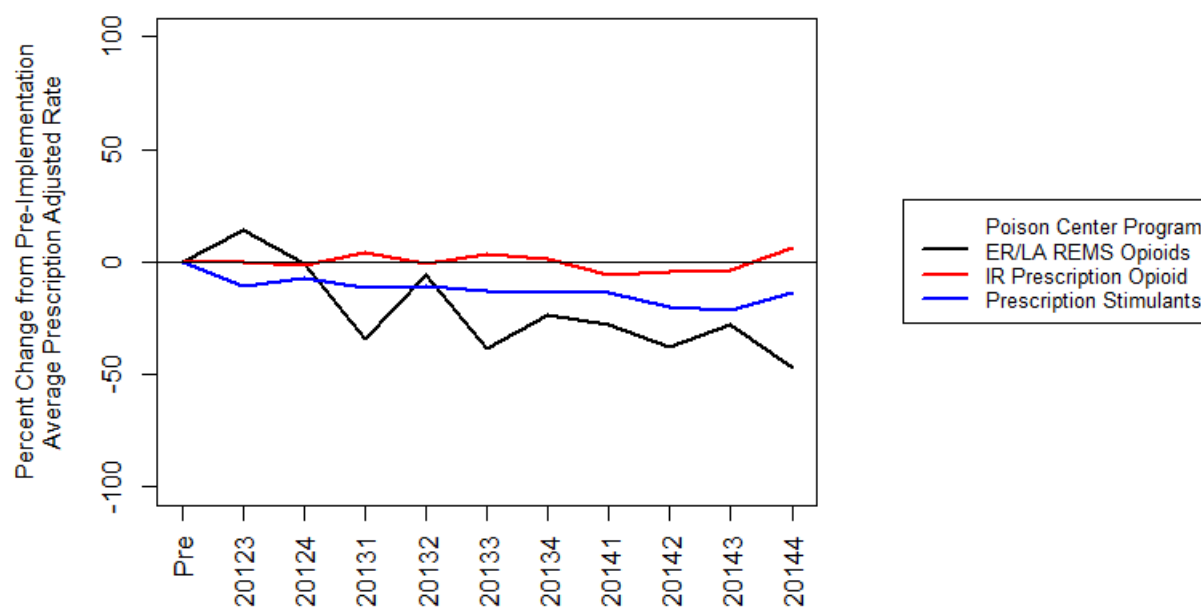
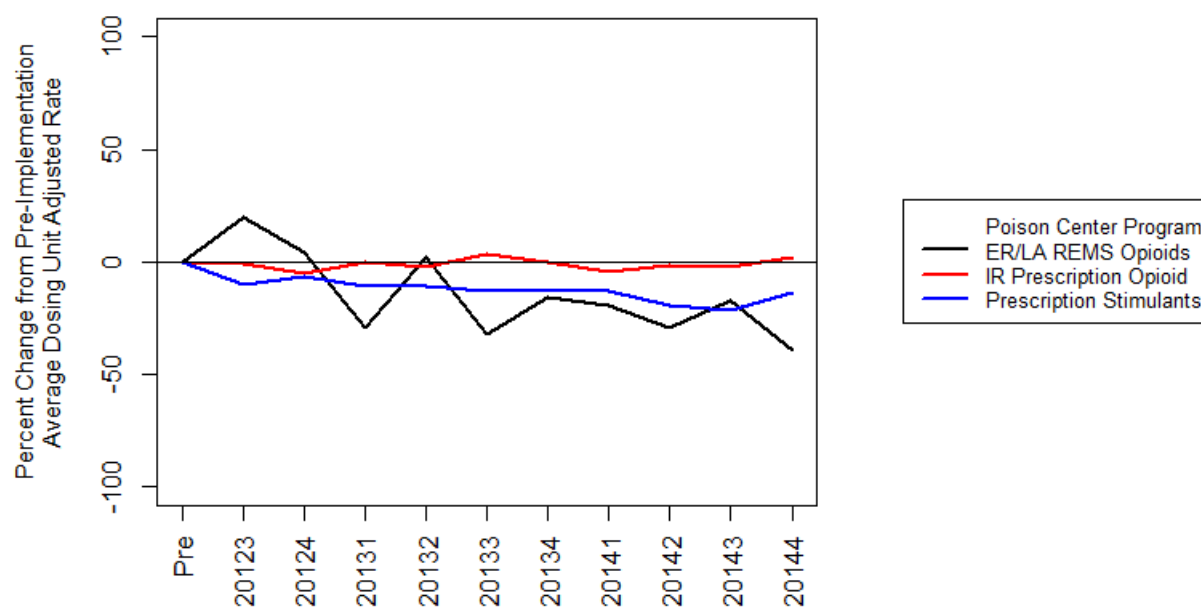


Figure 5.2.1.6

The RADARS System Poison Center Program
Under 20 Years Treated/Evaluated and Released
Percent Change from Average Pre-Implementation Dosing Unit Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014



5.2.2. Adult Treated/Evaluated and Released from the RADARS System Poison Center Program

Figure 5.2.2.1 through Figure 5.2.2.3 show the observed and predicted population, prescription dispensed, and dosing unit mean adult (≥ 20 years) treated/ evaluated and released rates and 95% confidence intervals for ER/LA REMS opioids and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 5.2.2.1

The RADARS System Poison Center Program
Adult Treated/Evaluated and Released Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

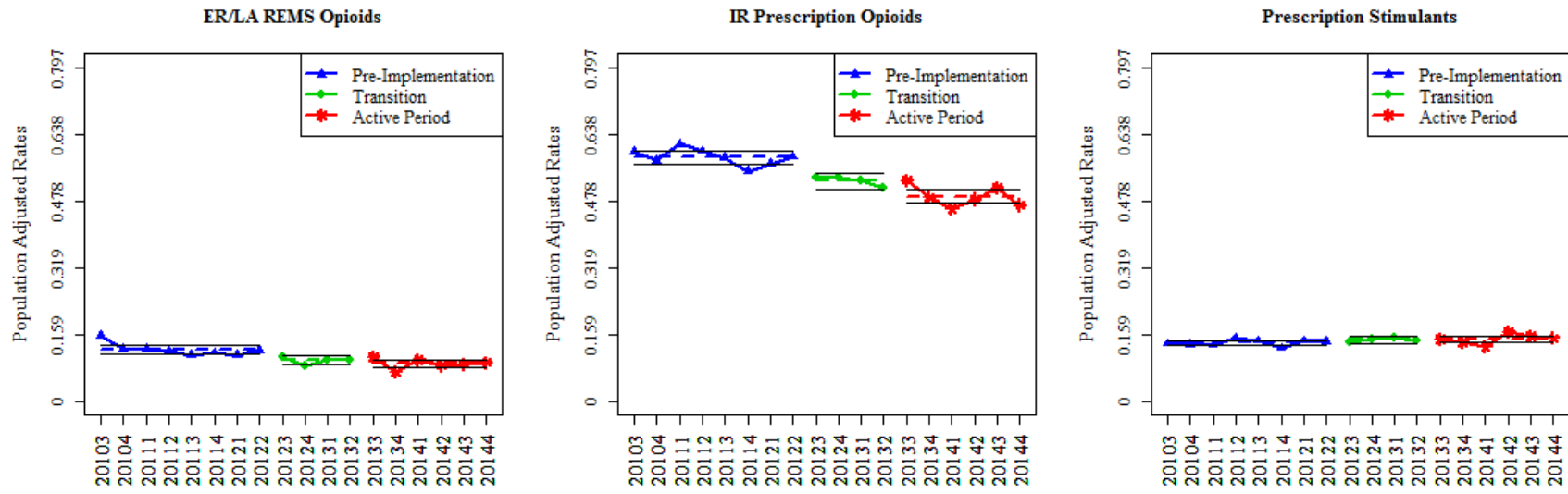


Table 5.2.2.1

The RADARS System Poison Center Program
Adult Treated/Evaluated and Released Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.123	Pre versus Transition	-20.22%(-30.92%,-7.88%)	0.002	.
	Transition	0.098	Transition versus Active	-7.92%(-21.33%,7.78%)	0.304	.
	Active	0.090	Pre versus Active	-26.54%(-35.37%,-16.50%)	<.001	.
IR Prescription Opioids	Pre	0.582	Pre versus Transition	-9.74%(-13.87%,-5.40%)	<.001	0.110
	Transition	0.525	Transition versus Active	-6.95%(-11.50%,-2.16%)	0.005	0.901
	Active	0.489	Pre versus Active	-16.01%(-19.44%,-12.42%)	<.001	0.051
Prescription Stimulants	Pre	0.140	Pre versus Transition	4.87%(-2.90%,13.26%)	0.226	0.001
	Transition	0.146	Transition versus Active	1.61%(-6.11%,9.96%)	0.692	0.273
	Active	0.149	Pre versus Active	6.55%(-0.40%,13.99%)	0.065	<.001

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids adult treated/ evaluated and released population rate decreased 20.22% between the Pre-Implementation and Transition time periods. This decrease is statistically significant.

The mean IR prescription opioids adult treated/ evaluated and released population rate decreased 9.74% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the adult treated/ evaluated and released population rate is not statistically significant, indicating that the mean difference in adult treated/ evaluated and released population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.110).

The mean prescription stimulants adult treated/ evaluated and released population rate increased 4.87% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the adult treated/ evaluated and released population rate is statistically significant, indicating that the mean difference in adult treated/ evaluated and released population rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants (p=0.001).

The mean ER/LA REMS opioids adult treated/ evaluated and released population rate decreased 7.92% between the Transition and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids adult treated/ evaluated and released population rate decreased 6.95% between the Transition and Active Period time periods. The interaction of drug by time period for the adult treated/ evaluated and released population rate is not statistically significant, indicating that the mean difference in adult treated/ evaluated and released population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.901$).

The mean prescription stimulants adult treated/ evaluated and released population rate increased 1.61% between the Transition and Active Period time periods. The interaction of drug by time period for the adult treated/ evaluated and released population rate is not statistically significant, indicating that the mean difference in adult treated/ evaluated and released population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.273$).

The mean ER/LA REMS opioids adult treated/ evaluated and released population rate decreased 26.54% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids adult treated/ evaluated and released population rate decreased 16.01% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adult treated/ evaluated and released population rate is not statistically significant, indicating that the mean difference in adult treated/ evaluated and released population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.051$).

The mean prescription stimulants adult treated/ evaluated and released population rate increased 6.55% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adult treated/ evaluated and released population rate is statistically significant, indicating that the mean difference in adult treated/ evaluated and released population rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p<.001$).

Figure 5.2.2.2

The RADARS System Poison Center Program
Adult Treated/Evaluated and Released Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

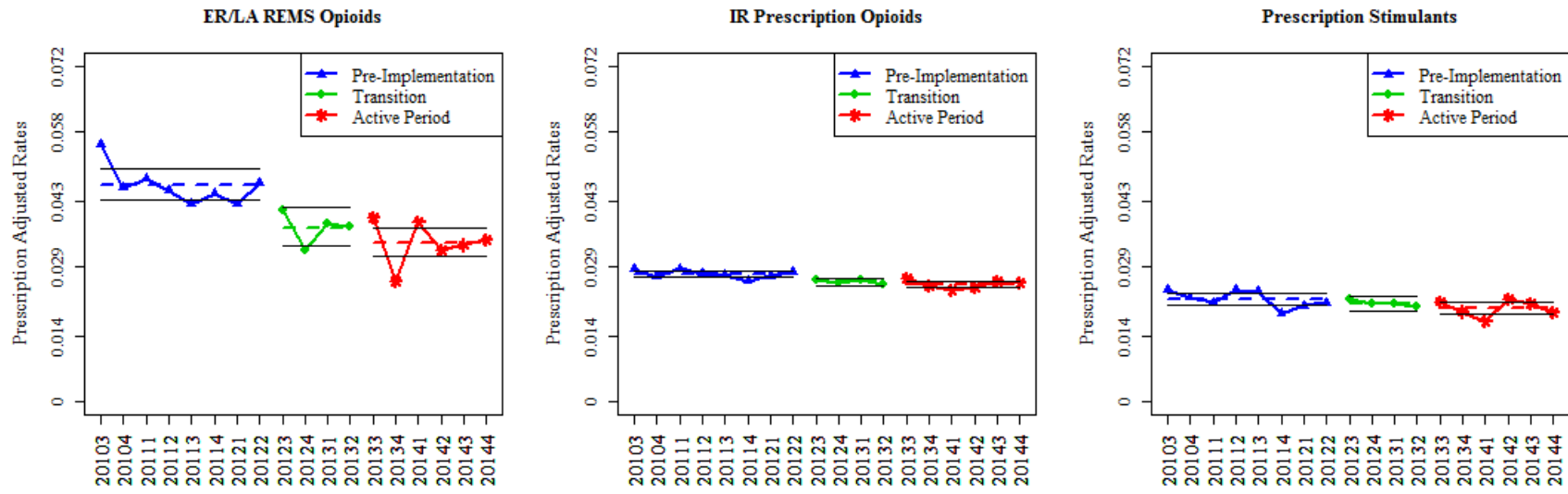


Table 5.2.2.2

The RADARS System Poison Center Program
Adult Treated/Evaluated and Released Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.046	Pre versus Transition	-19.64%(-29.57%,-8.31%)	0.001	.
	Transition	0.037	Transition versus Active	-8.57%(-20.86%,5.62%)	0.224	.
	Active	0.034	Pre versus Active	-26.53%(-34.67%,-17.38%)	<.001	.
IR Prescription Opioids	Pre	0.027	Pre versus Transition	-6.24%(-9.76%,-2.59%)	<.001	0.028
	Transition	0.026	Transition versus Active	-2.08%(-6.00%,2.01%)	0.315	0.370
	Active	0.025	Pre versus Active	-8.19%(-11.26%,-5.01%)	<.001	<.001
Prescription Stimulants	Pre	0.022	Pre versus Transition	-3.99%(-12.56%,5.43%)	0.394	0.031
	Transition	0.021	Transition versus Active	-4.87%(-13.57%,4.70%)	0.307	0.654
	Active	0.020	Pre versus Active	-8.66%(-15.85%,-0.87%)	0.030	0.003

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids adult treated/ evaluated and released prescriptions dispensed rate decreased 19.64% between the Pre-Implementation and Transition time periods. This decrease is statistically significant.

The mean IR prescription opioids adult treated/ evaluated and released prescriptions dispensed rate decreased 6.24% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the adult treated/ evaluated and released prescriptions dispensed rate is statistically significant, indicating that the mean difference in adult treated/ evaluated and released prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids (p=0.028).

The mean prescription stimulants adult treated/ evaluated and released prescriptions dispensed rate decreased 3.99% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the adult treated/ evaluated and released prescriptions dispensed rate is statistically significant, indicating that the mean difference in adult treated/ evaluated and released prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants (p=0.031).

The mean ER/LA REMS opioids adult treated/ evaluated and released prescriptions dispensed rate decreased 8.57% between the Transition and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids adult treated/ evaluated and released prescriptions dispensed rate decreased 2.08% between the Transition and Active Period time periods. The interaction of drug by time period for the adult treated/ evaluated and released prescriptions dispensed rate is not statistically significant, indicating that the mean difference in adult treated/ evaluated and released prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.370$).

The mean prescription stimulants adult treated/ evaluated and released prescriptions dispensed rate decreased 4.87% between the Transition and Active Period time periods. The interaction of drug by time period for the adult treated/ evaluated and released prescriptions dispensed rate is not statistically significant, indicating that the mean difference in adult treated/ evaluated and released prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.654$).

The mean ER/LA REMS opioids adult treated/ evaluated and released prescriptions dispensed rate decreased 26.53% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids adult treated/ evaluated and released prescriptions dispensed rate decreased 8.19% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adult treated/ evaluated and released prescriptions dispensed rate is statistically significant, indicating that the mean difference in adult treated/ evaluated and released prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids ($p<.001$).

The mean prescription stimulants adult treated/ evaluated and released prescriptions dispensed rate decreased 8.66% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adult treated/ evaluated and released prescriptions dispensed rate is statistically significant, indicating that the mean difference in adult treated/ evaluated and released prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p=0.003$).

Figure 5.2.2.3

The RADARS System Poison Center Program
Adult Treated/Evaluated and Released Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

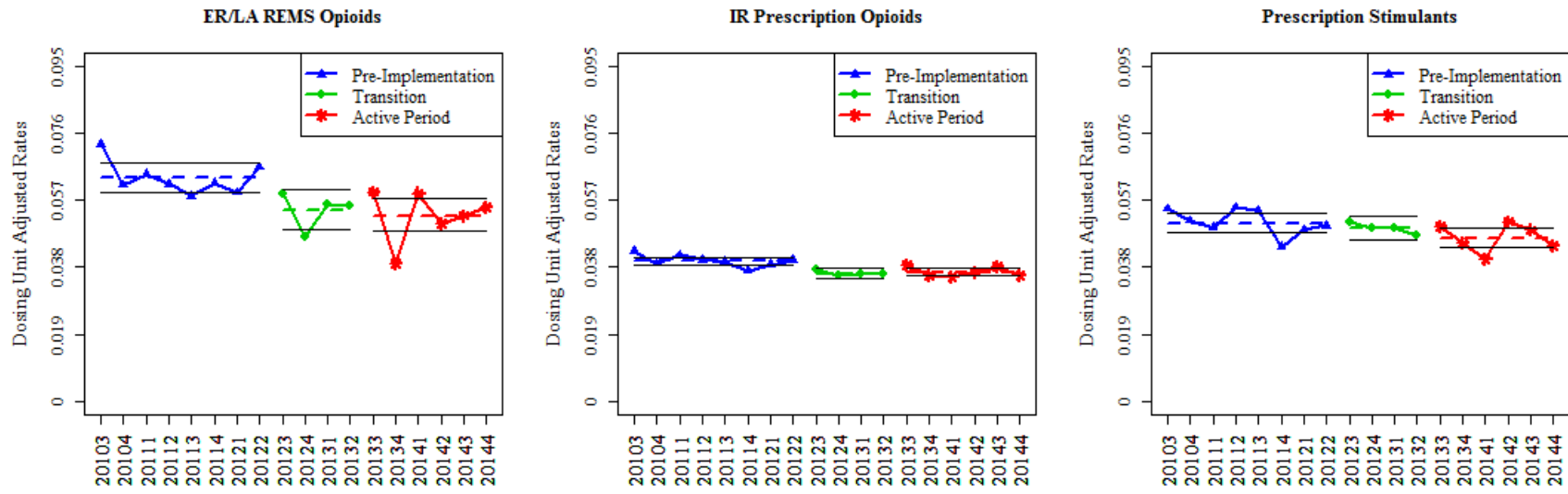


Table 5.2.2.3

The RADARS System Poison Center Program
Adult Treated/Evaluated and Released Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.063	Pre versus Transition	-14.46%(-24.52%,-3.05%)	0.014	.
	Transition	0.054	Transition versus Active	-2.97%(-15.38%,11.27%)	0.666	.
	Active	0.053	Pre versus Active	-17.00%(-25.74%,-7.22%)	0.001	.
IR Prescription Opioids	Pre	0.040	Pre versus Transition	-8.79%(-12.75%,-4.65%)	<.001	0.344
	Transition	0.036	Transition versus Active	0.87%(-3.81%,5.78%)	0.720	0.600
	Active	0.037	Pre versus Active	-8.00%(-11.57%,-4.29%)	<.001	0.088
Prescription Stimulants	Pre	0.051	Pre versus Transition	-3.24%(-11.36%,5.63%)	0.462	0.114
	Transition	0.049	Transition versus Active	-5.34%(-13.48%,3.57%)	0.232	0.767
	Active	0.046	Pre versus Active	-8.40%(-15.17%,-1.09%)	0.025	0.154

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids adult treated/ evaluated and released dosing units rate decreased 14.46% between the Pre-Implementation and Transition time periods. This decrease is statistically significant.

The mean IR prescription opioids adult treated/ evaluated and released dosing units rate decreased 8.79% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the adult treated/ evaluated and released dosing units rate is not statistically significant, indicating that the mean difference in adult treated/ evaluated and released dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.344).

The mean prescription stimulants adult treated/ evaluated and released dosing units rate decreased 3.24% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the adult treated/ evaluated and released dosing units rate is not statistically significant, indicating that the mean difference in adult treated/ evaluated and released dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.114).

The mean ER/LA REMS opioids adult treated/ evaluated and released dosing units rate decreased 2.97% between the Transition and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids adult treated/ evaluated and released dosing units rate increased 0.87% between the Transition and Active Period time periods. The interaction of drug by time period for the adult treated/ evaluated and released dosing units rate is not statistically significant, indicating that the mean difference in adult treated/ evaluated and released dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.600$).

The mean prescription stimulants adult treated/ evaluated and released dosing units rate decreased 5.34% between the Transition and Active Period time periods. The interaction of drug by time period for the adult treated/ evaluated and released dosing units rate is not statistically significant, indicating that the mean difference in adult treated/ evaluated and released dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.767$).

The mean ER/LA REMS opioids adult treated/ evaluated and released dosing units rate decreased 17.00% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids adult treated/ evaluated and released dosing units rate decreased 8.00% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adult treated/ evaluated and released dosing units rate is not statistically significant, indicating that the mean difference in adult treated/ evaluated and released dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.088$).

The mean prescription stimulants adult treated/ evaluated and released dosing units rate decreased 8.40% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adult treated/ evaluated and released dosing units rate is not statistically significant, indicating that the mean difference in adult treated/ evaluated and released dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.154$).

Figure 5.2.2.4 through Figure 5.2.2.6 display the mean adult (≥ 20 years) treated/evaluated and released rate percent change from the pre-implementation average population-, prescription dispensed-, and dosing unit- adjusted rates for ER/LA REMS opioids and comparator drugs.

Figure 5.2.2.4
 The RADARS System Poison Center Program
Adult Treated/Evaluated and Released
Percent Change from Average Pre-Implementation Population Adjusted Rates
 From Third Quarter 2010 to Fourth Quarter 2014

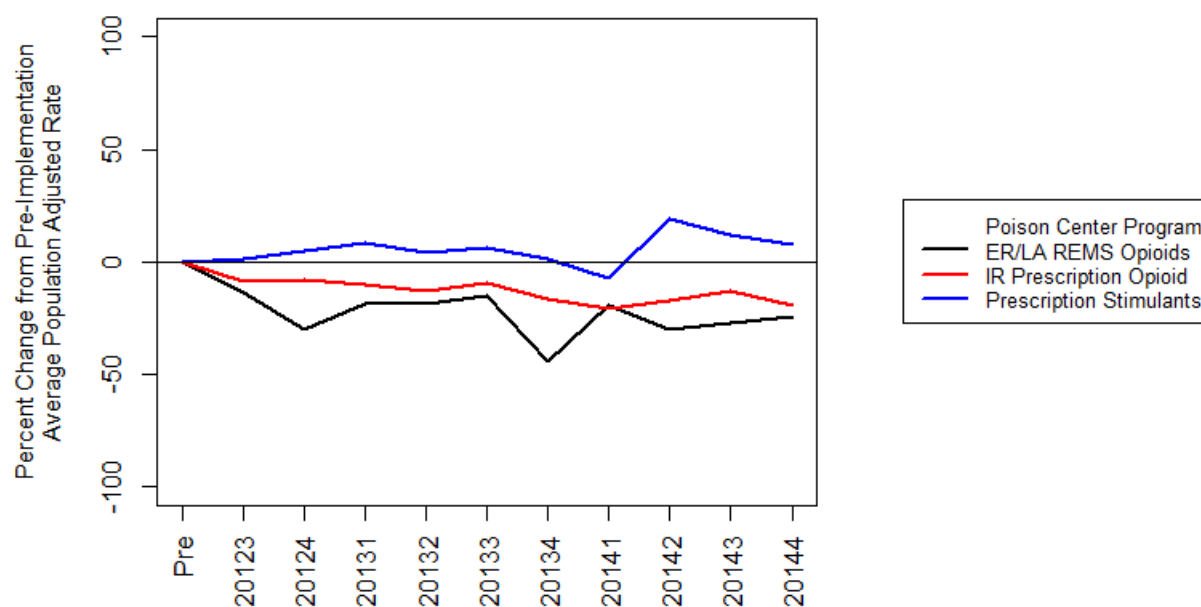


Figure 5.2.2.5

The RADARS System Poison Center Program
Adult Treated/Evaluated and Released
Percent Change from Average Pre-Implementation Prescription Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

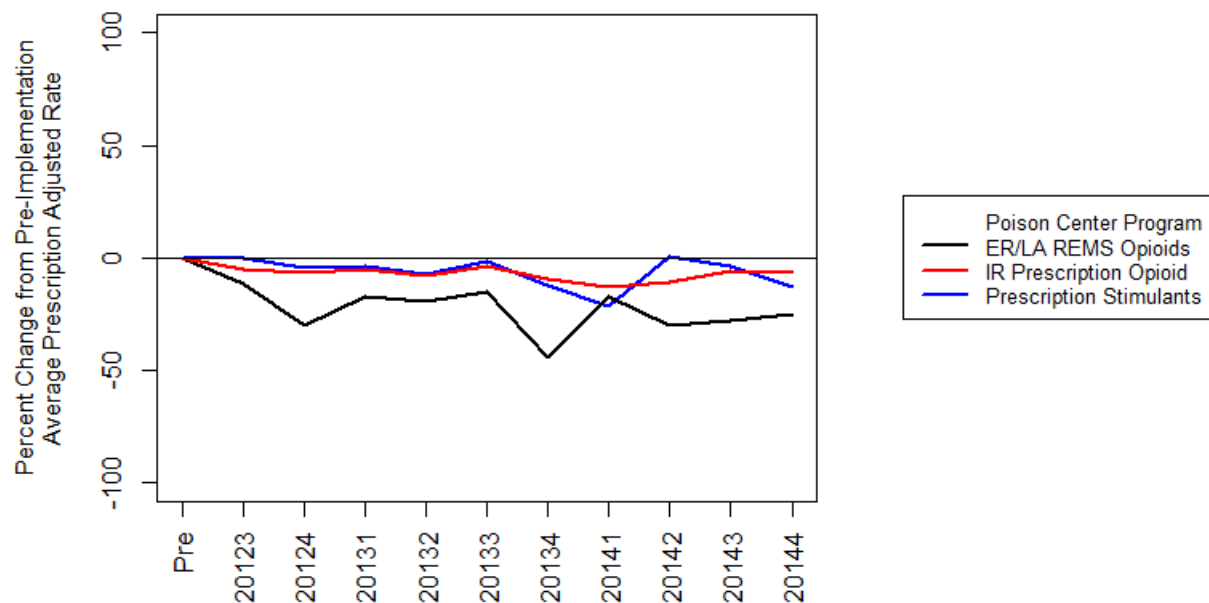
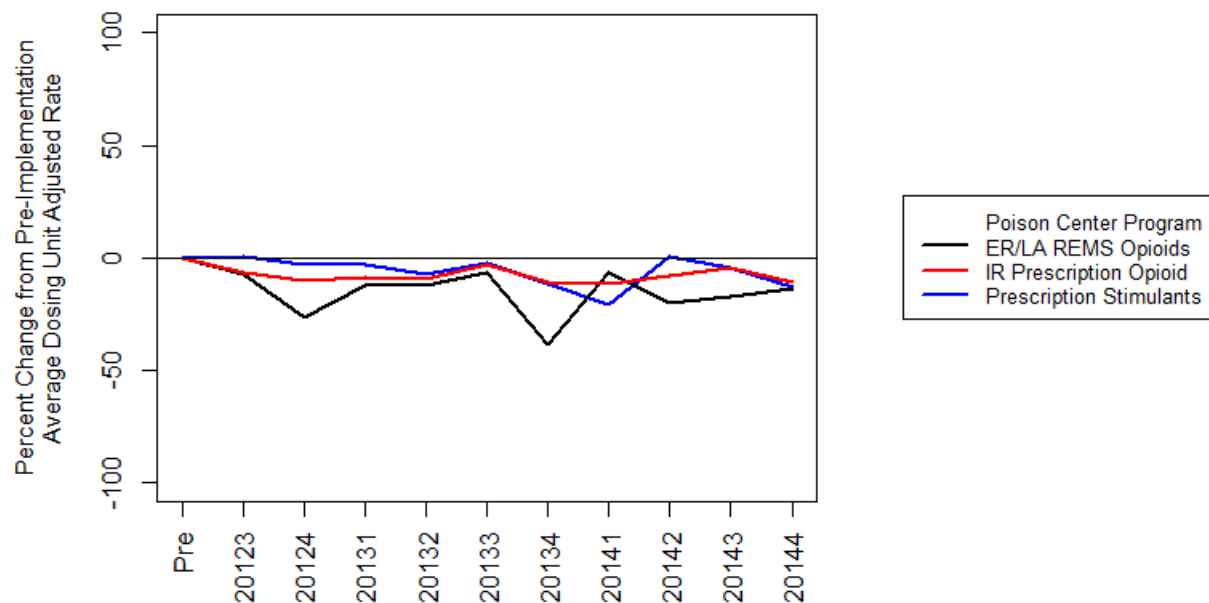


Figure 5.2.2.6

The RADARS System Poison Center Program
Adult Treated/Evaluated and Released
Percent Change from Average Pre-Implementation Dosing Unit Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014



5.3. Abuse from the RADARS System Poison Center Program

5.3.1. Intentional Abuse Exposures from the RADARS System Poison Center Program

Figure 5.3.1.1 through Figure 5.3.1.3 show the observed and predicted population, prescription dispensed, and dosing unit mean intentional abuse exposure rates and 95% confidence intervals for ER/LA REMS opioids and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 5.3.1.1

The RADARS System Poison Center Program
Intentional Abuse Exposure Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

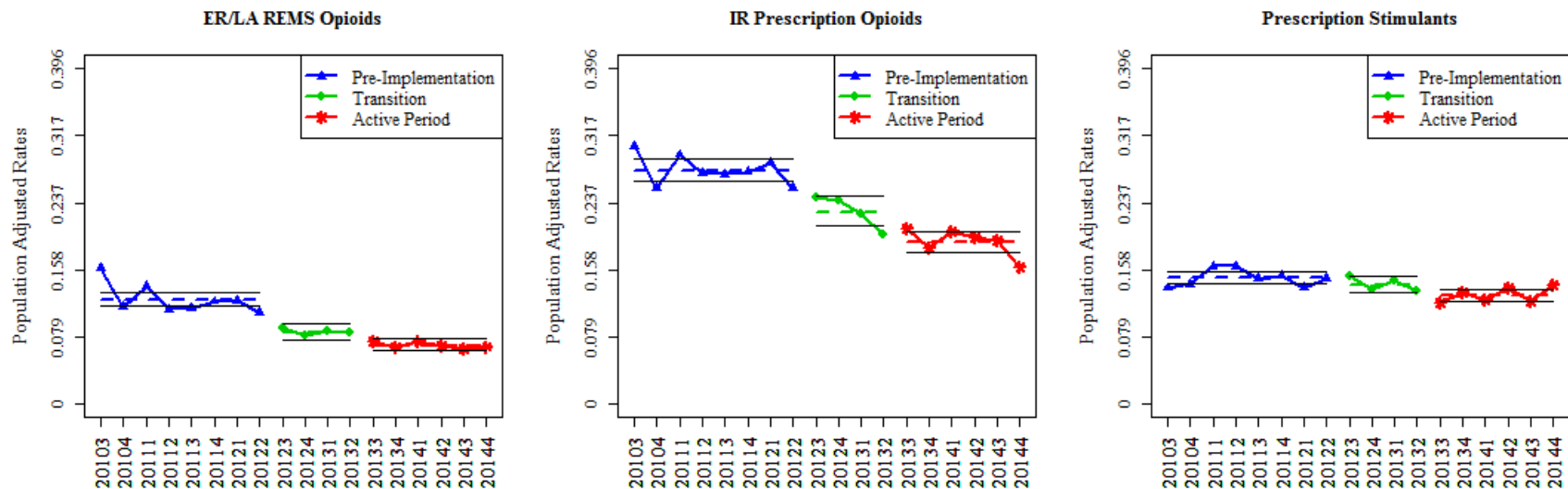


Table 5.3.1.1
The RADARS System Poison Center Program
Intentional Abuse Exposure Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.123	Pre versus Transition	-31.19%(-39.84%,-21.29%)	<.001	.
	Transition	0.085	Transition versus Active	-18.67%(-30.31%,-5.10%)	0.009	.
	Active	0.069	Pre versus Active	-44.04%(-50.57%,-36.64%)	<.001	.
IR Prescription Opioids	Pre	0.276	Pre versus Transition	-17.77%(-24.88%,-9.98%)	<.001	0.031
	Transition	0.227	Transition versus Active	-15.96%(-24.00%,-7.06%)	<.001	0.727
	Active	0.191	Pre versus Active	-30.89%(-36.40%,-24.90%)	<.001	0.006
Prescription Stimulants	Pre	0.148	Pre versus Transition	-4.92%(-12.21%,2.98%)	0.215	<.001
	Transition	0.141	Transition versus Active	-8.87%(-16.31%,-0.76%)	0.033	0.205
	Active	0.129	Pre versus Active	-13.35%(-19.35%,-6.90%)	<.001	<.001

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids intentional abuse exposure population rate decreased 31.19% between the Pre-Implementation and Transition time periods. This decrease is statistically significant.

The mean IR prescription opioids intentional abuse exposure population rate decreased 17.77% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the intentional abuse exposure population rate is statistically significant, indicating that the mean difference in intentional abuse exposure population rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids (p=0.031).

The mean prescription stimulants intentional abuse exposure population rate decreased 4.92% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the intentional abuse exposure population rate is statistically significant, indicating that the mean difference in intentional abuse exposure population rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants (p<.001).

The mean ER/LA REMS opioids intentional abuse exposure population rate decreased 18.67% between the Transition and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids intentional abuse exposure population rate decreased 15.96% between the Transition and Active Period time periods. The interaction of drug by time period for the intentional abuse exposure population rate is not statistically significant, indicating that the mean difference in intentional abuse exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.727$).

The mean prescription stimulants intentional abuse exposure population rate decreased 8.87% between the Transition and Active Period time periods. The interaction of drug by time period for the intentional abuse exposure population rate is not statistically significant, indicating that the mean difference in intentional abuse exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.205$).

The mean ER/LA REMS opioids intentional abuse exposure population rate decreased 44.04% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids intentional abuse exposure population rate decreased 30.89% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the intentional abuse exposure population rate is statistically significant, indicating that the mean difference in intentional abuse exposure population rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids ($p=0.006$).

The mean prescription stimulants intentional abuse exposure population rate decreased 13.35% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the intentional abuse exposure population rate is statistically significant, indicating that the mean difference in intentional abuse exposure population rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p<.001$).

Figure 5.3.1.2

The RADARS System Poison Center Program
Intentional Abuse Exposure Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

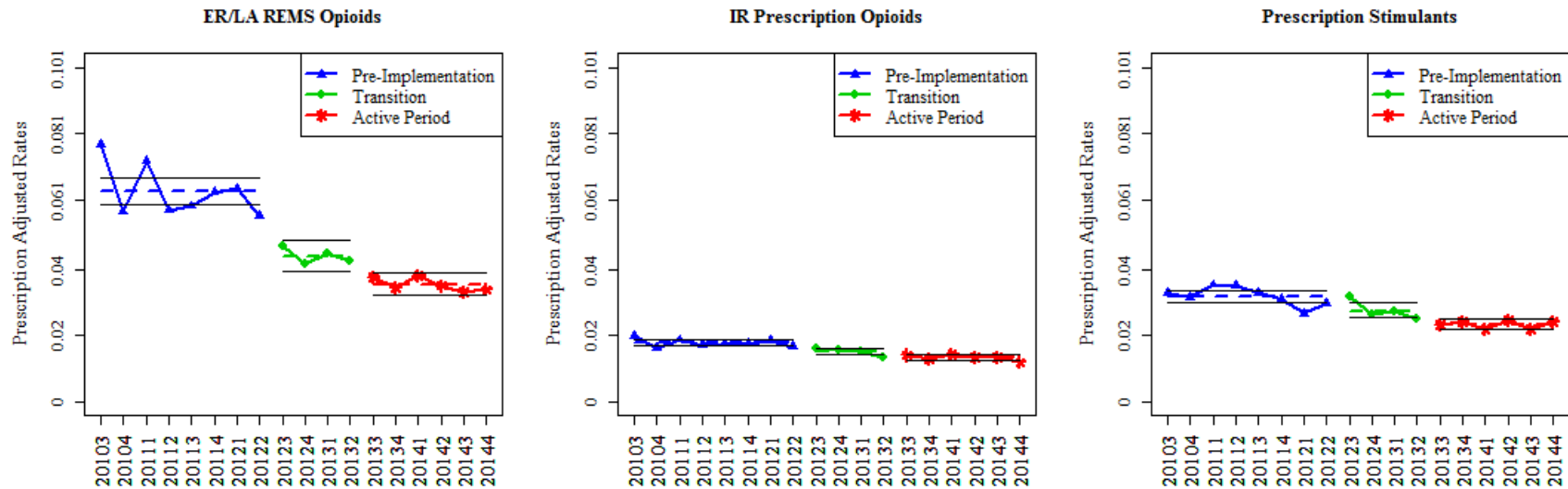


Table 5.3.1.2

The RADARS System Poison Center Program
Intentional Abuse Exposure Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.064	Pre versus Transition	-30.96% (-38.89%, -22.01%)	<.001	.
	Transition	0.044	Transition versus Active	-19.49% (-30.02%, -7.39%)	0.002	.
	Active	0.035	Pre versus Active	-44.42% (-50.34%, -37.79%)	<.001	.
IR Prescription Opioids	Pre	0.018	Pre versus Transition	-14.93% (-21.66%, -7.62%)	<.001	0.005
	Transition	0.015	Transition versus Active	-11.82% (-19.54%, -3.37%)	0.007	0.286
	Active	0.013	Pre versus Active	-24.99% (-30.45%, -19.10%)	<.001	<.001
Prescription Stimulants	Pre	0.032	Pre versus Transition	-13.30% (-21.43%, -4.32%)	0.005	0.004
	Transition	0.028	Transition versus Active	-14.93% (-23.42%, -5.50%)	0.003	0.537
	Active	0.023	Pre versus Active	-26.25% (-32.50%, -19.41%)	<.001	<.001

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids intentional abuse exposure prescriptions dispensed rate decreased 30.96% between the Pre-Implementation and Transition time periods. This decrease is statistically significant.

The mean IR prescription opioids intentional abuse exposure prescriptions dispensed rate decreased 14.93% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the intentional abuse exposure prescriptions dispensed rate is statistically significant, indicating that the mean difference in intentional abuse exposure prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids (p=0.005).

The mean prescription stimulants intentional abuse exposure prescriptions dispensed rate decreased 13.30% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the intentional abuse exposure prescriptions dispensed rate is statistically significant, indicating that the mean difference in intentional abuse exposure prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants (p=0.004).

The mean ER/LA REMS opioids intentional abuse exposure prescriptions dispensed rate

decreased 19.49% between the Transition and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids intentional abuse exposure prescriptions dispensed rate decreased 11.82% between the Transition and Active Period time periods. The interaction of drug by time period for the intentional abuse exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in intentional abuse exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.286$).

The mean prescription stimulants intentional abuse exposure prescriptions dispensed rate decreased 14.93% between the Transition and Active Period time periods. The interaction of drug by time period for the intentional abuse exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in intentional abuse exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.537$).

The mean ER/LA REMS opioids intentional abuse exposure prescriptions dispensed rate decreased 44.42% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids intentional abuse exposure prescriptions dispensed rate decreased 24.99% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the intentional abuse exposure prescriptions dispensed rate is statistically significant, indicating that the mean difference in intentional abuse exposure prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids ($p<.001$).

The mean prescription stimulants intentional abuse exposure prescriptions dispensed rate decreased 26.25% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the intentional abuse exposure prescriptions dispensed rate is statistically significant, indicating that the mean difference in intentional abuse exposure prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p<.001$).

Figure 5.3.1.3

The RADARS System Poison Center Program
Intentional Abuse Exposure Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

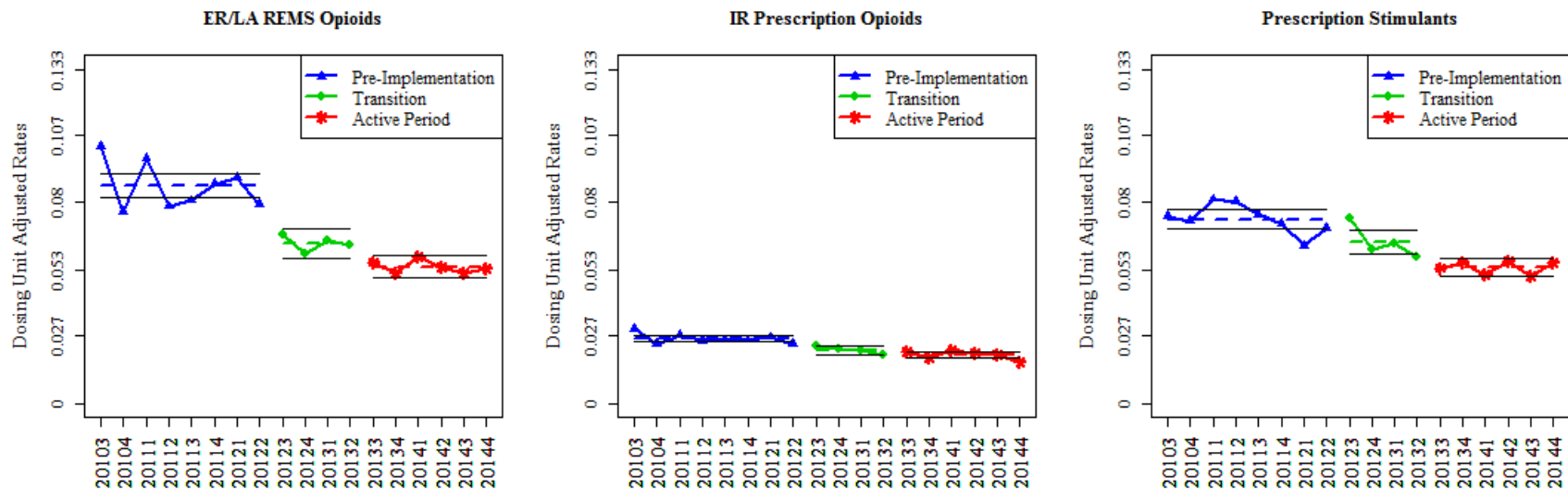


Table 5.3.1.3
The RADARS System Poison Center Program
Intentional Abuse Exposure Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.087	Pre versus Transition	-26.51%(-34.09%,-18.06%)	<.001	.
	Transition	0.064	Transition versus Active	-14.56%(-24.59%,-3.19%)	0.014	.
	Active	0.054	Pre versus Active	-37.21%(-43.21%,-30.57%)	<.001	.
IR Prescription Opioids	Pre	0.026	Pre versus Transition	-17.24%(-24.70%,-9.05%)	<.001	0.106
	Transition	0.021	Transition versus Active	-9.17%(-18.22%,0.89%)	0.073	0.462
	Active	0.019	Pre versus Active	-24.83%(-31.07%,-18.02%)	<.001	0.008
Prescription Stimulants	Pre	0.073	Pre versus Transition	-12.63%(-20.40%,-4.09%)	0.005	0.018
	Transition	0.064	Transition versus Active	-15.35%(-23.36%,-6.49%)	0.001	0.910
	Active	0.054	Pre versus Active	-26.03%(-31.98%,-19.56%)	<.001	0.014

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids intentional abuse exposure dosing units rate decreased 26.51% between the Pre-Implementation and Transition time periods. This decrease is statistically significant.

The mean IR prescription opioids intentional abuse exposure dosing units rate decreased 17.24% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the intentional abuse exposure dosing units rate is not statistically significant, indicating that the mean difference in intentional abuse exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.106).

The mean prescription stimulants intentional abuse exposure dosing units rate decreased 12.63% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the intentional abuse exposure dosing units rate is statistically significant, indicating that the mean difference in intentional abuse exposure dosing units rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants (p=0.018).

The mean ER/LA REMS opioids intentional abuse exposure dosing units rate decreased 14.56% between the Transition and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids intentional abuse exposure dosing units rate decreased 9.17% between the Transition and Active Period time periods. The interaction of drug by time period for the intentional abuse exposure dosing units rate is not statistically significant, indicating that the mean difference in intentional abuse exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.462$).

The mean prescription stimulants intentional abuse exposure dosing units rate decreased 15.35% between the Transition and Active Period time periods. The interaction of drug by time period for the intentional abuse exposure dosing units rate is not statistically significant, indicating that the mean difference in intentional abuse exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.910$).

The mean ER/LA REMS opioids intentional abuse exposure dosing units rate decreased 37.21% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids intentional abuse exposure dosing units rate decreased 24.83% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the intentional abuse exposure dosing units rate is statistically significant, indicating that the mean difference in intentional abuse exposure dosing units rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids ($p=0.008$).

The mean prescription stimulants intentional abuse exposure dosing units rate decreased 26.03% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the intentional abuse exposure dosing units rate is statistically significant, indicating that the mean difference in intentional abuse exposure dosing units rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p=0.014$).

Figure 5.3.1.4 through Figure 5.3.1.6 display the mean intentional abuse exposure rate percent change from the pre-implementation average population-, prescription dispensed-, and dosing unit- adjusted rates for ER/LA REMS opioids and comparator drugs.

Figure 5.3.1.4
The RADARS System Poison Center Program
Intentional Abuse Exposures
Percent Change from Average Pre-Implementation Population Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

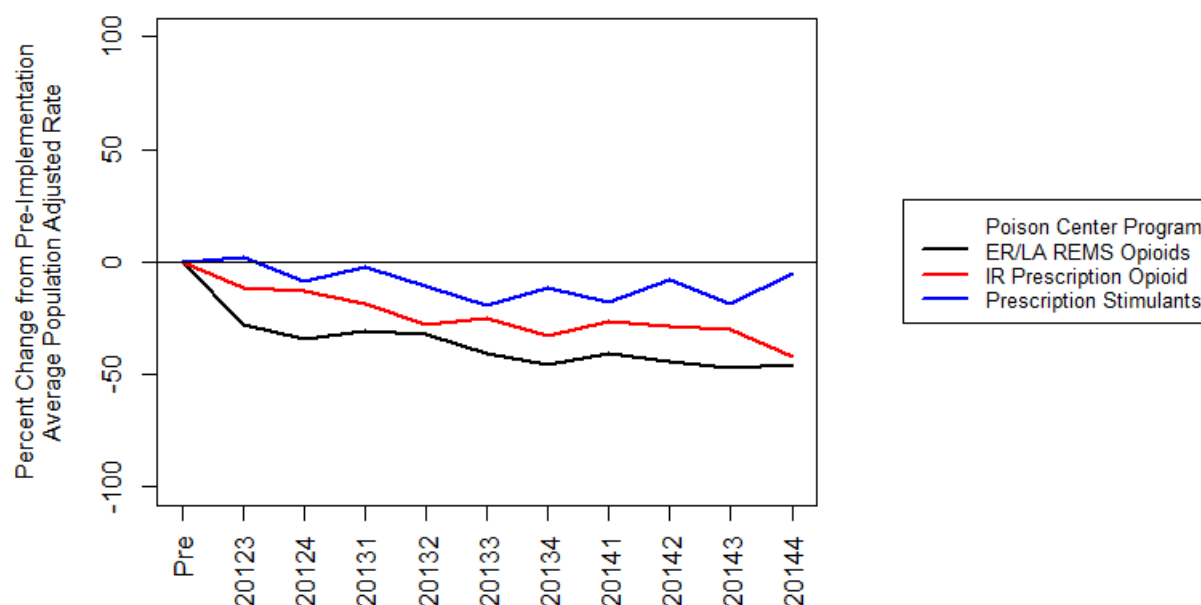


Figure 5.3.1.5

The RADARS System Poison Center Program
Intentional Abuse Exposures
Percent Change from Average Pre-Implementation Prescription Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

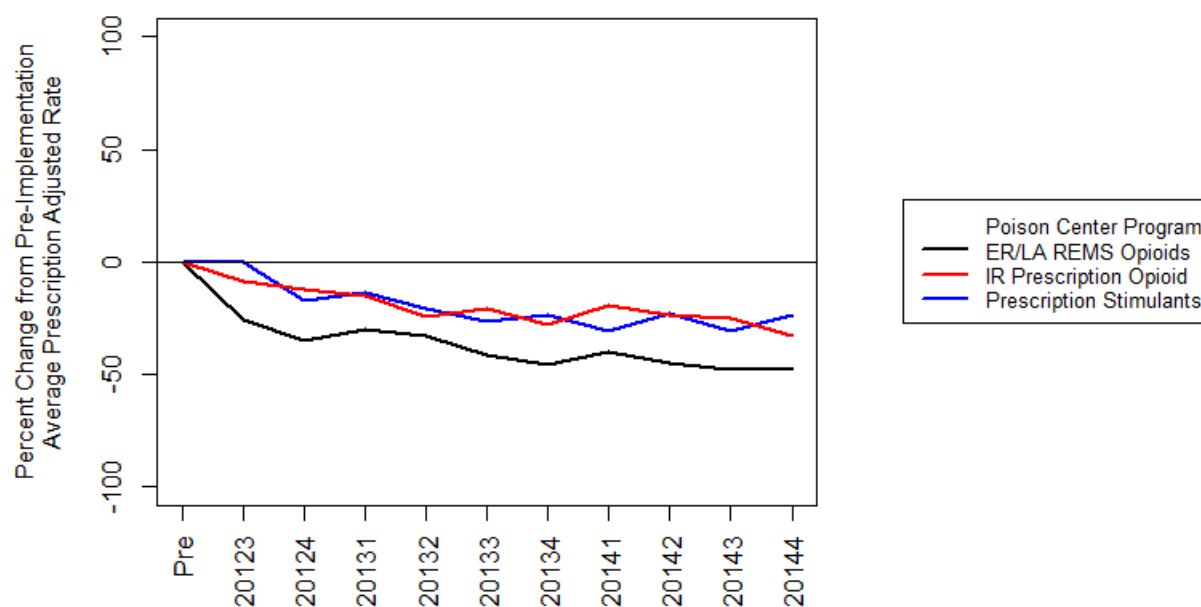
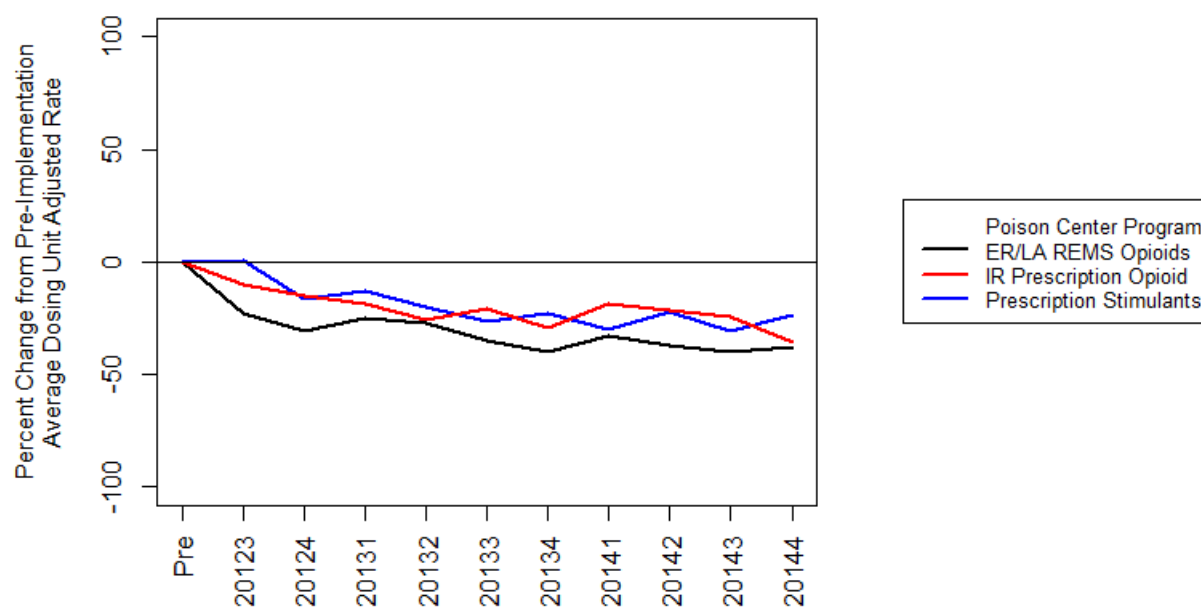


Figure 5.3.1.6

The RADARS System Poison Center Program
Intentional Abuse Exposures
Percent Change from Average Pre-Implementation Dosing Unit Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014



5.3.2. Adolescent Intentional Abuse Exposures from the RADARS System Poison Center Program

[Figure 5.3.2.1](#) through [Figure 5.3.2.3](#) show the observed and predicted population, prescription dispensed, and dosing unit mean adolescent (13-19 years) intentional abuse exposure rates and 95% confidence intervals for ER/LA REMS opioids and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 5.3.2.1

The RADARS System Poison Center Program
Adolescent Intentional Abuse Exposure Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

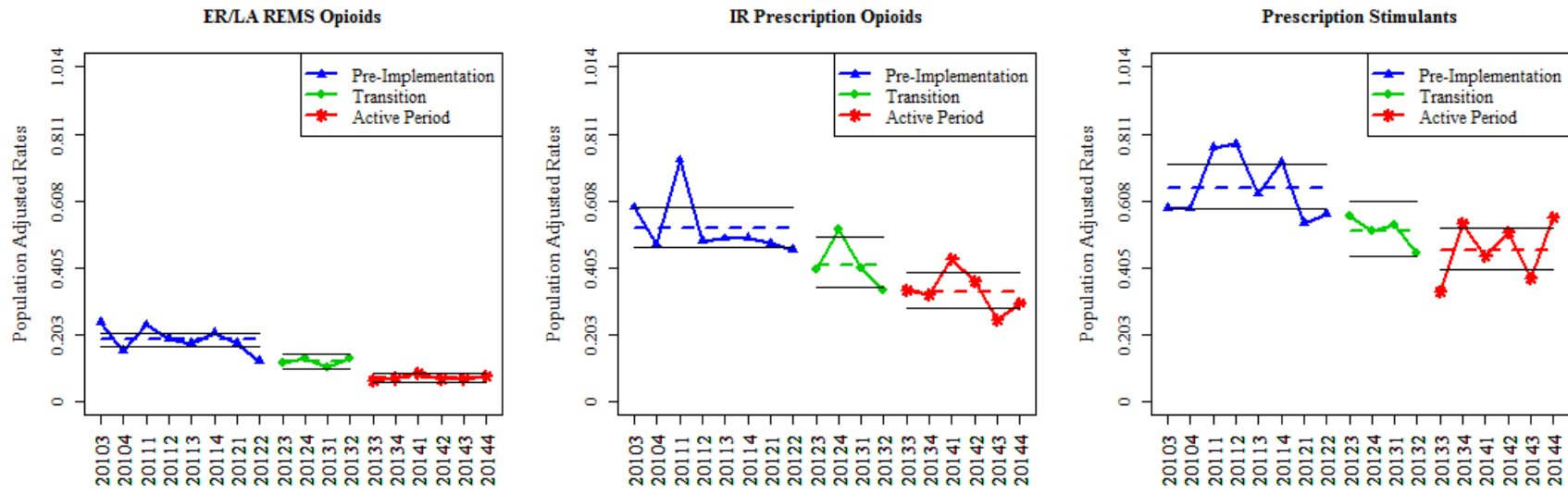


Table 5.3.2.1

The RADARS System Poison Center Program
Adolescent Intentional Abuse Exposure Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.187	Pre versus Transition	-35.73%(-48.17%,-20.30%)	<.001	.
	Transition	0.120	Transition versus Active	-40.64%(-54.65%,-22.30%)	<.001	.
	Active	0.071	Pre versus Active	-61.85%(-69.47%,-52.33%)	<.001	.
IR Prescription Opioids	Pre	0.525	Pre versus Transition	-20.94%(-36.09%,-2.20%)	0.030	0.180
	Transition	0.415	Transition versus Active	-19.83%(-36.97%,1.97%)	0.072	0.103
	Active	0.333	Pre versus Active	-36.62%(-48.01%,-22.73%)	<.001	<.001
Prescription Stimulants	Pre	0.647	Pre versus Transition	-20.24%(-34.04%,-3.56%)	0.020	0.140
	Transition	0.516	Transition versus Active	-10.97%(-27.81%,9.80%)	0.277	0.020
	Active	0.459	Pre versus Active	-28.99%(-40.15%,-15.74%)	<.001	<.001

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids adolescent intentional abuse exposure population rate decreased 35.73% between the Pre-Implementation and Transition time periods. This decrease is statistically significant.

The mean IR prescription opioids adolescent intentional abuse exposure population rate decreased 20.94% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the adolescent intentional abuse exposure population rate is not statistically significant, indicating that the mean difference in adolescent intentional abuse exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.180).

The mean prescription stimulants adolescent intentional abuse exposure population rate decreased 20.24% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the adolescent intentional abuse exposure population rate is not statistically significant, indicating that the mean difference in adolescent intentional abuse exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.140).

The mean ER/LA REMS opioids adolescent intentional abuse exposure population rate decreased 40.64% between the Transition and Active Period time periods. This decrease is

statistically significant.

The mean IR prescription opioids adolescent intentional abuse exposure population rate decreased 19.83% between the Transition and Active Period time periods. The interaction of drug by time period for the adolescent intentional abuse exposure population rate is not statistically significant, indicating that the mean difference in adolescent intentional abuse exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.103$).

The mean prescription stimulants adolescent intentional abuse exposure population rate decreased 10.97% between the Transition and Active Period time periods. The interaction of drug by time period for the adolescent intentional abuse exposure population rate is statistically significant, indicating that the mean difference in adolescent intentional abuse exposure population rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p=0.020$).

The mean ER/LA REMS opioids adolescent intentional abuse exposure population rate decreased 61.85% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids adolescent intentional abuse exposure population rate decreased 36.62% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adolescent intentional abuse exposure population rate is statistically significant, indicating that the mean difference in adolescent intentional abuse exposure population rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids ($p<.001$).

The mean prescription stimulants adolescent intentional abuse exposure population rate decreased 28.99% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adolescent intentional abuse exposure population rate is statistically significant, indicating that the mean difference in adolescent intentional abuse exposure population rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p<.001$).

Figure 5.3.2.2

The RADARS System Poison Center Program
Adolescent Intentional Abuse Exposure Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

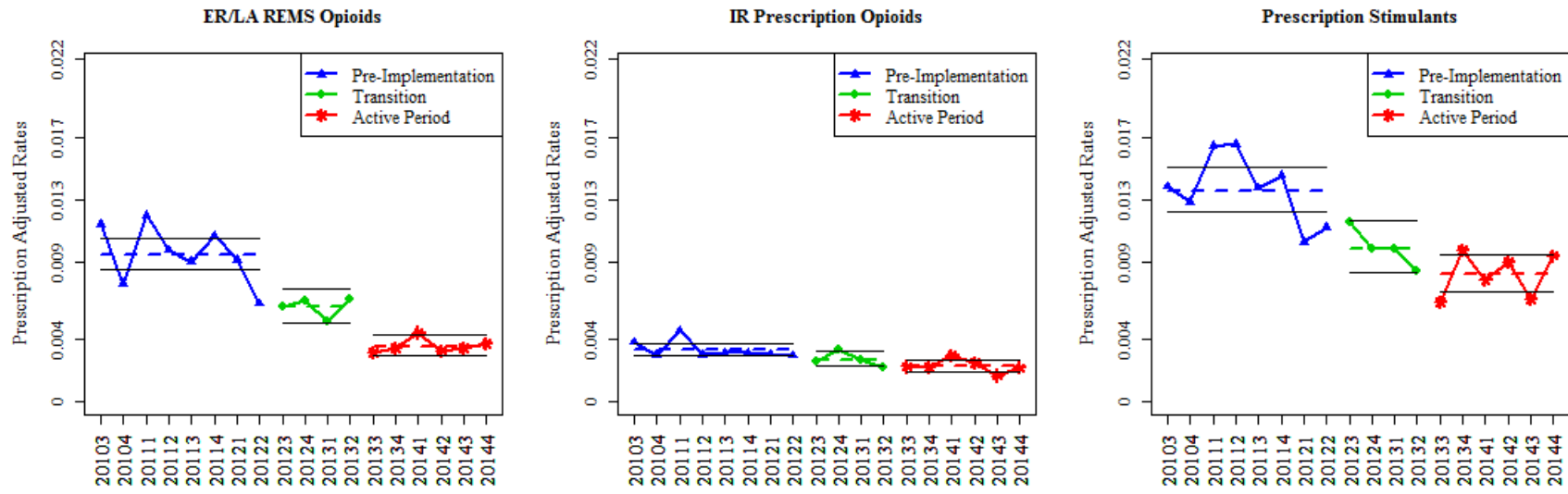


Table 5.3.2.2

The RADARS System Poison Center Program
Adolescent Intentional Abuse Exposure Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.009	Pre versus Transition	-35.71% (-47.89%, -20.69%)	<.001	.
	Transition	0.006	Transition versus Active	-41.34% (-54.89%, -23.71%)	<.001	.
	Active	0.004	Pre versus Active	-62.29% (-69.66%, -53.13%)	<.001	.
IR Prescription Opioids	Pre	0.003	Pre versus Transition	-18.46% (-33.87%, 0.56%)	0.056	0.116
	Transition	0.003	Transition versus Active	-16.03% (-33.75%, 6.43%)	0.149	0.047
	Active	0.002	Pre versus Active	-31.52% (-43.67%, -16.76%)	<.001	<.001
Prescription Stimulants	Pre	0.014	Pre versus Transition	-27.49% (-40.47%, -11.68%)	0.001	0.413
	Transition	0.010	Transition versus Active	-17.04% (-33.26%, 3.14%)	0.093	0.046
	Active	0.008	Pre versus Active	-39.84% (-49.63%, -28.15%)	<.001	0.001

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids adolescent intentional abuse exposure prescriptions dispensed rate decreased 35.71% between the Pre-Implementation and Transition time periods. This decrease is statistically significant.

The mean IR prescription opioids adolescent intentional abuse exposure prescriptions dispensed rate decreased 18.46% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the adolescent intentional abuse exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in adolescent intentional abuse exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.116).

The mean prescription stimulants adolescent intentional abuse exposure prescriptions dispensed rate decreased 27.49% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the adolescent intentional abuse exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in adolescent intentional abuse exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.413).

The mean ER/LA REMS opioids adolescent intentional abuse exposure prescriptions dispensed rate decreased 41.34% between the Transition and Active Period time periods. This decrease is

statistically significant.

The mean IR prescription opioids adolescent intentional abuse exposure prescriptions dispensed rate decreased 16.03% between the Transition and Active Period time periods. The interaction of drug by time period for the adolescent intentional abuse exposure prescriptions dispensed rate is statistically significant, indicating that the mean difference in adolescent intentional abuse exposure prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids ($p=0.047$).

The mean prescription stimulants adolescent intentional abuse exposure prescriptions dispensed rate decreased 17.04% between the Transition and Active Period time periods. The interaction of drug by time period for the adolescent intentional abuse exposure prescriptions dispensed rate is statistically significant, indicating that the mean difference in adolescent intentional abuse exposure prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p=0.046$).

The mean ER/LA REMS opioids adolescent intentional abuse exposure prescriptions dispensed rate decreased 62.29% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids adolescent intentional abuse exposure prescriptions dispensed rate decreased 31.52% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adolescent intentional abuse exposure prescriptions dispensed rate is statistically significant, indicating that the mean difference in adolescent intentional abuse exposure prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids ($p<.001$).

The mean prescription stimulants adolescent intentional abuse exposure prescriptions dispensed rate decreased 39.84% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adolescent intentional abuse exposure prescriptions dispensed rate is statistically significant, indicating that the mean difference in adolescent intentional abuse exposure prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p=0.001$).

Figure 5.3.2.3

The RADARS System Poison Center Program
Adolescent Intentional Abuse Exposure Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

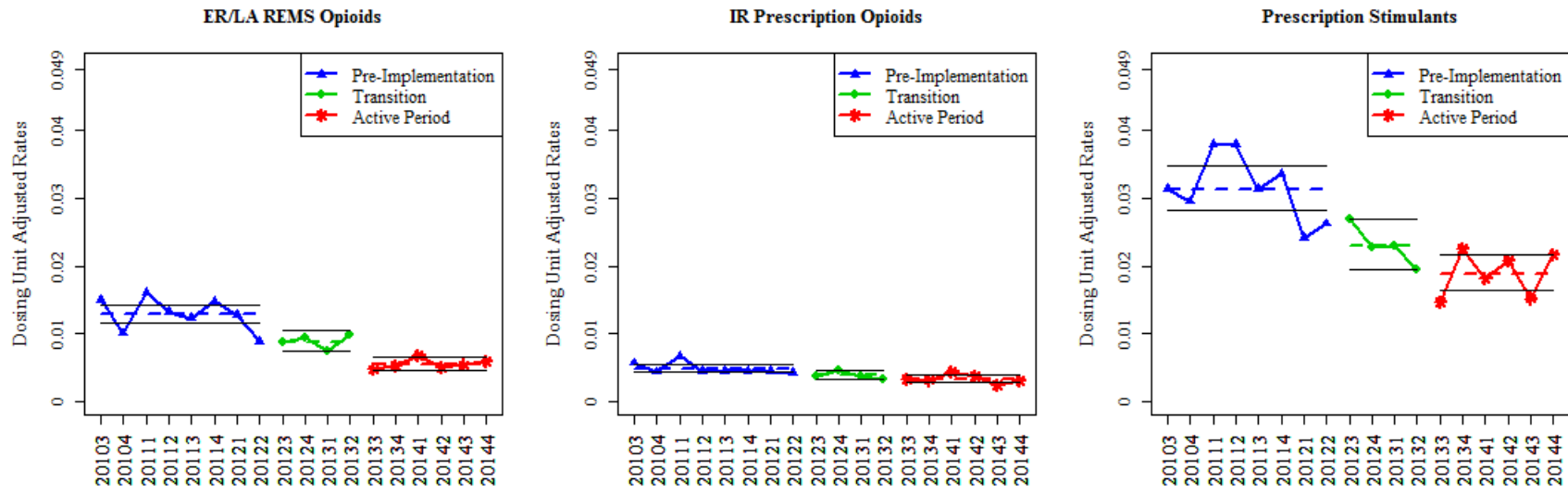


Table 5.3.2.3

The RADARS System Poison Center Program
Adolescent Intentional Abuse Exposure Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.013	Pre versus Transition	-31.57% (-44.08%, -16.25%)	<.001	.
	Transition	0.009	Transition versus Active	-37.74% (-51.64%, -19.85%)	<.001	.
	Active	0.005	Pre versus Active	-57.39% (-65.43%, -47.49%)	<.001	.
IR Prescription Opioids	Pre	0.005	Pre versus Transition	-20.67% (-35.99%, -1.70%)	0.034	0.326
	Transition	0.004	Transition versus Active	-13.50% (-32.13%, 10.24%)	0.241	0.066
	Active	0.003	Pre versus Active	-31.38% (-43.81%, -16.21%)	<.001	0.001
Prescription Stimulants	Pre	0.031	Pre versus Transition	-26.93% (-39.78%, -11.33%)	0.001	0.646
	Transition	0.023	Transition versus Active	-17.44% (-33.31%, 2.21%)	0.079	0.094
	Active	0.019	Pre versus Active	-39.67% (-49.31%, -28.19%)	<.001	0.012

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids adolescent intentional abuse exposure dosing units rate decreased 31.57% between the Pre-Implementation and Transition time periods. This decrease is statistically significant.

The mean IR prescription opioids adolescent intentional abuse exposure dosing units rate decreased 20.67% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the adolescent intentional abuse exposure dosing units rate is not statistically significant, indicating that the mean difference in adolescent intentional abuse exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.326).

The mean prescription stimulants adolescent intentional abuse exposure dosing units rate decreased 26.93% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the adolescent intentional abuse exposure dosing units rate is not statistically significant, indicating that the mean difference in adolescent intentional abuse exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.646).

The mean ER/LA REMS opioids adolescent intentional abuse exposure dosing units rate decreased 37.74% between the Transition and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids adolescent intentional abuse exposure dosing units rate decreased 13.50% between the Transition and Active Period time periods. The interaction of drug by time period for the adolescent intentional abuse exposure dosing units rate is not statistically significant, indicating that the mean difference in adolescent intentional abuse exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.066$).

The mean prescription stimulants adolescent intentional abuse exposure dosing units rate decreased 17.44% between the Transition and Active Period time periods. The interaction of drug by time period for the adolescent intentional abuse exposure dosing units rate is not statistically significant, indicating that the mean difference in adolescent intentional abuse exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.094$).

The mean ER/LA REMS opioids adolescent intentional abuse exposure dosing units rate decreased 57.39% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids adolescent intentional abuse exposure dosing units rate decreased 31.38% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adolescent intentional abuse exposure dosing units rate is statistically significant, indicating that the mean difference in adolescent intentional abuse exposure dosing units rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids ($p=0.001$).

The mean prescription stimulants adolescent intentional abuse exposure dosing units rate decreased 39.67% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adolescent intentional abuse exposure dosing units rate is statistically significant, indicating that the mean difference in adolescent intentional abuse exposure dosing units rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p=0.012$).

Figure 5.3.2.4 through Figure 5.3.2.6 display the mean adolescent (13-19 years) intentional abuse exposure rate percent change from the pre-implementation average population-, prescription dispensed-, and dosing unit- adjusted rates for ER/LA REMS opioids and comparator drugs.

Figure 5.3.2.4
The RADARS System Poison Center Program
Adolescent Intentional Abuse Exposures
Percent Change from Average Pre-Implementation Population Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

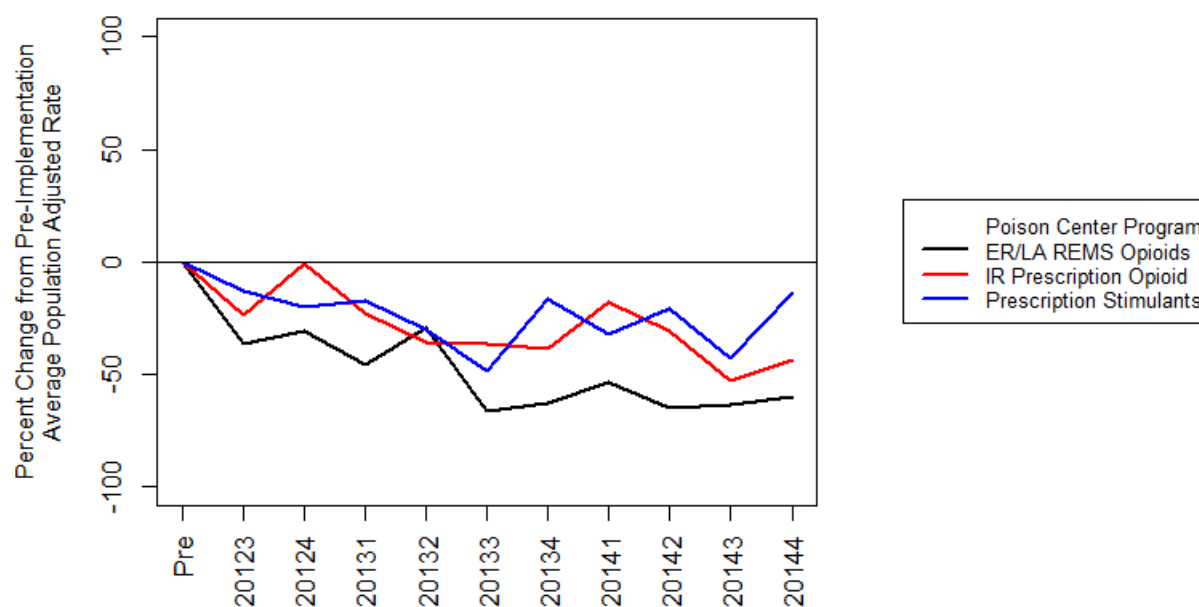


Figure 5.3.2.5

The RADARS System Poison Center Program
Adolescent Intentional Abuse Exposures
Percent Change from Average Pre-Implementation Prescription Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

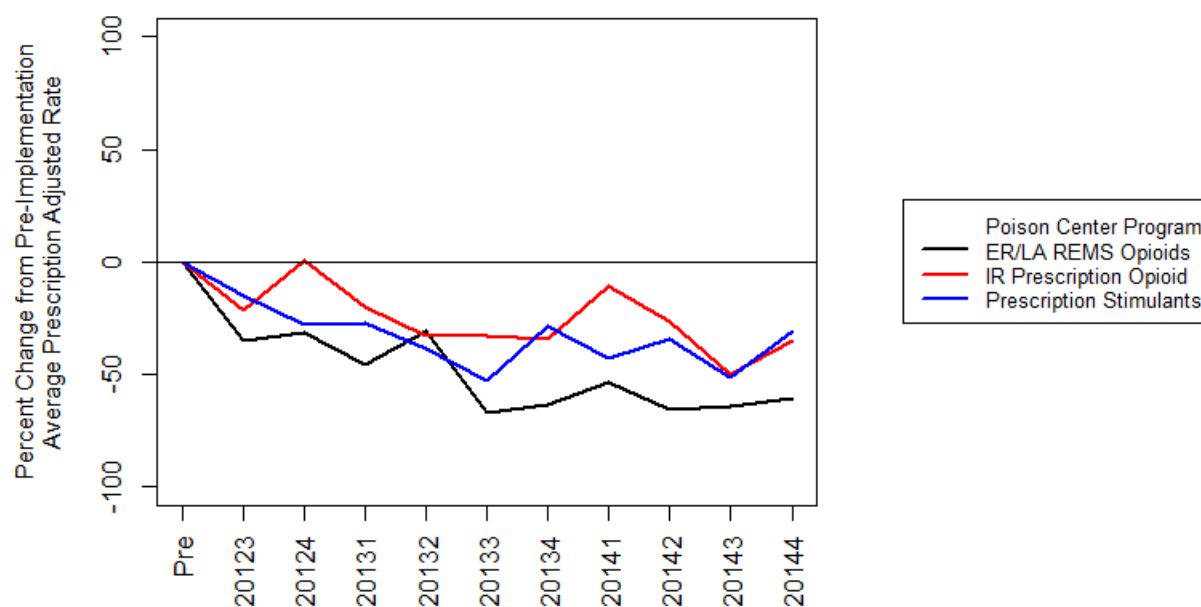
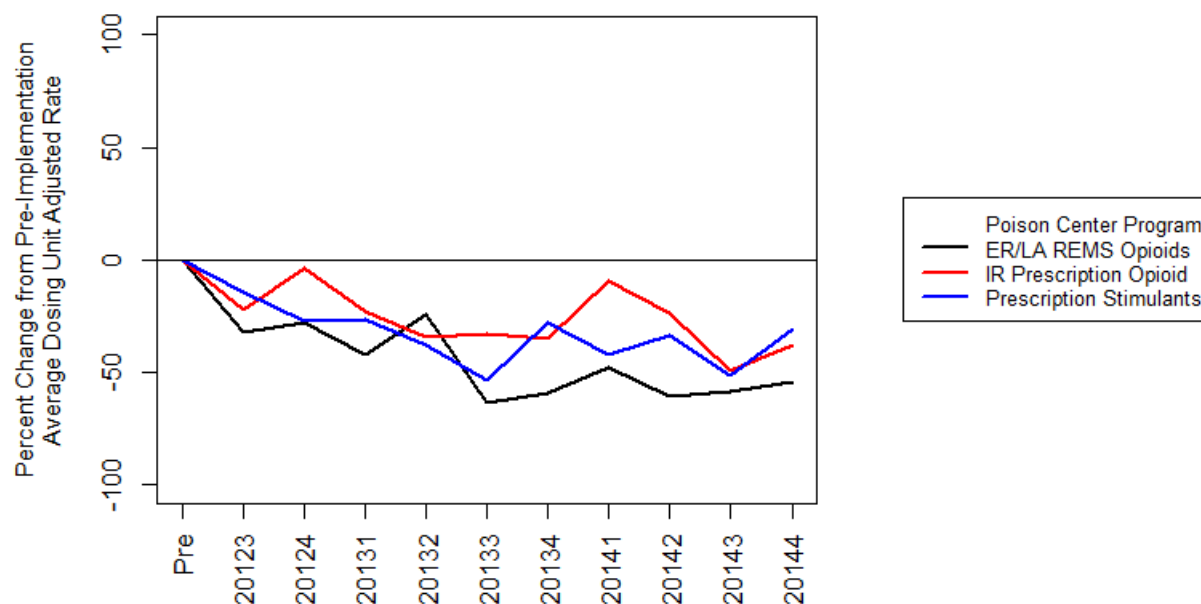


Figure 5.3.2.6
The RADARS System Poison Center Program
Adolescent Intentional Abuse Exposures
Percent Change from Average Pre-Implementation Dosing Unit Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014



5.4. Misuse from the RADARS System Poison Center Program

5.4.1. Misuse Exposures from the RADARS System Poison Center Program

Figure 5.4.1.1 through Figure 5.4.1.3 show the observed and predicted population, prescription dispensed, and dosing unit mean misuse exposure rates and 95% confidence intervals for ER/LA REMS opioids and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 5.4.1.1

The RADARS System Poison Center Program
Misuse Exposure Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

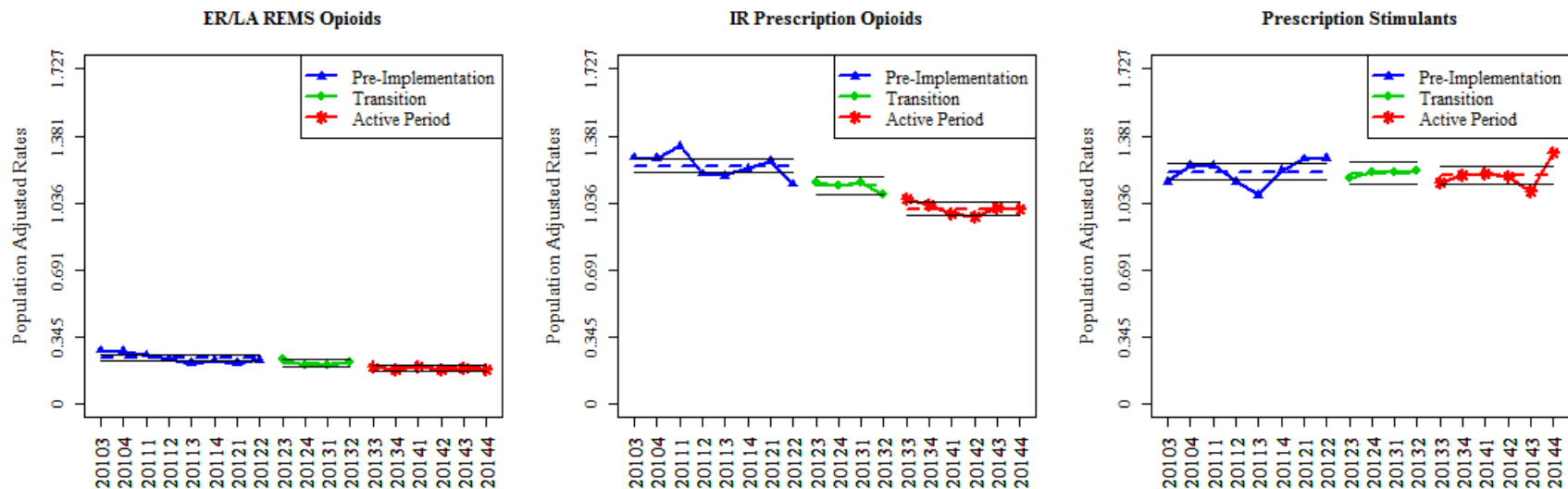


Table 5.4.1.1

The RADARS System Poison Center Program
Misuse Exposure Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.236	Pre versus Transition	-11.17%(-19.73%,-1.69%)	0.022	.
	Transition	0.209	Transition versus Active	-12.75%(-21.87%,-2.57%)	0.015	.
	Active	0.183	Pre versus Active	-22.49%(-29.32%,-15.01%)	<.001	.
IR Prescription Opioids	Pre	1.226	Pre versus Transition	-8.32%(-12.76%,-3.66%)	<.001	0.584
	Transition	1.124	Transition versus Active	-10.49%(-15.15%,-5.58%)	<.001	0.683
	Active	1.006	Pre versus Active	-17.94%(-21.54%,-14.19%)	<.001	0.275
Prescription Stimulants	Pre	1.195	Pre versus Transition	-0.71%(-6.54%,5.49%)	0.818	0.065
	Transition	1.186	Transition versus Active	-0.75%(-6.82%,5.71%)	0.815	0.047
	Active	1.177	Pre versus Active	-1.46%(-6.57%,3.94%)	0.589	<.001

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids misuse exposure population rate decreased 11.17% between the Pre-Implementation and Transition time periods. This decrease is statistically significant.

The mean IR prescription opioids misuse exposure population rate decreased 8.32% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the misuse exposure population rate is not statistically significant, indicating that the mean difference in misuse exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.584).

The mean prescription stimulants misuse exposure population rate decreased 0.71% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the misuse exposure population rate is not statistically significant, indicating that the mean difference in misuse exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.065).

The mean ER/LA REMS opioids misuse exposure population rate decreased 12.75% between the Transition and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids misuse exposure population rate decreased 10.49% between the Transition and Active Period time periods. The interaction of drug by time period for the misuse exposure population rate is not statistically significant, indicating that the mean

difference in misuse exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.683$).

The mean prescription stimulants misuse exposure population rate decreased 0.75% between the Transition and Active Period time periods. The interaction of drug by time period for the misuse exposure population rate is statistically significant, indicating that the mean difference in misuse exposure population rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p=0.047$).

The mean ER/LA REMS opioids misuse exposure population rate decreased 22.49% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids misuse exposure population rate decreased 17.94% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the misuse exposure population rate is not statistically significant, indicating that the mean difference in misuse exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.275$).

The mean prescription stimulants misuse exposure population rate decreased 1.46% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the misuse exposure population rate is statistically significant, indicating that the mean difference in misuse exposure population rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p<.001$).

Figure 5.4.1.2

The RADARS System Poison Center Program
Misuse Exposure Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

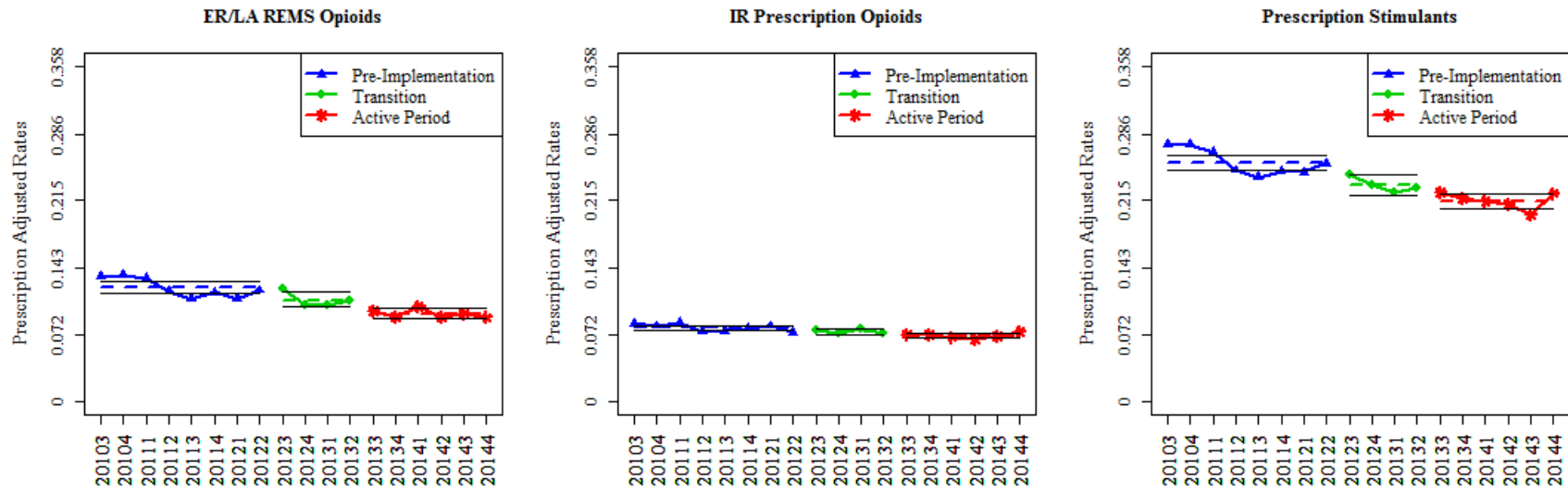


Table 5.4.1.2
The RADARS System Poison Center Program
Misuse Exposure Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.122	Pre versus Transition	-10.88%(-18.42%,-2.64%)	0.011	.
	Transition	0.108	Transition versus Active	-13.63%(-21.56%,-4.90%)	0.003	.
	Active	0.094	Pre versus Active	-23.03%(-28.97%,-16.59%)	<.001	.
IR Prescription Opioids	Pre	0.079	Pre versus Transition	-5.16%(-9.91%,-0.16%)	0.043	0.233
	Transition	0.075	Transition versus Active	-6.09%(-11.15%,-0.74%)	0.026	0.140
	Active	0.070	Pre versus Active	-10.93%(-14.97%,-6.70%)	<.001	0.002
Prescription Stimulants	Pre	0.256	Pre versus Transition	-9.46%(-14.38%,-4.26%)	<.001	0.768
	Transition	0.231	Transition versus Active	-7.36%(-12.59%,-1.81%)	0.010	0.222
	Active	0.214	Pre versus Active	-16.12%(-20.14%,-11.90%)	<.001	0.074

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids misuse exposure prescriptions dispensed rate decreased 10.88% between the Pre-Implementation and Transition time periods. This decrease is statistically significant.

The mean IR prescription opioids misuse exposure prescriptions dispensed rate decreased 5.16% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the misuse exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in misuse exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.233).

The mean prescription stimulants misuse exposure prescriptions dispensed rate decreased 9.46% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the misuse exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in misuse exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.768).

The mean ER/LA REMS opioids misuse exposure prescriptions dispensed rate decreased 13.63% between the Transition and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids misuse exposure prescriptions dispensed rate decreased 6.09% between the Transition and Active Period time periods. The interaction of drug by time period for the misuse exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in misuse exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.140$).

The mean prescription stimulants misuse exposure prescriptions dispensed rate decreased 7.36% between the Transition and Active Period time periods. The interaction of drug by time period for the misuse exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in misuse exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.222$).

The mean ER/LA REMS opioids misuse exposure prescriptions dispensed rate decreased 23.03% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids misuse exposure prescriptions dispensed rate decreased 10.93% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the misuse exposure prescriptions dispensed rate is statistically significant, indicating that the mean difference in misuse exposure prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids ($p=0.002$).

The mean prescription stimulants misuse exposure prescriptions dispensed rate decreased 16.12% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the misuse exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in misuse exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.074$).

Figure 5.4.1.3

The RADARS System Poison Center Program
Misuse Exposure Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

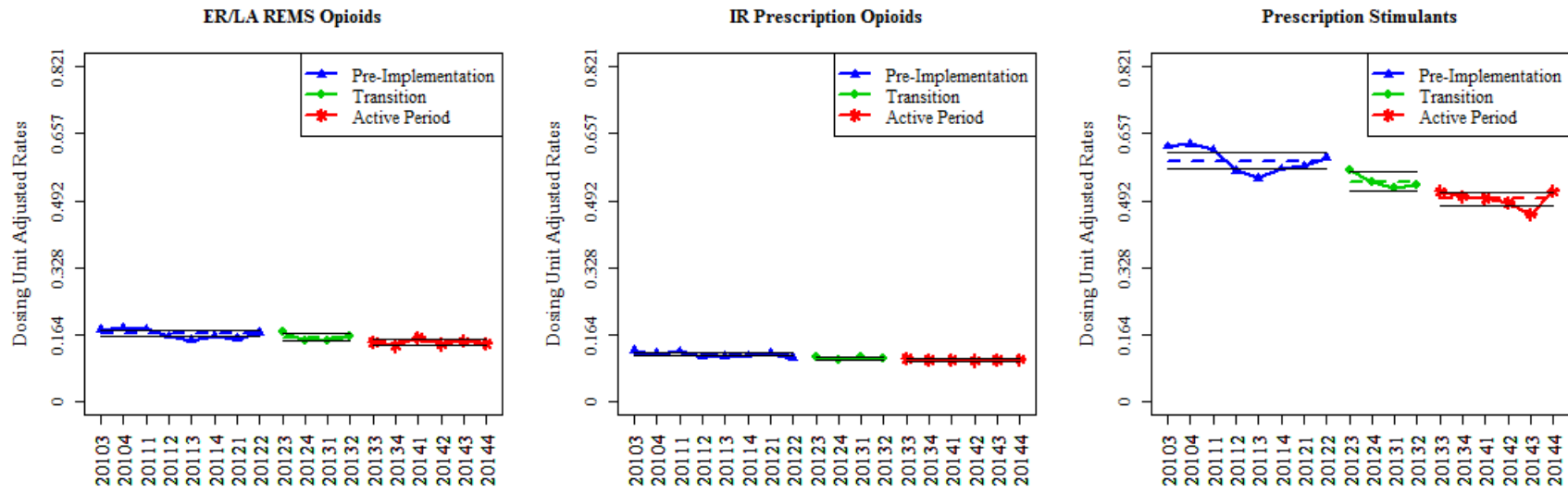


Table 5.4.1.3
The RADARS System Poison Center Program
Misuse Exposure Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.166	Pre versus Transition	-5.13%(-11.95%,2.22%)	0.167	.
	Transition	0.157	Transition versus Active	-8.34%(-15.50%,-0.57%)	0.036	.
	Active	0.144	Pre versus Active	-13.04%(-18.74%,-6.93%)	<.001	.
IR Prescription Opioids	Pre	0.114	Pre versus Transition	-7.74%(-12.38%,-2.86%)	0.002	0.547
	Transition	0.106	Transition versus Active	-3.26%(-8.50%,2.27%)	0.242	0.284
	Active	0.102	Pre versus Active	-10.75%(-14.81%,-6.49%)	<.001	0.536
Prescription Stimulants	Pre	0.590	Pre versus Transition	-8.76%(-13.57%,-3.68%)	<.001	0.407
	Transition	0.539	Transition versus Active	-7.81%(-12.87%,-2.46%)	0.005	0.909
	Active	0.497	Pre versus Active	-15.88%(-19.80%,-11.78%)	<.001	0.432

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids misuse exposure dosing units rate decreased 5.13% between the Pre-Implementation and Transition time periods. This decrease is not statistically significant.

The mean IR prescription opioids misuse exposure dosing units rate decreased 7.74% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the misuse exposure dosing units rate is not statistically significant, indicating that the mean difference in misuse exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.547).

The mean prescription stimulants misuse exposure dosing units rate decreased 8.76% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the misuse exposure dosing units rate is not statistically significant, indicating that the mean difference in misuse exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.407).

The mean ER/LA REMS opioids misuse exposure dosing units rate decreased 8.34% between the Transition and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids misuse exposure dosing units rate decreased 3.26% between the Transition and Active Period time periods. The interaction of drug by time period for the misuse exposure dosing units rate is not statistically significant, indicating that the mean

difference in misuse exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.284$).

The mean prescription stimulants misuse exposure dosing units rate decreased 7.81% between the Transition and Active Period time periods. The interaction of drug by time period for the misuse exposure dosing units rate is not statistically significant, indicating that the mean difference in misuse exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.909$).

The mean ER/LA REMS opioids misuse exposure dosing units rate decreased 13.04% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids misuse exposure dosing units rate decreased 10.75% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the misuse exposure dosing units rate is not statistically significant, indicating that the mean difference in misuse exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.536$).

The mean prescription stimulants misuse exposure dosing units rate decreased 15.88% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the misuse exposure dosing units rate is not statistically significant, indicating that the mean difference in misuse exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.432$).

Figure 5.4.1.4 through Figure 5.4.1.6 display the mean misuse exposure rate percent change from the pre-implementation average population-, prescription dispensed-, and dosing unit- adjusted rates for ER/LA REMS opioids and comparator drugs.

Figure 5.4.1.4
The RADARS System Poison Center Program
Misuse Exposures
Percent Change from Average Pre-Implementation Population Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

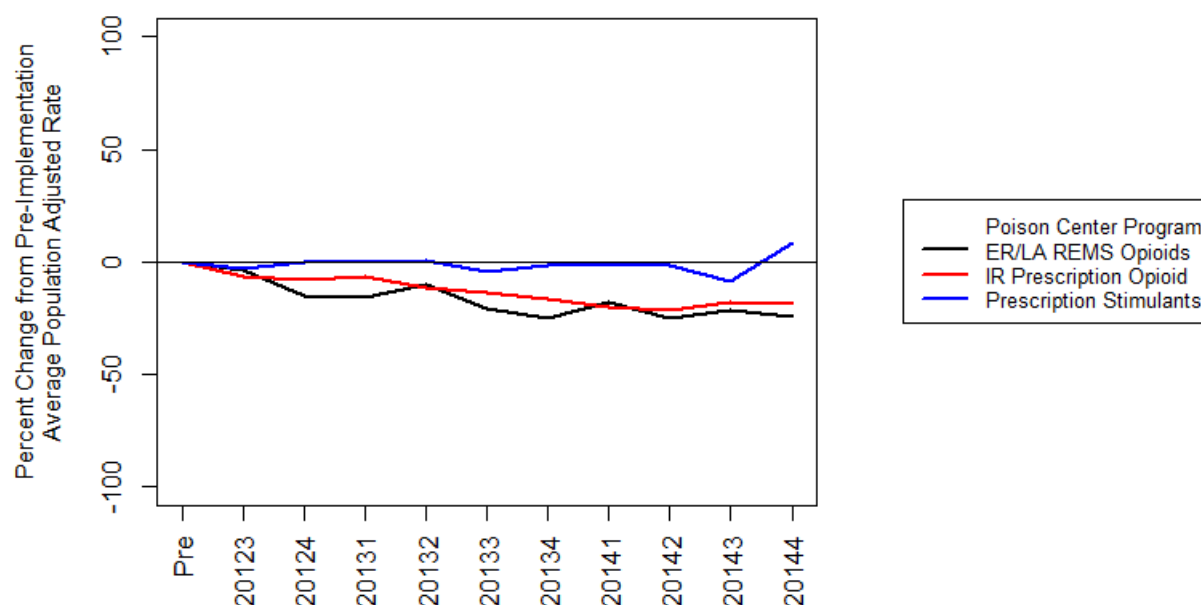


Figure 5.4.1.5
The RADARS System Poison Center Program
Misuse Exposures
Percent Change from Average Pre-Implementation Prescription Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

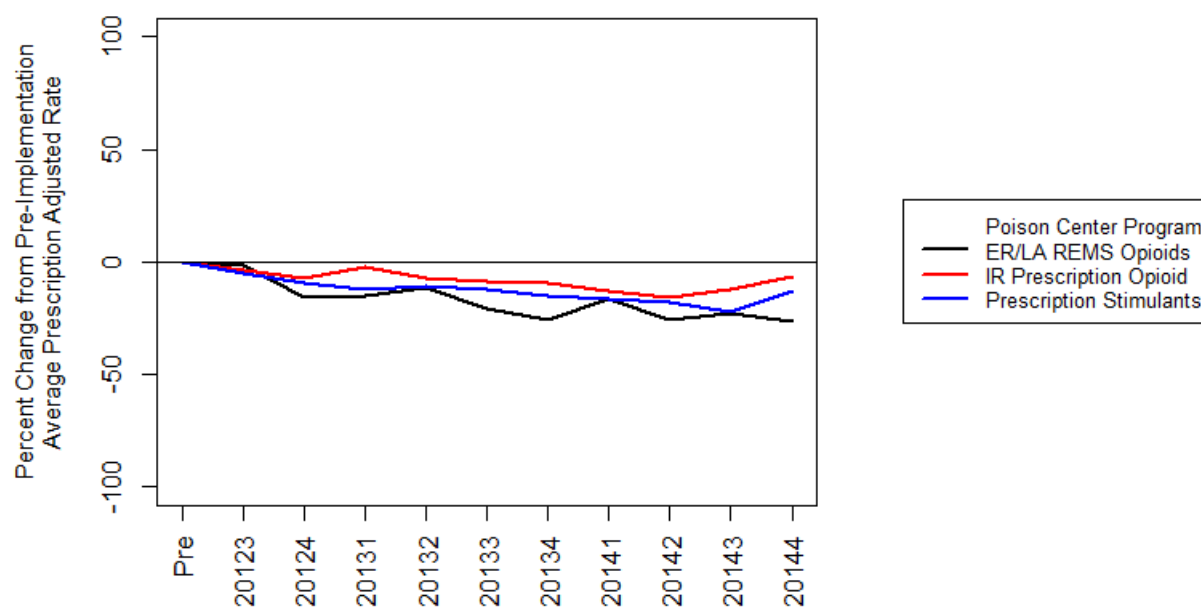
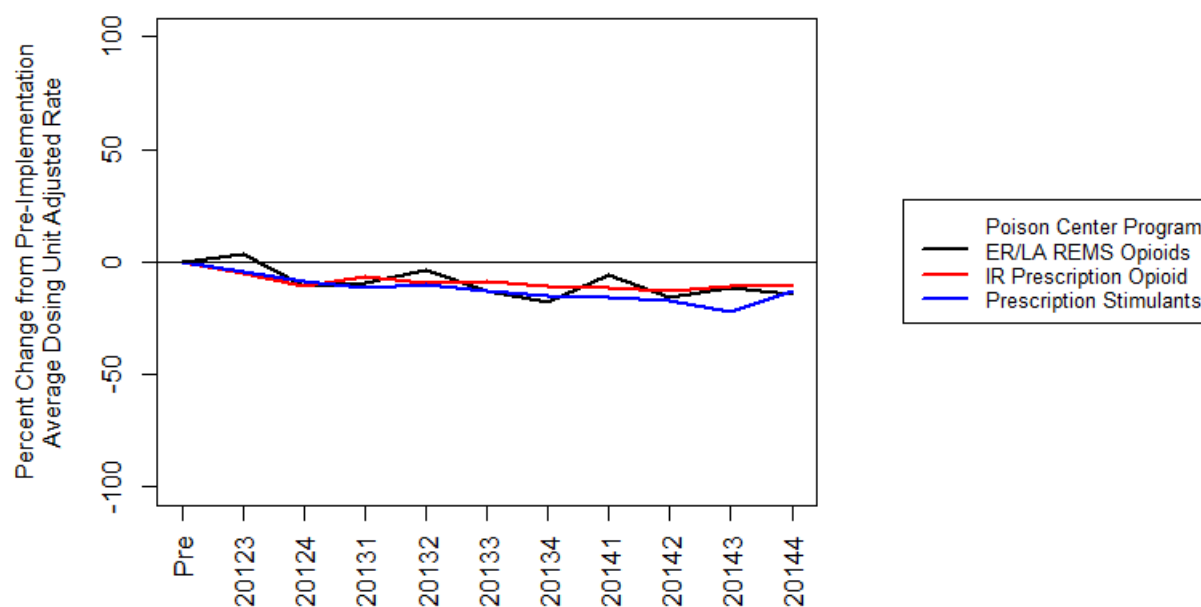


Figure 5.4.1.6
The RADARS System Poison Center Program
Misuse Exposures
Percent Change from Average Pre-Implementation Dosing Unit Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014



5.4.2. Adult Unintentional Exposures from the RADARS System Poison Center Program

Figure 5.4.2.1 through Figure 5.4.2.3 show the observed and predicted population, prescription dispensed, and dosing unit mean adult (≥ 20 years) unintentional exposure rates and 95% confidence intervals for ER/LA REMS opioids and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 5.4.2.1

The RADARS System Poison Center Program

Adult Unintentional Exposure Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

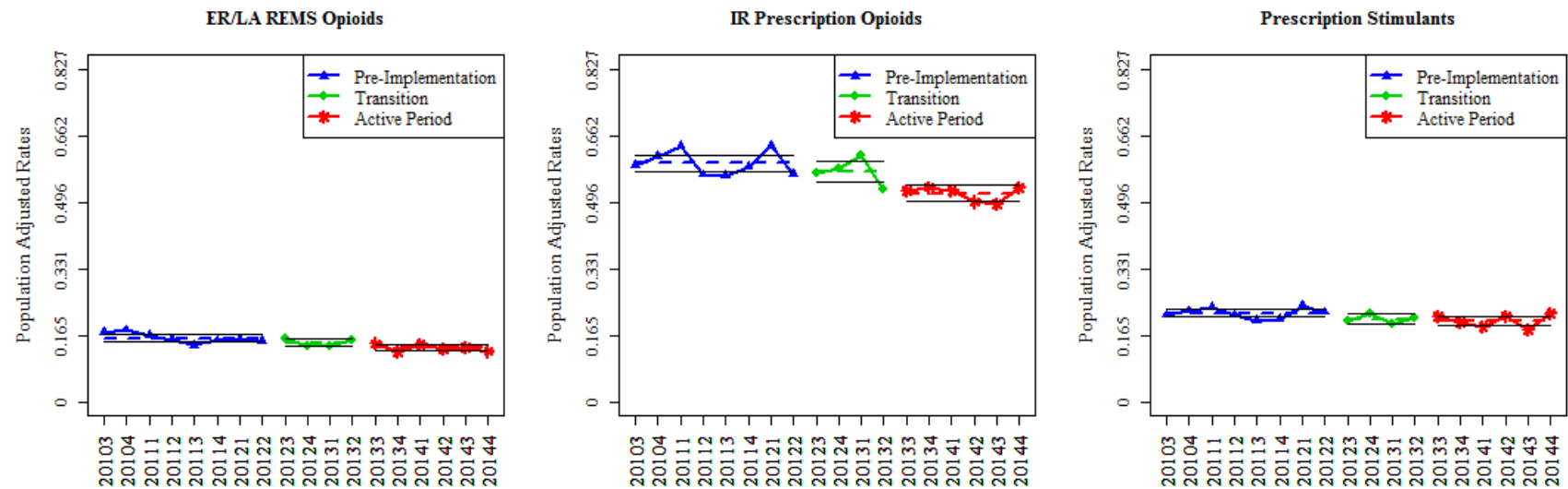


Table 5.4.2.1

The RADARS System Poison Center Program
Adult Unintentional Exposure Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.159	Pre versus Transition	-6.98%(-14.60%,1.32%)	0.097	.
	Transition	0.148	Transition versus Active	-9.22%(-17.16%,-0.52%)	0.038	.
	Active	0.134	Pre versus Active	-15.55%(-21.80%,-8.81%)	<.001	.
IR Prescription Opioids	Pre	0.593	Pre versus Transition	-3.54%(-8.94%,2.18%)	0.220	0.490
	Transition	0.572	Transition versus Active	-9.57%(-14.95%,-3.85%)	0.001	0.945
	Active	0.517	Pre versus Active	-12.77%(-17.19%,-8.13%)	<.001	0.493
Prescription Stimulants	Pre	0.221	Pre versus Transition	-6.60%(-13.81%,1.21%)	0.096	0.946
	Transition	0.206	Transition versus Active	-2.19%(-10.14%,6.45%)	0.608	0.241
	Active	0.202	Pre versus Active	-8.65%(-14.88%,-1.96%)	0.012	0.140

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids adult unintentional exposure population rate decreased 6.98% between the Pre-Implementation and Transition time periods. This decrease is not statistically significant.

The mean IR prescription opioids adult unintentional exposure population rate decreased 3.54% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the adult unintentional exposure population rate is not statistically significant, indicating that the mean difference in adult unintentional exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.490).

The mean prescription stimulants adult unintentional exposure population rate decreased 6.60% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the adult unintentional exposure population rate is not statistically significant, indicating that the mean difference in adult unintentional exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.946).

The mean ER/LA REMS opioids adult unintentional exposure population rate decreased 9.22% between the Transition and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids adult unintentional exposure population rate decreased 9.57%

between the Transition and Active Period time periods. The interaction of drug by time period for the adult unintentional exposure population rate is not statistically significant, indicating that the mean difference in adult unintentional exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.945$).

The mean prescription stimulants adult unintentional exposure population rate decreased 2.19% between the Transition and Active Period time periods. The interaction of drug by time period for the adult unintentional exposure population rate is not statistically significant, indicating that the mean difference in adult unintentional exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.241$).

The mean ER/LA REMS opioids adult unintentional exposure population rate decreased 15.55% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids adult unintentional exposure population rate decreased 12.77% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adult unintentional exposure population rate is not statistically significant, indicating that the mean difference in adult unintentional exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.493$).

The mean prescription stimulants adult unintentional exposure population rate decreased 8.65% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adult unintentional exposure population rate is not statistically significant, indicating that the mean difference in adult unintentional exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.140$).

Figure 5.4.2.2

The RADARS System Poison Center Program
Adult Unintentional Exposure Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

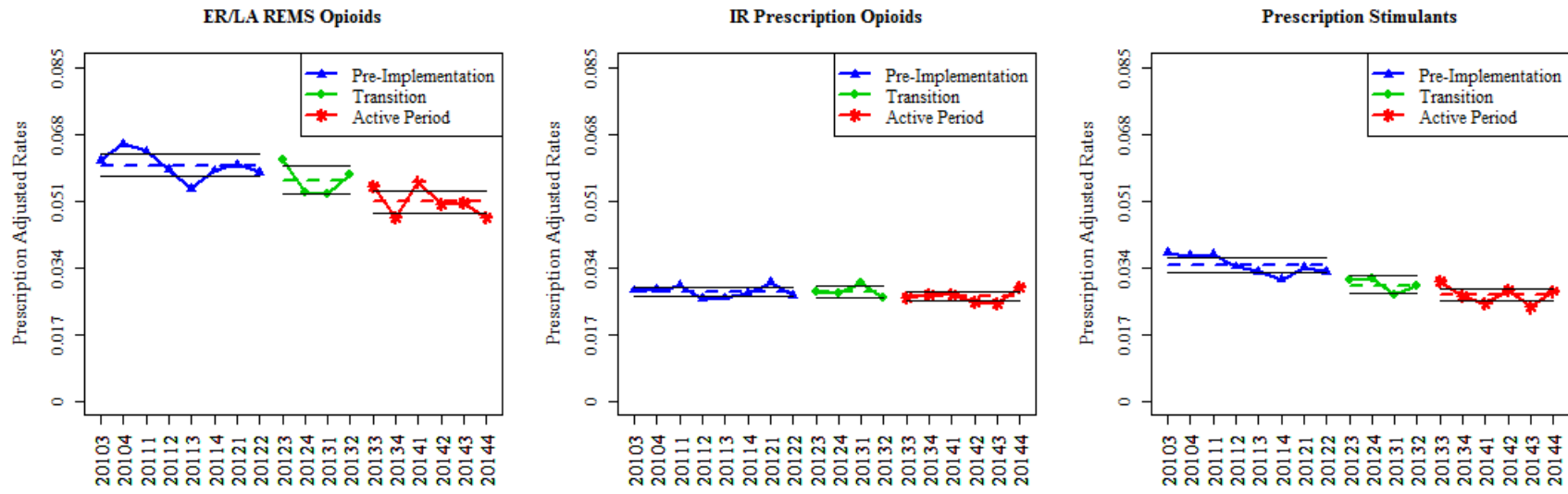


Table 5.4.2.2

The RADARS System Poison Center Program
Adult Unintentional Exposure Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.060	Pre versus Transition	-6.30%(-13.46%,1.45%)	0.109	.
	Transition	0.056	Transition versus Active	-9.86%(-17.22%,-1.86%)	0.017	.
	Active	0.051	Pre versus Active	-15.54%(-21.36%,-9.29%)	<.001	.
IR Prescription Opioids	Pre	0.028	Pre versus Transition	0.19%(-6.15%,6.96%)	0.954	0.202
	Transition	0.028	Transition versus Active	-4.84%(-11.24%,2.02%)	0.163	0.333
	Active	0.027	Pre versus Active	-4.65%(-10.11%,1.13%)	0.113	0.010
Prescription Stimulants	Pre	0.035	Pre versus Transition	-14.49%(-22.01%,-6.24%)	<.001	0.141
	Transition	0.030	Transition versus Active	-8.43%(-16.90%,0.91%)	0.075	0.810
	Active	0.027	Pre versus Active	-21.70%(-27.79%,-15.09%)	<.001	0.170

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids adult unintentional exposure prescriptions dispensed rate decreased 6.30% between the Pre-Implementation and Transition time periods. This decrease is not statistically significant.

The mean IR prescription opioids adult unintentional exposure prescriptions dispensed rate increased 0.19% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the adult unintentional exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in adult unintentional exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.202).

The mean prescription stimulants adult unintentional exposure prescriptions dispensed rate decreased 14.49% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the adult unintentional exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in adult unintentional exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.141).

The mean ER/LA REMS opioids adult unintentional exposure prescriptions dispensed rate decreased 9.86% between the Transition and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids adult unintentional exposure prescriptions dispensed rate decreased 4.84% between the Transition and Active Period time periods. The interaction of drug by time period for the adult unintentional exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in adult unintentional exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.333$).

The mean prescription stimulants adult unintentional exposure prescriptions dispensed rate decreased 8.43% between the Transition and Active Period time periods. The interaction of drug by time period for the adult unintentional exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in adult unintentional exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.810$).

The mean ER/LA REMS opioids adult unintentional exposure prescriptions dispensed rate decreased 15.54% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids adult unintentional exposure prescriptions dispensed rate decreased 4.65% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adult unintentional exposure prescriptions dispensed rate is statistically significant, indicating that the mean difference in adult unintentional exposure prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids ($p=0.010$).

The mean prescription stimulants adult unintentional exposure prescriptions dispensed rate decreased 21.70% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adult unintentional exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in adult unintentional exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.170$).

Figure 5.4.2.3

The RADARS System Poison Center Program
Adult Unintentional Exposure Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

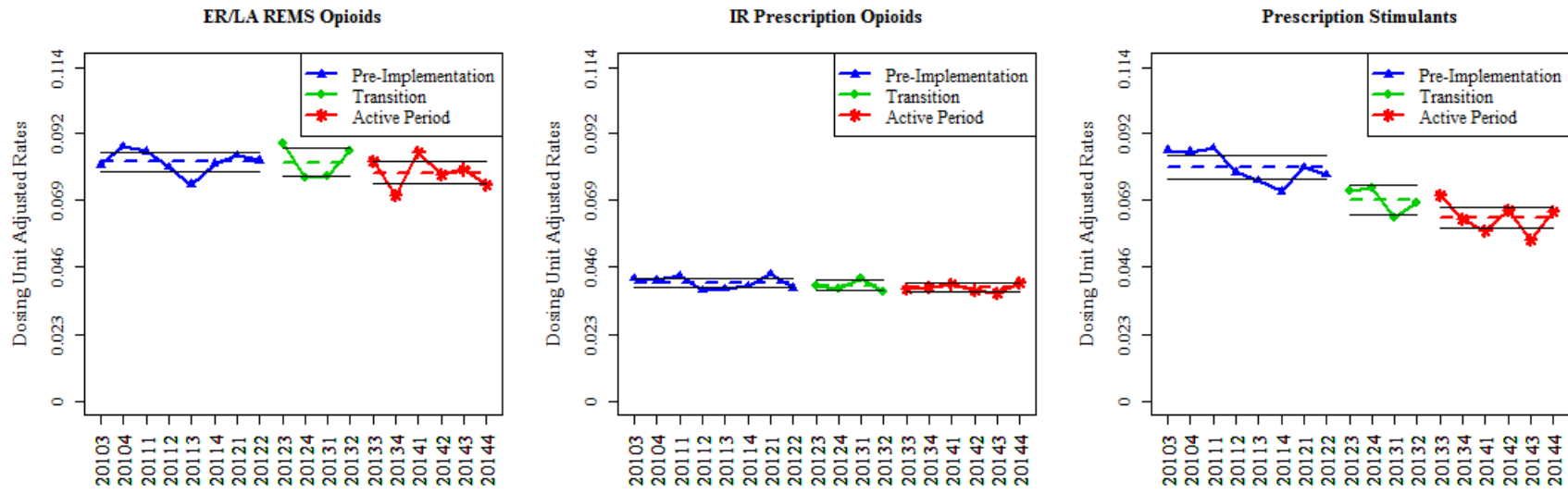


Table 5.4.2.3
The RADARS System Poison Center Program
Adult Unintentional Exposure Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.082	Pre versus Transition	-0.26%(-7.18%,7.19%)	0.945	.
	Transition	0.082	Transition versus Active	-4.34%(-11.44%,3.33%)	0.259	.
	Active	0.078	Pre versus Active	-4.58%(-10.56%,1.80%)	0.155	.
IR Prescription Opioids	Pre	0.041	Pre versus Transition	-2.53%(-7.92%,3.17%)	0.377	0.622
	Transition	0.040	Transition versus Active	-1.97%(-7.74%,4.15%)	0.519	0.625
	Active	0.039	Pre versus Active	-4.46%(-9.23%,0.57%)	0.081	0.975
Prescription Stimulants	Pre	0.080	Pre versus Transition	-13.82%(-21.19%,-5.77%)	0.001	0.013
	Transition	0.069	Transition versus Active	-8.87%(-17.07%,0.13%)	0.053	0.434
	Active	0.063	Pre versus Active	-21.47%(-27.41%,-15.05%)	<.001	<.001

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids adult unintentional exposure dosing units rate decreased 0.26% between the Pre-Implementation and Transition time periods. This decrease is not statistically significant.

The mean IR prescription opioids adult unintentional exposure dosing units rate decreased 2.53% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the adult unintentional exposure dosing units rate is not statistically significant, indicating that the mean difference in adult unintentional exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.622).

The mean prescription stimulants adult unintentional exposure dosing units rate decreased 13.82% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the adult unintentional exposure dosing units rate is statistically significant, indicating that the mean difference in adult unintentional exposure dosing units rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants (p=0.013).

The mean ER/LA REMS opioids adult unintentional exposure dosing units rate decreased 4.34% between the Transition and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids adult unintentional exposure dosing units rate decreased 1.97% between the Transition and Active Period time periods. The interaction of drug by time period for the adult unintentional exposure dosing units rate is not statistically significant, indicating that the mean difference in adult unintentional exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.625$).

The mean prescription stimulants adult unintentional exposure dosing units rate decreased 8.87% between the Transition and Active Period time periods. The interaction of drug by time period for the adult unintentional exposure dosing units rate is not statistically significant, indicating that the mean difference in adult unintentional exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.434$).

The mean ER/LA REMS opioids adult unintentional exposure dosing units rate decreased 4.58% between the Pre-Implementation and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids adult unintentional exposure dosing units rate decreased 4.46% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adult unintentional exposure dosing units rate is not statistically significant, indicating that the mean difference in adult unintentional exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.975$).

The mean prescription stimulants adult unintentional exposure dosing units rate decreased 21.47% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adult unintentional exposure dosing units rate is statistically significant, indicating that the mean difference in adult unintentional exposure dosing units rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p<.001$).

Figure 5.4.2.4 through Figure 5.4.2.6 display the mean adult (≥ 20 years) unintentional exposure rate percent change from the pre-implementation average population-, prescription dispensed-, and dosing unit- adjusted rates for ER/LA REMS opioids and comparator drugs.

Figure 5.4.2.4
The RADARS System Poison Center Program
Adult Unintentional Exposures
Percent Change from Average Pre-Implementation Population Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

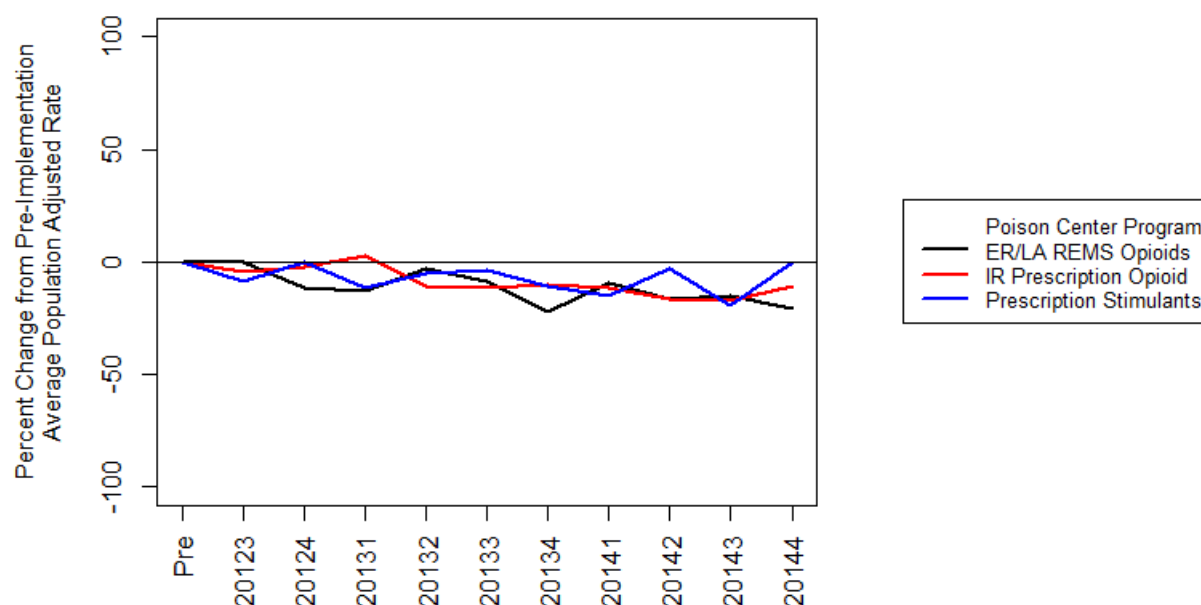


Figure 5.4.2.5

The RADARS System Poison Center Program
Adult Unintentional Exposures
Percent Change from Average Pre-Implementation Prescription Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

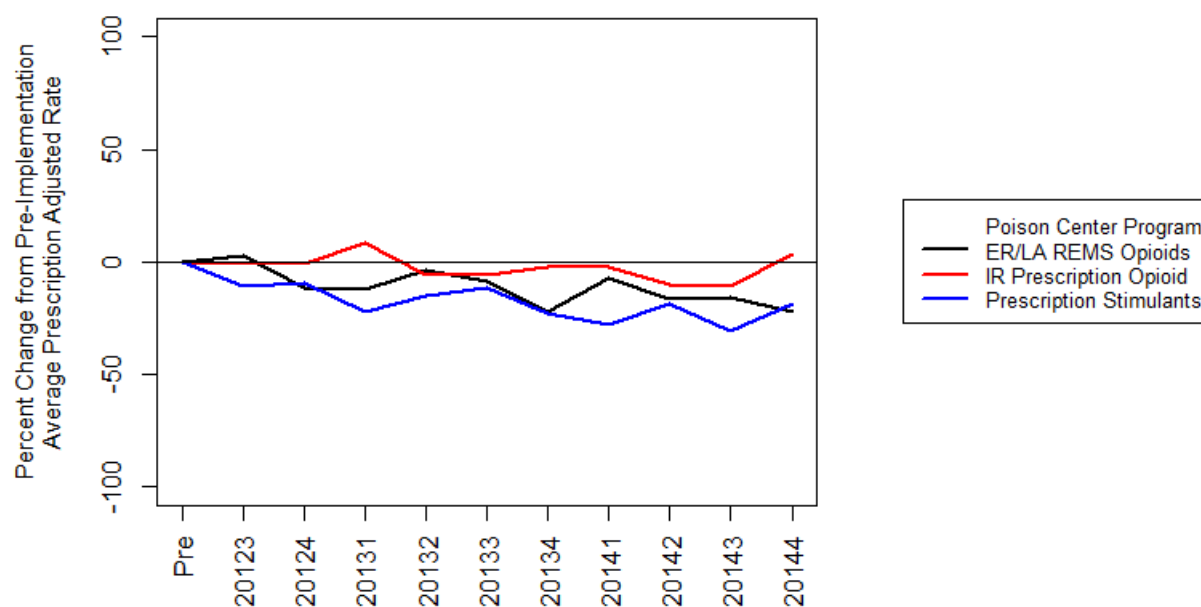
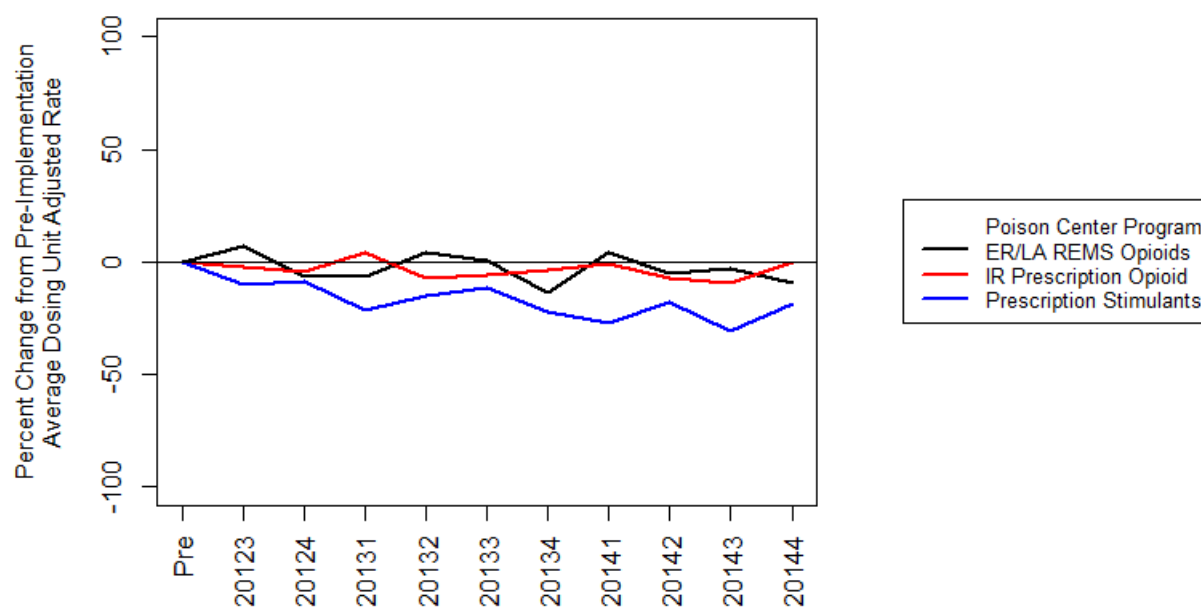


Figure 5.4.2.6

The RADARS System Poison Center Program
Adult Unintentional Exposures
Percent Change from Average Pre-Implementation Dosing Unit Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014



5.4.3. Child and Adolescent Unintentional Exposures from the RADARS System Poison Center Program

[Figure 5.4.3.1](#) through [Figure 5.4.3.3](#) show the observed and predicted population, prescription dispensed, and dosing unit mean child and adolescent (6-19 years) unintentional exposure rates and 95% confidence intervals for ER/LA REMS opioids and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 5.4.3.1

The RADARS System Poison Center Program
Child and Adolescent Unintentional Exposure Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

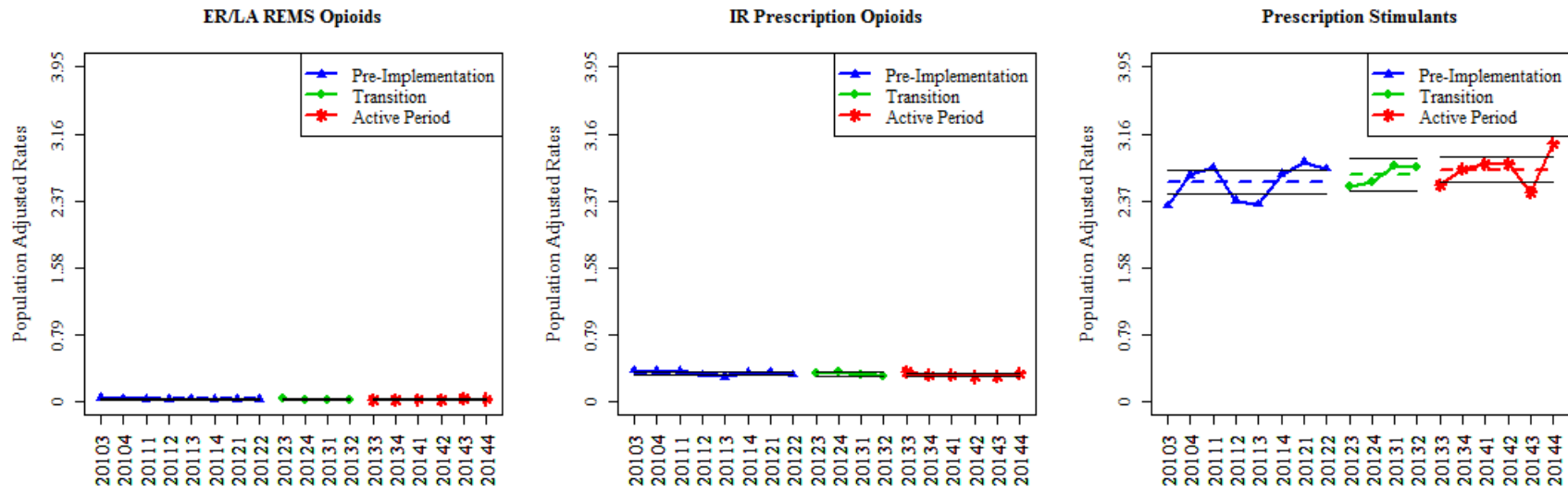


Table 5.4.3.1

The RADARS System Poison Center Program
Child and Adolescent Unintentional Exposure Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.026	Pre versus Transition	-14.34%(-40.19%,22.68%)	0.398	.
	Transition	0.022	Transition versus Active	-5.85%(-36.16%,38.86%)	0.761	.
	Active	0.021	Pre versus Active	-19.35%(-41.39%,10.98%)	0.187	.
IR Prescription Opioids	Pre	0.334	Pre versus Transition	-3.22%(-11.27%,5.57%)	0.461	0.517
	Transition	0.323	Transition versus Active	-4.32%(-12.71%,4.88%)	0.346	0.937
	Active	0.309	Pre versus Active	-7.39%(-14.28%,0.04%)	0.051	0.409
Prescription Stimulants	Pre	2.590	Pre versus Transition	3.24%(-5.51%,12.80%)	0.480	0.323
	Transition	2.673	Transition versus Active	2.29%(-6.65%,12.07%)	0.628	0.684
	Active	2.735	Pre versus Active	5.60%(-2.28%,14.11%)	0.168	0.108

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids child and adolescent unintentional exposure population rate decreased 14.34% between the Pre-Implementation and Transition time periods. This decrease is not statistically significant.

The mean IR prescription opioids child and adolescent unintentional exposure population rate decreased 3.22% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the child and adolescent unintentional exposure population rate is not statistically significant, indicating that the mean difference in child and adolescent unintentional exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.517).

The mean prescription stimulants child and adolescent unintentional exposure population rate increased 3.24% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the child and adolescent unintentional exposure population rate is not statistically significant, indicating that the mean difference in child and adolescent unintentional exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.323).

The mean ER/LA REMS opioids child and adolescent unintentional exposure population rate decreased 5.85% between the Transition and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids child and adolescent unintentional exposure population rate decreased 4.32% between the Transition and Active Period time periods. The interaction of drug by time period for the child and adolescent unintentional exposure population rate is not statistically significant, indicating that the mean difference in child and adolescent unintentional exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.937$).

The mean prescription stimulants child and adolescent unintentional exposure population rate increased 2.29% between the Transition and Active Period time periods. The interaction of drug by time period for the child and adolescent unintentional exposure population rate is not statistically significant, indicating that the mean difference in child and adolescent unintentional exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.684$).

The mean ER/LA REMS opioids child and adolescent unintentional exposure population rate decreased 19.35% between the Pre-Implementation and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids child and adolescent unintentional exposure population rate decreased 7.39% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the child and adolescent unintentional exposure population rate is not statistically significant, indicating that the mean difference in child and adolescent unintentional exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.409$).

The mean prescription stimulants child and adolescent unintentional exposure population rate increased 5.60% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the child and adolescent unintentional exposure population rate is not statistically significant, indicating that the mean difference in child and adolescent unintentional exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.108$).

Figure 5.4.3.2

The RADARS System Poison Center Program
Child and Adolescent Unintentional Exposure Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

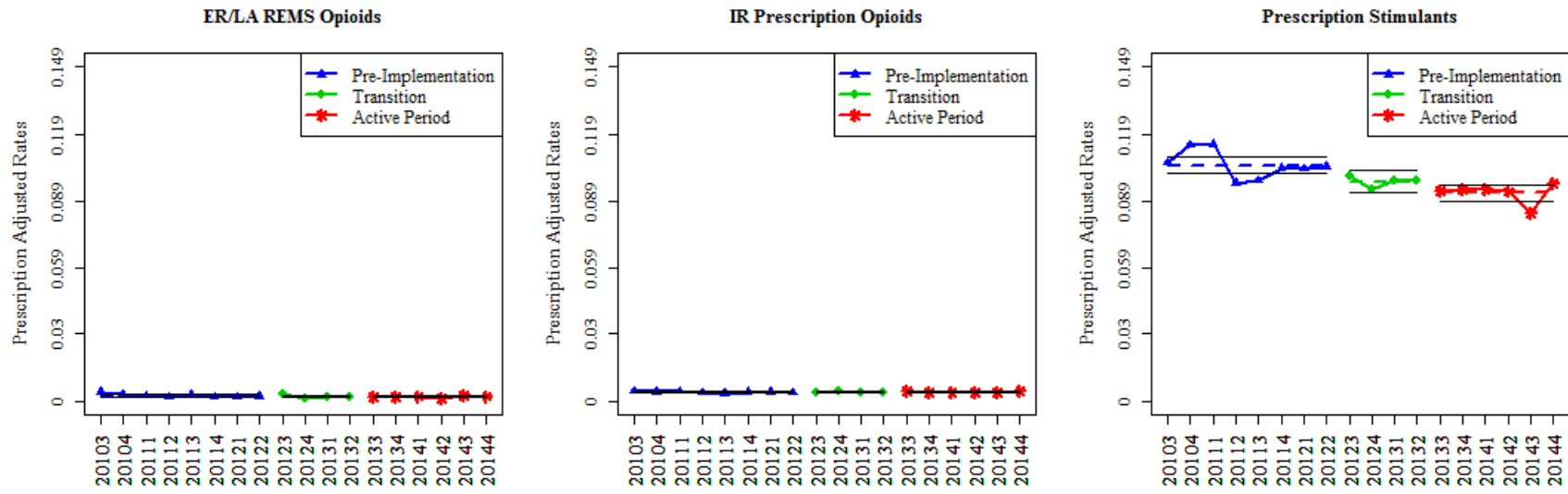


Table 5.4.3.2

The RADARS System Poison Center Program
Child and Adolescent Unintentional Exposure Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.003	Pre versus Transition	-14.97%(-39.64%,19.80%)	0.354	.
	Transition	0.002	Transition versus Active	-7.51%(-36.17%,34.01%)	0.680	.
	Active	0.002	Pre versus Active	-21.35%(-42.01%,6.66%)	0.122	.
IR Prescription Opioids	Pre	0.004	Pre versus Transition	-0.93%(-9.79%,8.80%)	0.845	0.399
	Transition	0.004	Transition versus Active	-0.38%(-9.78%,10.00%)	0.940	0.704
	Active	0.004	Pre versus Active	-1.31%(-9.20%,7.27%)	0.757	0.159
Prescription Stimulants	Pre	0.105	Pre versus Transition	-6.85%(-12.38%,-0.97%)	0.023	0.608
	Transition	0.098	Transition versus Active	-5.25%(-11.05%,0.92%)	0.094	0.900
	Active	0.093	Pre versus Active	-11.75%(-16.35%,-6.89%)	<.001	0.465

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids child and adolescent unintentional exposure prescriptions dispensed rate decreased 14.97% between the Pre-Implementation and Transition time periods. This decrease is not statistically significant.

The mean IR prescription opioids child and adolescent unintentional exposure prescriptions dispensed rate decreased 0.93% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the child and adolescent unintentional exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in child and adolescent unintentional exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.399).

The mean prescription stimulants child and adolescent unintentional exposure prescriptions dispensed rate decreased 6.85% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the child and adolescent unintentional exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in child and adolescent unintentional exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.608).

The mean ER/LA REMS opioids child and adolescent unintentional exposure prescriptions dispensed rate decreased 7.51% between the Transition and Active Period time periods. This

decrease is not statistically significant.

The mean IR prescription opioids child and adolescent unintentional exposure prescriptions dispensed rate decreased 0.38% between the Transition and Active Period time periods. The interaction of drug by time period for the child and adolescent unintentional exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in child and adolescent unintentional exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.704$).

The mean prescription stimulants child and adolescent unintentional exposure prescriptions dispensed rate decreased 5.25% between the Transition and Active Period time periods. The interaction of drug by time period for the child and adolescent unintentional exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in child and adolescent unintentional exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.900$).

The mean ER/LA REMS opioids child and adolescent unintentional exposure prescriptions dispensed rate decreased 21.35% between the Pre-Implementation and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids child and adolescent unintentional exposure prescriptions dispensed rate decreased 1.31% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the child and adolescent unintentional exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in child and adolescent unintentional exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.159$).

The mean prescription stimulants child and adolescent unintentional exposure prescriptions dispensed rate decreased 11.75% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the child and adolescent unintentional exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in child and adolescent unintentional exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.465$).

Figure 5.4.3.3
The RADARS System Poison Center Program
Child and Adolescent Unintentional Exposure Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

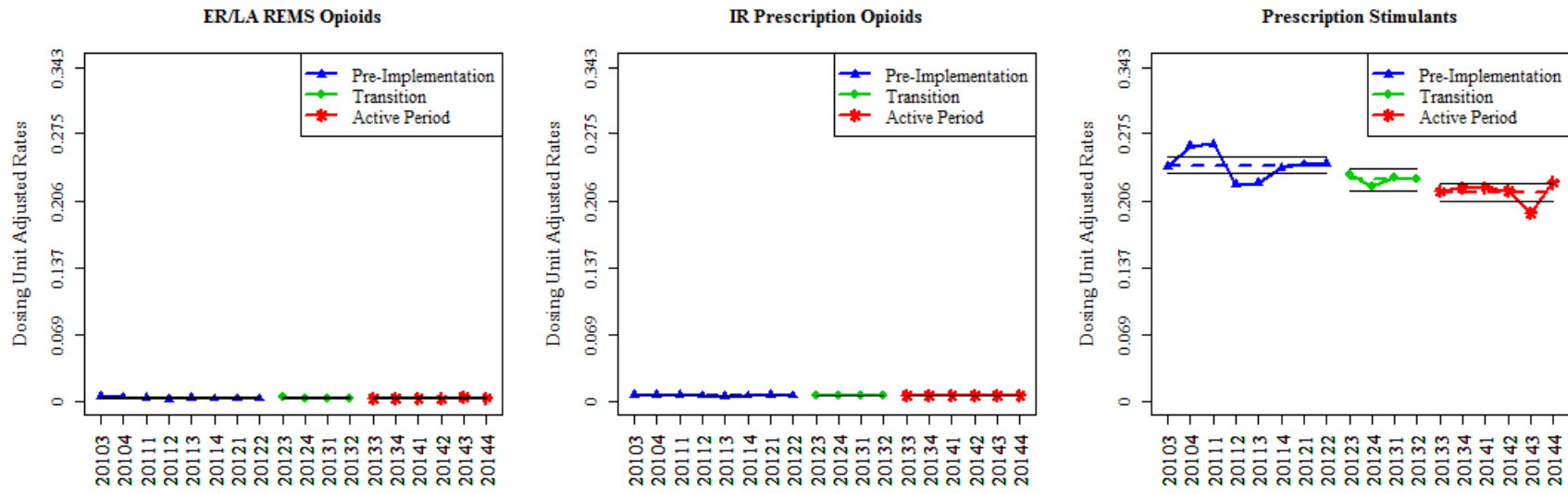


Table 5.4.3.3

The RADARS System Poison Center Program
Child and Adolescent Unintentional Exposure Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.003	Pre versus Transition	-9.48%(-34.93%,25.93%)	0.554	.
	Transition	0.003	Transition versus Active	-1.84%(-31.32%,40.29%)	0.919	.
	Active	0.003	Pre versus Active	-11.15%(-33.74%,19.15%)	0.430	.
IR Prescription Opioids	Pre	0.006	Pre versus Transition	-3.62%(-11.95%,5.48%)	0.423	0.720
	Transition	0.006	Transition versus Active	2.62%(-6.73%,12.90%)	0.596	0.814
	Active	0.006	Pre versus Active	-1.10%(-8.73%,7.17%)	0.787	0.490
Prescription Stimulants	Pre	0.243	Pre versus Transition	-6.13%(-11.86%,-0.02%)	0.049	0.832
	Transition	0.228	Transition versus Active	-5.72%(-11.65%,0.62%)	0.076	0.828
	Active	0.215	Pre versus Active	-11.49%(-16.25%,-6.47%)	<.001	0.980

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids child and adolescent unintentional exposure dosing units rate decreased 9.48% between the Pre-Implementation and Transition time periods. This decrease is not statistically significant.

The mean IR prescription opioids child and adolescent unintentional exposure dosing units rate decreased 3.62% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the child and adolescent unintentional exposure dosing units rate is not statistically significant, indicating that the mean difference in child and adolescent unintentional exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.720).

The mean prescription stimulants child and adolescent unintentional exposure dosing units rate decreased 6.13% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the child and adolescent unintentional exposure dosing units rate is not statistically significant, indicating that the mean difference in child and adolescent unintentional exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.832).

The mean ER/LA REMS opioids child and adolescent unintentional exposure dosing units rate decreased 1.84% between the Transition and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids child and adolescent unintentional exposure dosing units rate increased 2.62% between the Transition and Active Period time periods. The interaction of drug by time period for the child and adolescent unintentional exposure dosing units rate is not statistically significant, indicating that the mean difference in child and adolescent unintentional exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.814$).

The mean prescription stimulants child and adolescent unintentional exposure dosing units rate decreased 5.72% between the Transition and Active Period time periods. The interaction of drug by time period for the child and adolescent unintentional exposure dosing units rate is not statistically significant, indicating that the mean difference in child and adolescent unintentional exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.828$).

The mean ER/LA REMS opioids child and adolescent unintentional exposure dosing units rate decreased 11.15% between the Pre-Implementation and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids child and adolescent unintentional exposure dosing units rate decreased 1.10% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the child and adolescent unintentional exposure dosing units rate is not statistically significant, indicating that the mean difference in child and adolescent unintentional exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.490$).

The mean prescription stimulants child and adolescent unintentional exposure dosing units rate decreased 11.49% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the child and adolescent unintentional exposure dosing units rate is not statistically significant, indicating that the mean difference in child and adolescent unintentional exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.980$).

Figure 5.4.3.4 through Figure 5.4.3.6 display the mean child and adolescent (6-19 years) unintentional exposure rate percent change from the pre-implementation average population-, prescription dispensed-, and dosing unit- adjusted rates for ER/LA REMS opioids and comparator drugs.

Figure 5.4.3.4
The RADARS System Poison Center Program
Child and Adolescent Unintentional Exposures
Percent Change from Average Pre-Implementation Population Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

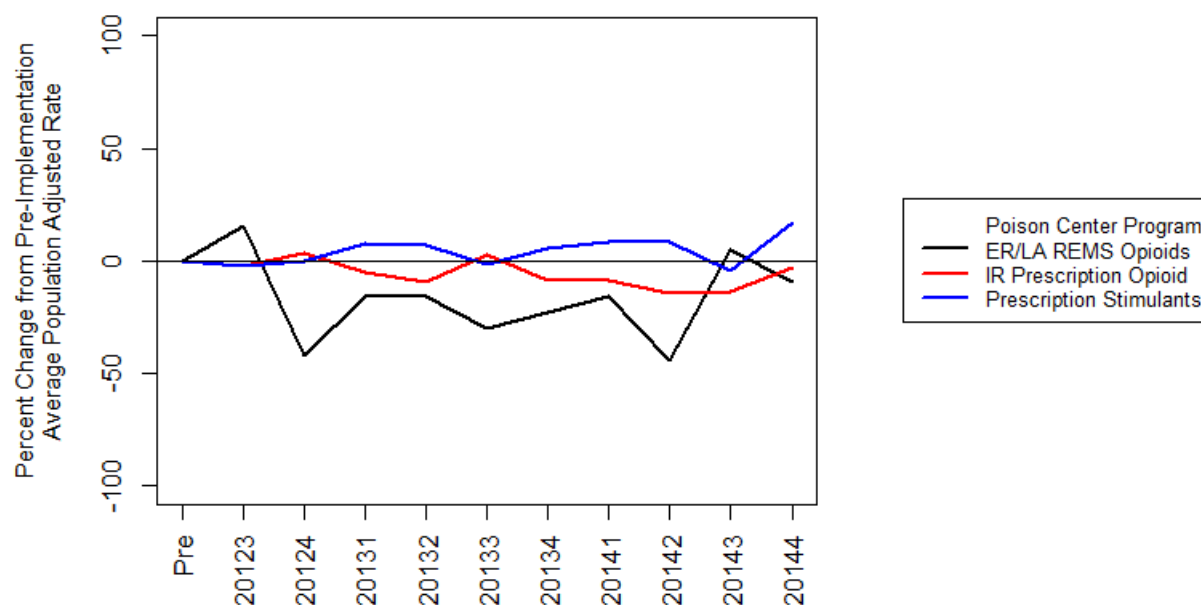


Figure 5.4.3.5

The RADARS System Poison Center Program
Child and Adolescent Unintentional Exposures
Percent Change from Average Pre-Implementation Prescription Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

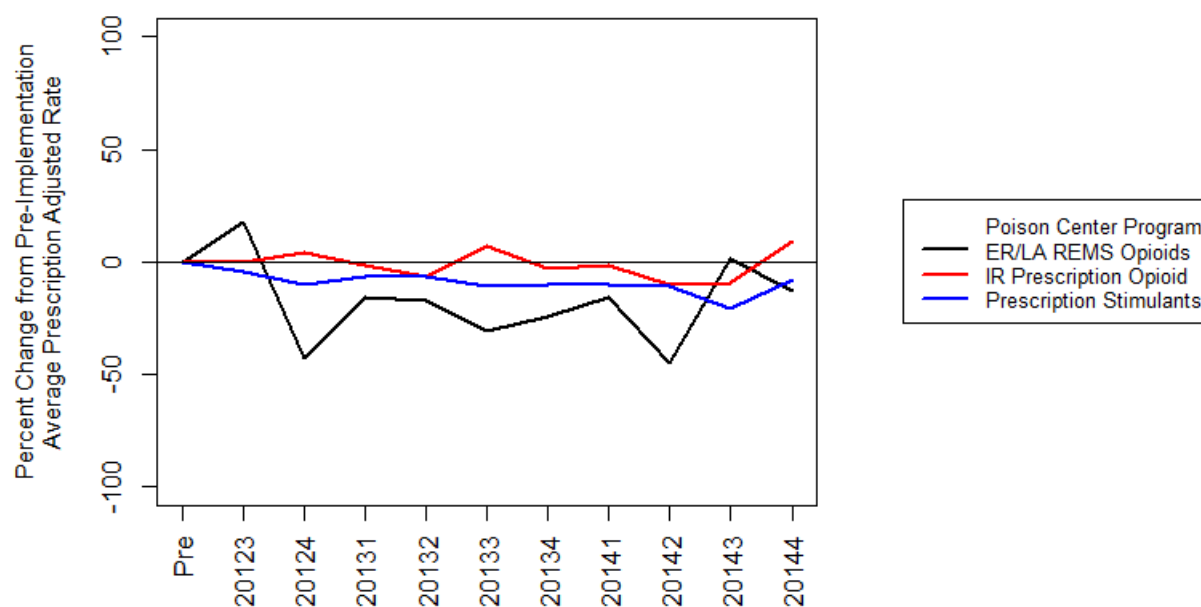
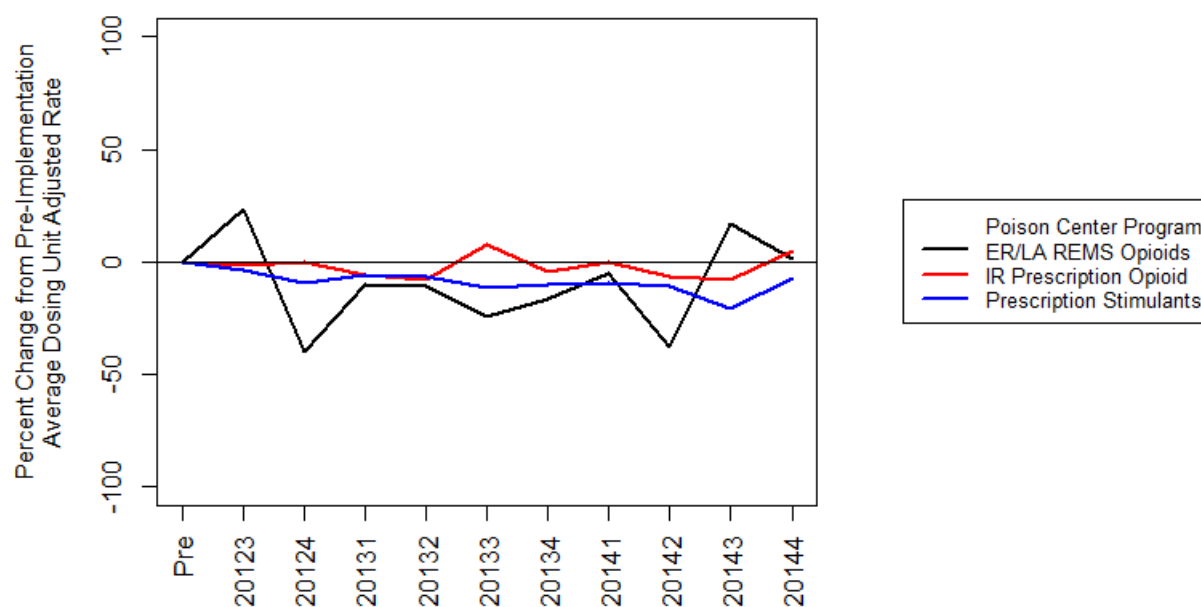


Figure 5.4.3.6

The RADARS System Poison Center Program
Child and Adolescent Unintentional Exposures
Percent Change from Average Pre-Implementation Dosing Unit Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014



5.4.4. Pediatric Unintentional Exposures from the RADARS System Poison Center Program

[Figure 5.4.4.1](#) through [Figure 5.4.4.3](#) show the observed and predicted population, prescription dispensed, and dosing unit mean pediatric (≤ 5 years) unintentional exposure rates and 95% confidence intervals for ER/LA REMS opioids and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 5.4.4.1

The RADARS System Poison Center Program
Pediatric Unintentional Exposure Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

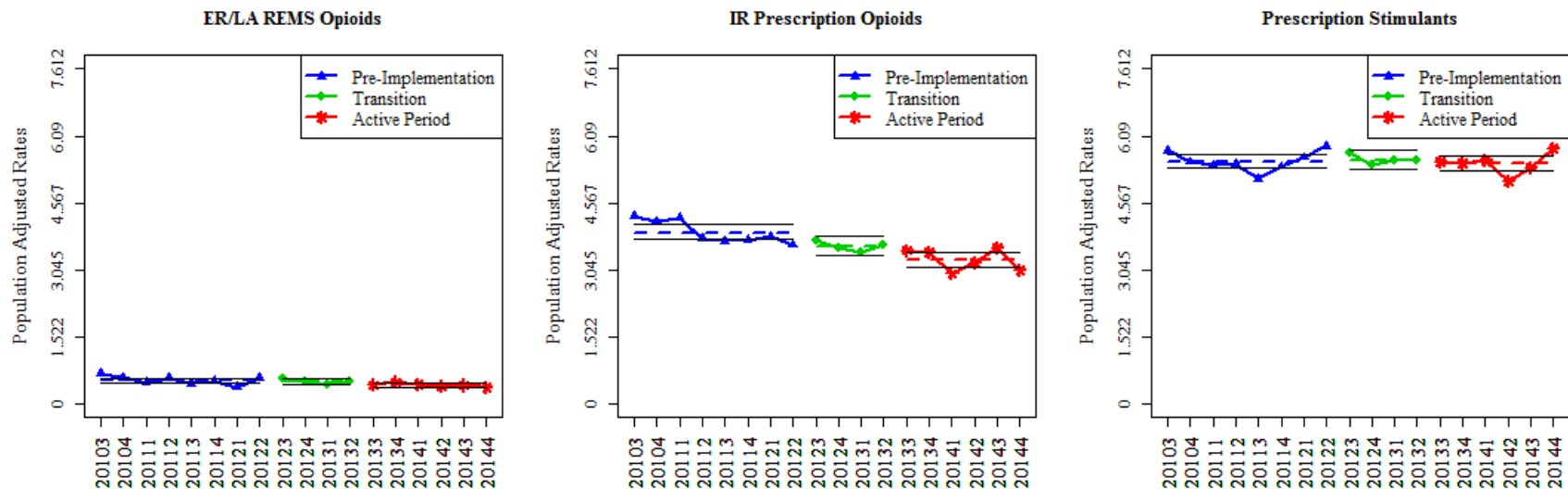


Table 5.4.4.1

The RADARS System Poison Center Program

Pediatric Unintentional Exposure Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.530	Pre versus Transition	-6.90%(-21.65%,10.61%)	0.416	.
	Transition	0.494	Transition versus Active	-14.88%(-29.46%,2.71%)	0.093	.
	Active	0.420	Pre versus Active	-20.76%(-32.37%,-7.16%)	0.004	.
IR Prescription Opioids	Pre	3.895	Pre versus Transition	-8.16%(-14.98%,-0.78%)	0.031	0.888
	Transition	3.578	Transition versus Active	-8.42%(-15.71%,-0.49%)	0.038	0.485
	Active	3.276	Pre versus Active	-15.89%(-21.52%,-9.84%)	<.001	0.499
Prescription Stimulants	Pre	5.511	Pre versus Transition	0.58%(-4.05%,5.43%)	0.810	0.397
	Transition	5.543	Transition versus Active	-1.62%(-6.34%,3.34%)	0.515	0.144
	Active	5.453	Pre versus Active	-1.05%(-5.09%,3.16%)	0.619	0.008
*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group. #The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.						

The mean ER/LA REMS opioids pediatric unintentional exposure population rate decreased 6.90% between the Pre-Implementation and Transition time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional exposure population rate decreased 8.16% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the pediatric unintentional exposure population rate is not statistically significant, indicating that the mean difference in pediatric unintentional exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.888).

The mean prescription stimulants pediatric unintentional exposure population rate increased 0.58% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the pediatric unintentional exposure population rate is not statistically significant, indicating that the mean difference in pediatric unintentional exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.397).

The mean ER/LA REMS opioids pediatric unintentional exposure population rate decreased 14.88% between the Transition and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional exposure population rate decreased

8.42% between the Transition and Active Period time periods. The interaction of drug by time period for the pediatric unintentional exposure population rate is not statistically significant, indicating that the mean difference in pediatric unintentional exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.485$).

The mean prescription stimulants pediatric unintentional exposure population rate decreased 1.62% between the Transition and Active Period time periods. The interaction of drug by time period for the pediatric unintentional exposure population rate is not statistically significant, indicating that the mean difference in pediatric unintentional exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.144$).

The mean ER/LA REMS opioids pediatric unintentional exposure population rate decreased 20.76% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids pediatric unintentional exposure population rate decreased 15.89% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional exposure population rate is not statistically significant, indicating that the mean difference in pediatric unintentional exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.499$).

The mean prescription stimulants pediatric unintentional exposure population rate decreased 1.05% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional exposure population rate is statistically significant, indicating that the mean difference in pediatric unintentional exposure population rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p=0.008$).

Figure 5.4.4.2

The RADARS System Poison Center Program
Pediatric Unintentional Exposure Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

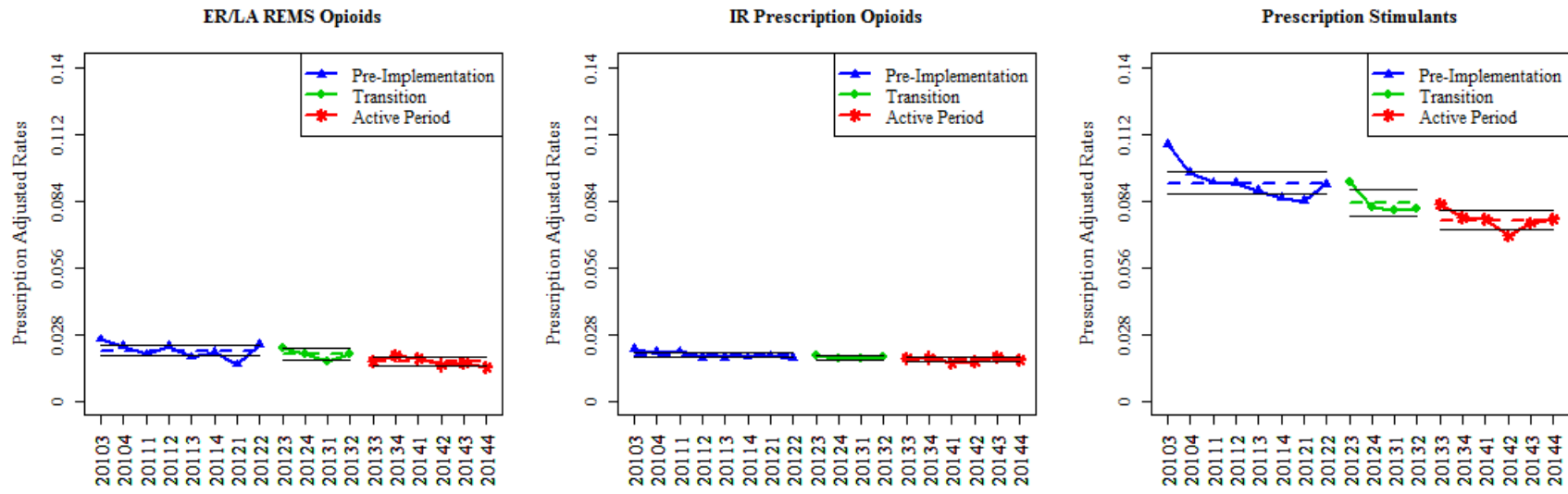


Table 5.4.4.2

The RADARS System Poison Center Program
Pediatric Unintentional Exposure Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.021	Pre versus Transition	-7.32%(-21.15%,8.92%)	0.356	.
	Transition	0.020	Transition versus Active	-16.26%(-29.77%,-0.14%)	0.048	.
	Active	0.016	Pre versus Active	-22.39%(-33.09%,-9.97%)	<.001	.
IR Prescription Opioids	Pre	0.019	Pre versus Transition	-5.72%(-12.48%,1.56%)	0.121	0.850
	Transition	0.018	Transition versus Active	-4.50%(-11.84%,3.45%)	0.259	0.183
	Active	0.018	Pre versus Active	-9.96%(-15.78%,-3.74%)	0.002	0.074
Prescription Stimulants	Pre	0.092	Pre versus Transition	-9.00%(-16.22%,-1.15%)	0.025	0.844
	Transition	0.083	Transition versus Active	-8.73%(-16.27%,-0.50%)	0.038	0.389
	Active	0.076	Pre versus Active	-16.94%(-22.79%,-10.65%)	<.001	0.421

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids pediatric unintentional exposure prescriptions dispensed rate decreased 7.32% between the Pre-Implementation and Transition time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional exposure prescriptions dispensed rate decreased 5.72% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the pediatric unintentional exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.850).

The mean prescription stimulants pediatric unintentional exposure prescriptions dispensed rate decreased 9.00% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the pediatric unintentional exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.844).

The mean ER/LA REMS opioids pediatric unintentional exposure prescriptions dispensed rate decreased 16.26% between the Transition and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids pediatric unintentional exposure prescriptions dispensed rate decreased 4.50% between the Transition and Active Period time periods. The interaction of drug by time period for the pediatric unintentional exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.183$).

The mean prescription stimulants pediatric unintentional exposure prescriptions dispensed rate decreased 8.73% between the Transition and Active Period time periods. The interaction of drug by time period for the pediatric unintentional exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.389$).

The mean ER/LA REMS opioids pediatric unintentional exposure prescriptions dispensed rate decreased 22.39% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids pediatric unintentional exposure prescriptions dispensed rate decreased 9.96% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.074$).

The mean prescription stimulants pediatric unintentional exposure prescriptions dispensed rate decreased 16.94% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.421$).

Figure 5.4.4.3

The RADARS System Poison Center Program
Pediatric Unintentional Exposure Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

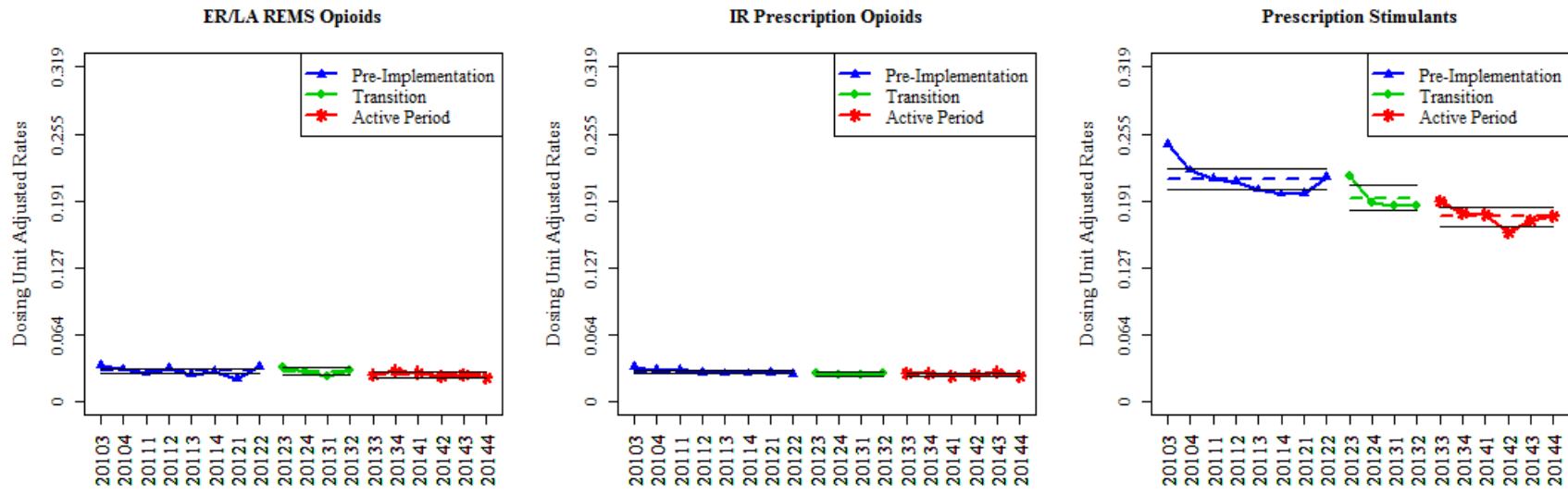


Table 5.4.4.3
The RADARS System Poison Center Program
Pediatric Unintentional Exposure Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.029	Pre versus Transition	-1.35%(-15.07%,14.60%)	0.859	.
	Transition	0.029	Transition versus Active	-11.12%(-24.51%,4.64%)	0.157	.
	Active	0.025	Pre versus Active	-12.32%(-23.60%,0.62%)	0.061	.
IR Prescription Opioids	Pre	0.028	Pre versus Transition	-8.28%(-15.63%,-0.30%)	0.042	0.405
	Transition	0.026	Transition versus Active	-1.62%(-10.07%,7.62%)	0.721	0.285
	Active	0.025	Pre versus Active	-9.77%(-16.29%,-2.75%)	0.007	0.720
Prescription Stimulants	Pre	0.211	Pre versus Transition	-8.29%(-15.14%,-0.88%)	0.029	0.397
	Transition	0.194	Transition versus Active	-9.17%(-16.24%,-1.51%)	0.020	0.815
	Active	0.176	Pre versus Active	-16.70%(-22.22%,-10.79%)	<.001	0.514

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids pediatric unintentional exposure dosing units rate decreased 1.35% between the Pre-Implementation and Transition time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional exposure dosing units rate decreased 8.28% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the pediatric unintentional exposure dosing units rate is not statistically significant, indicating that the mean difference in pediatric unintentional exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.405).

The mean prescription stimulants pediatric unintentional exposure dosing units rate decreased 8.29% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the pediatric unintentional exposure dosing units rate is not statistically significant, indicating that the mean difference in pediatric unintentional exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.397).

The mean ER/LA REMS opioids pediatric unintentional exposure dosing units rate decreased 11.12% between the Transition and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional exposure dosing units rate decreased 1.62% between the Transition and Active Period time periods. The interaction of drug by time period for the pediatric unintentional exposure dosing units rate is not statistically significant, indicating that the mean difference in pediatric unintentional exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.285$).

The mean prescription stimulants pediatric unintentional exposure dosing units rate decreased 9.17% between the Transition and Active Period time periods. The interaction of drug by time period for the pediatric unintentional exposure dosing units rate is not statistically significant, indicating that the mean difference in pediatric unintentional exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.815$).

The mean ER/LA REMS opioids pediatric unintentional exposure dosing units rate decreased 12.32% between the Pre-Implementation and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional exposure dosing units rate decreased 9.77% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional exposure dosing units rate is not statistically significant, indicating that the mean difference in pediatric unintentional exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.720$).

The mean prescription stimulants pediatric unintentional exposure dosing units rate decreased 16.70% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional exposure dosing units rate is not statistically significant, indicating that the mean difference in pediatric unintentional exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.514$).

Figure 5.4.4.4 through Figure 5.4.4.6 display the mean pediatric (≤ 5 years) unintentional exposure rate percent change from the pre-implementation average population-, prescription dispensed-, and dosing unit- adjusted rates for ER/LA REMS opioids and comparator drugs.

Figure 5.4.4.4
The RADARS System Poison Center Program
Pediatric Unintentional Exposures
Percent Change from Average Pre-Implementation Population Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

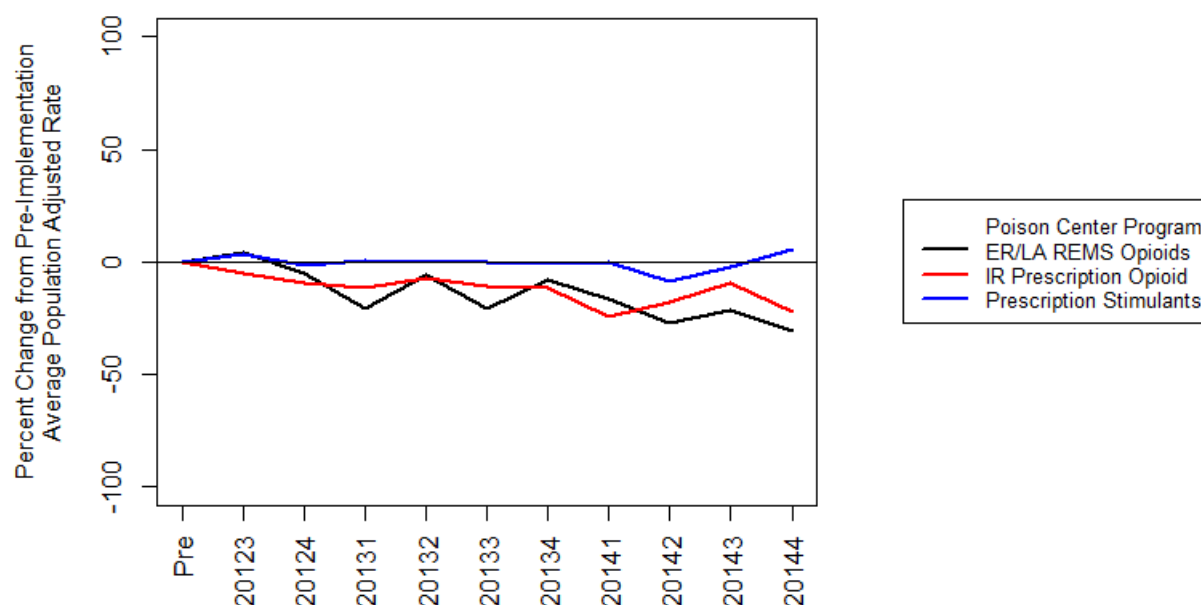


Figure 5.4.4.5

The RADARS System Poison Center Program
Pediatric Unintentional Exposures
Percent Change from Average Pre-Implementation Prescription Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

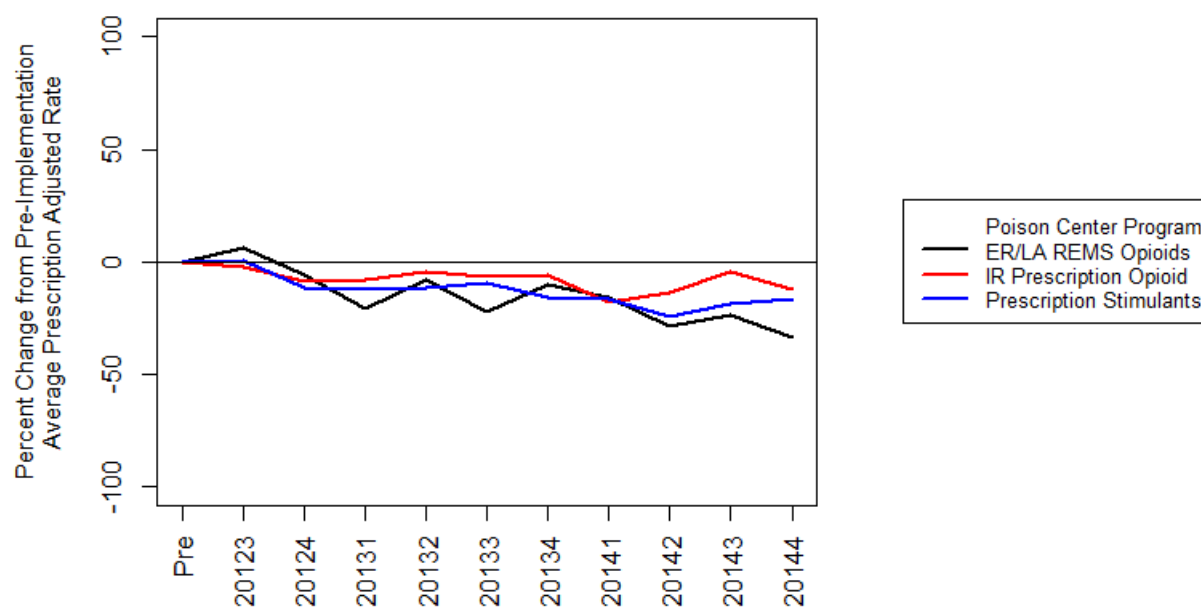
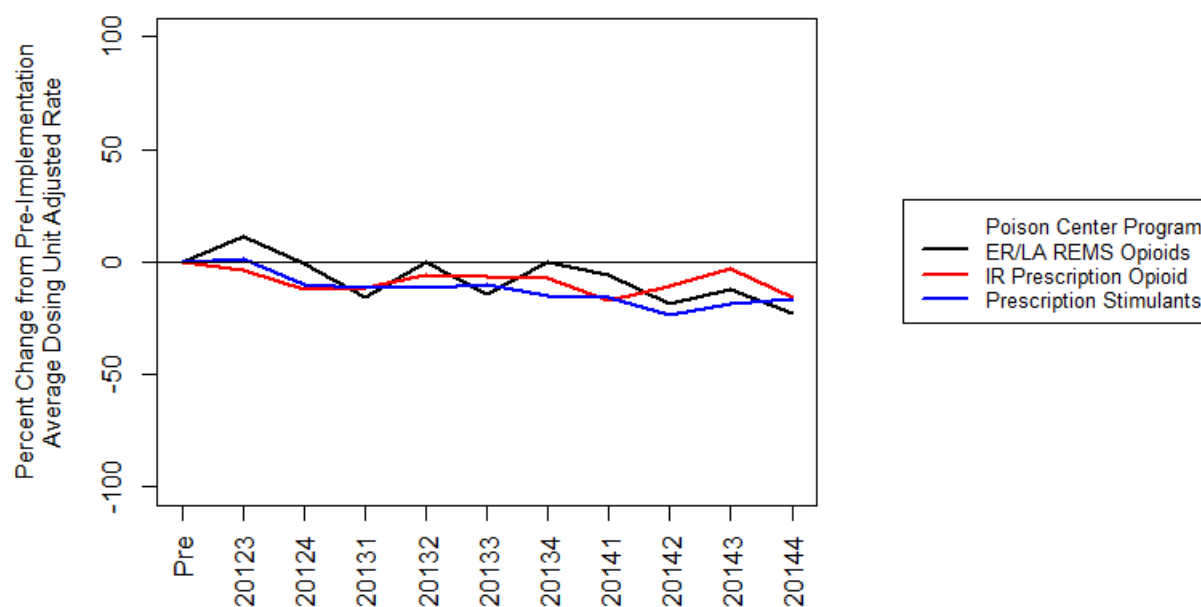


Figure 5.4.4.6

The RADARS System Poison Center Program
Pediatric Unintentional Exposures
Percent Change from Average Pre-Implementation Dosing Unit Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014



5.4.5. Pediatric Unintentional General Exposures from the RADARS System Poison Center Program

[Figure 5.4.5.1](#) through [Figure 5.4.5.3](#) show the observed and predicted population, prescription dispensed, and dosing unit mean pediatric (≤ 5 years) unintentional general exposure rates and 95% confidence intervals for ER/LA REMS opioids and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 5.4.5.1

The RADARS System Poison Center Program
Pediatric Unintentional General Exposure Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

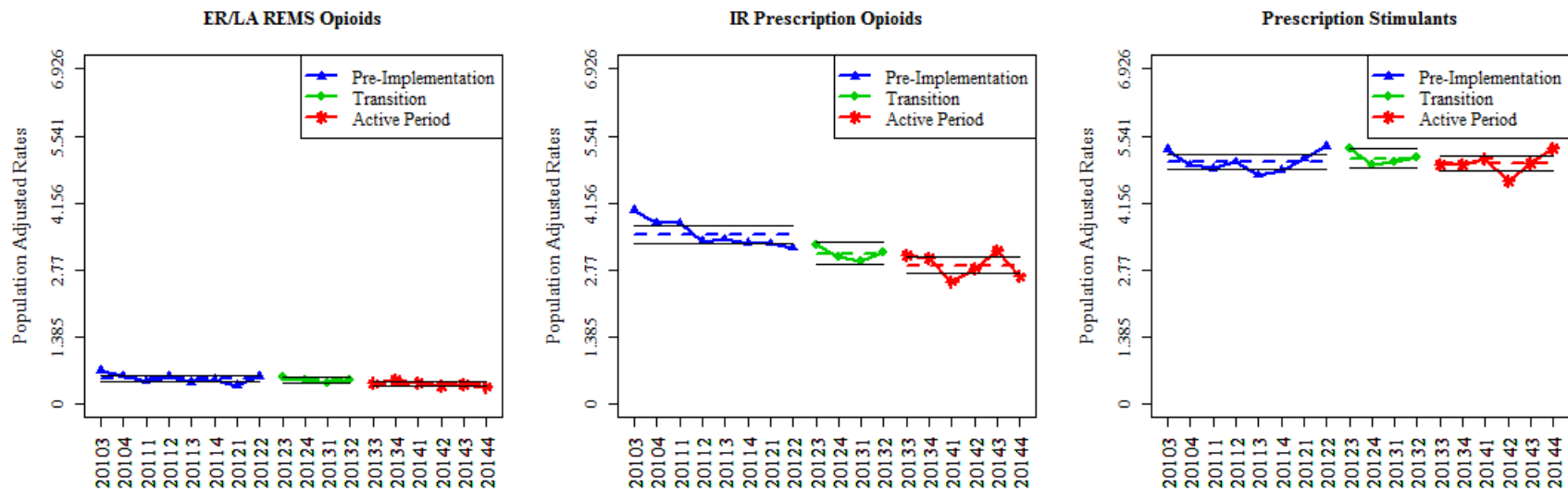


Table 5.4.5.1

The RADARS System Poison Center Program
Pediatric Unintentional General Exposure Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.520	Pre versus Transition	-7.59%(-22.54%,10.24%)	0.380	.
	Transition	0.480	Transition versus Active	-15.10%(-29.97%,2.94%)	0.096	.
	Active	0.408	Pre versus Active	-21.54%(-33.29%,-7.73%)	0.003	.
IR Prescription Opioids	Pre	3.504	Pre versus Transition	-11.47%(-19.22%,-2.97%)	0.009	0.673
	Transition	3.102	Transition versus Active	-7.68%(-16.38%,1.93%)	0.114	0.449
	Active	2.864	Pre versus Active	-18.27%(-24.71%,-11.28%)	<.001	0.659
Prescription Stimulants	Pre	5.001	Pre versus Transition	1.48%(-3.32%,6.53%)	0.552	0.316
	Transition	5.075	Transition versus Active	-2.14%(-6.97%,2.94%)	0.402	0.162
	Active	4.967	Pre versus Active	-0.69%(-4.86%,3.67%)	0.753	0.006

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids pediatric unintentional general exposure population rate decreased 7.59% between the Pre-Implementation and Transition time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure population rate decreased 11.47% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the pediatric unintentional general exposure population rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.673).

The mean prescription stimulants pediatric unintentional general exposure population rate increased 1.48% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the pediatric unintentional general exposure population rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.316).

The mean ER/LA REMS opioids pediatric unintentional general exposure population rate decreased 15.10% between the Transition and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure population rate decreased 7.68% between the Transition and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure population rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.449$).

The mean prescription stimulants pediatric unintentional general exposure population rate decreased 2.14% between the Transition and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure population rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.162$).

The mean ER/LA REMS opioids pediatric unintentional general exposure population rate decreased 21.54% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure population rate decreased 18.27% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure population rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.659$).

The mean prescription stimulants pediatric unintentional general exposure population rate decreased 0.69% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure population rate is statistically significant, indicating that the mean difference in pediatric unintentional general exposure population rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p=0.006$).

Figure 5.4.5.2

The RADARS System Poison Center Program
Pediatric Unintentional General Exposure Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

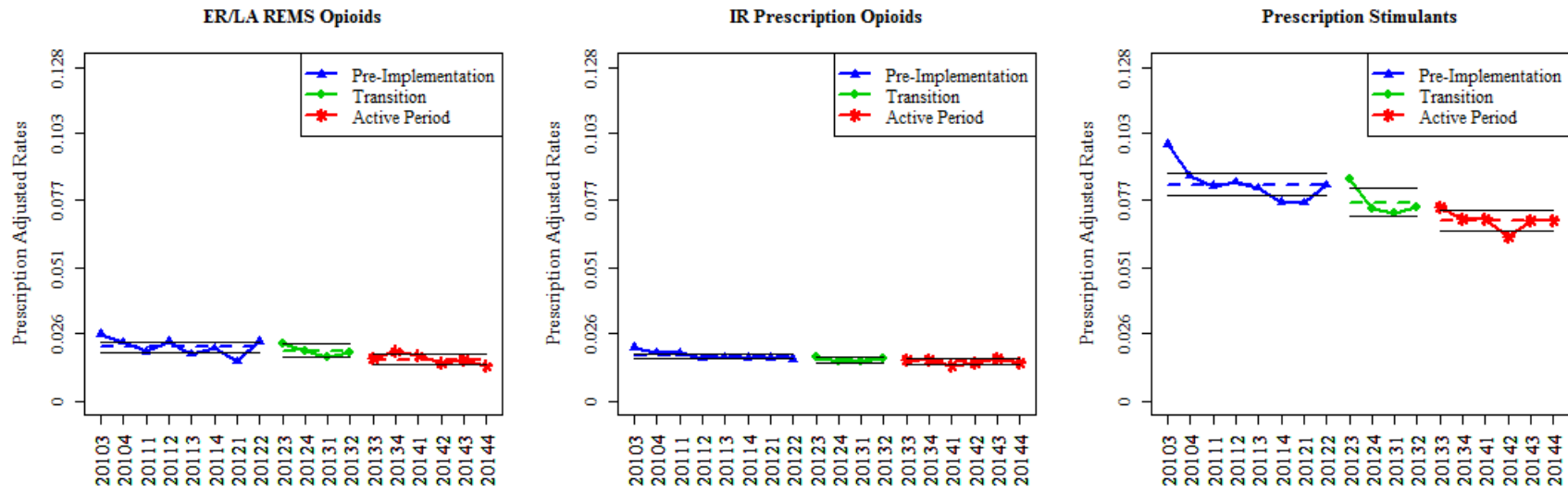


Table 5.4.5.2

The RADARS System Poison Center Program
Pediatric Unintentional General Exposure Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.021	Pre versus Transition	-8.01%(-22.05%,8.56%)	0.323	.
	Transition	0.019	Transition versus Active	-16.46%(-30.28%,0.09%)	0.051	.
	Active	0.016	Pre versus Active	-23.15%(-34.01%,-10.52%)	<.001	.
IR Prescription Opioids	Pre	0.017	Pre versus Transition	-9.12%(-16.91%,-0.61%)	0.036	0.899
	Transition	0.016	Transition versus Active	-3.73%(-12.60%,6.04%)	0.441	0.175
	Active	0.015	Pre versus Active	-12.51%(-19.25%,-5.21%)	0.001	0.140
Prescription Stimulants	Pre	0.083	Pre versus Transition	-8.18%(-15.76%,0.09%)	0.053	0.985
	Transition	0.076	Transition versus Active	-9.21%(-17.02%,-0.67%)	0.035	0.419
	Active	0.069	Pre versus Active	-16.63%(-22.76%,-10.02%)	<.001	0.349

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids pediatric unintentional general exposure prescriptions dispensed rate decreased 8.01% between the Pre-Implementation and Transition time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure prescriptions dispensed rate decreased 9.12% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the pediatric unintentional general exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.899).

The mean prescription stimulants pediatric unintentional general exposure prescriptions dispensed rate decreased 8.18% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the pediatric unintentional general exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.985).

The mean ER/LA REMS opioids pediatric unintentional general exposure prescriptions dispensed rate decreased 16.46% between the Transition and Active Period time periods. This

decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure prescriptions dispensed rate decreased 3.73% between the Transition and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.175$).

The mean prescription stimulants pediatric unintentional general exposure prescriptions dispensed rate decreased 9.21% between the Transition and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.419$).

The mean ER/LA REMS opioids pediatric unintentional general exposure prescriptions dispensed rate decreased 23.15% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure prescriptions dispensed rate decreased 12.51% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.140$).

The mean prescription stimulants pediatric unintentional general exposure prescriptions dispensed rate decreased 16.63% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.349$).

Figure 5.4.5.3

The RADARS System Poison Center Program
Pediatric Unintentional General Exposure Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

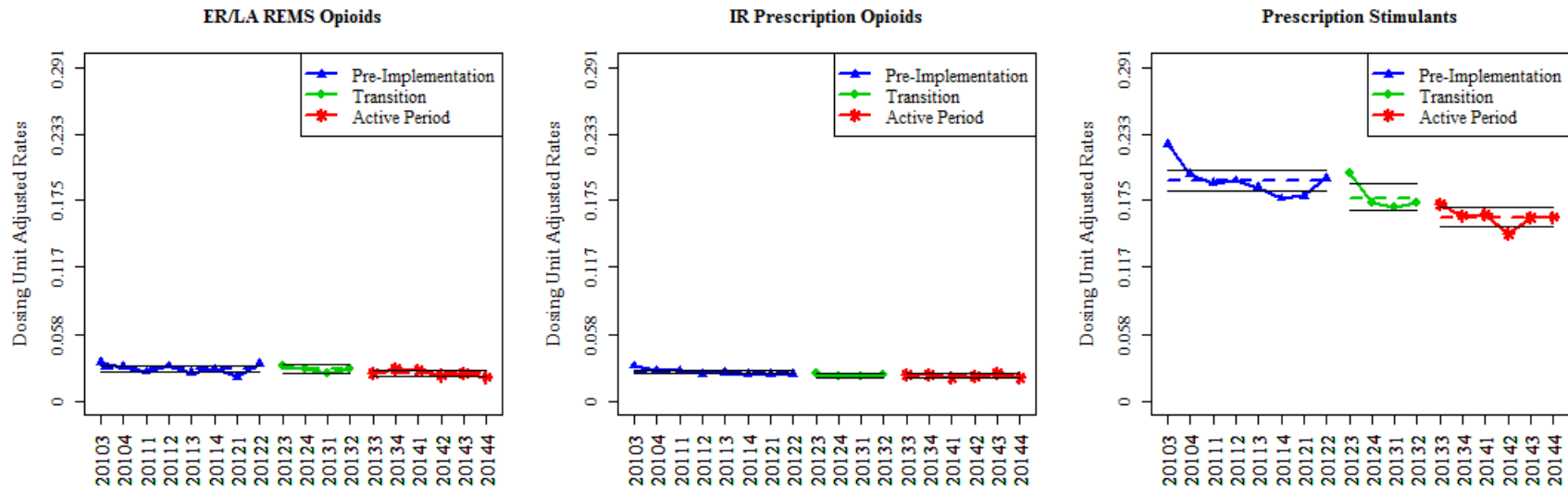


Table 5.4.5.3

The RADARS System Poison Center Program
Pediatric Unintentional General Exposure Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.028	Pre versus Transition	-2.08%(-15.97%,14.12%)	0.788	.
	Transition	0.028	Transition versus Active	-11.34%(-24.98%,4.78%)	0.158	.
	Active	0.025	Pre versus Active	-13.18%(-24.58%,-0.07%)	0.049	.
IR Prescription Opioids	Pre	0.025	Pre versus Transition	-11.59%(-20.03%,-2.27%)	0.016	0.273
	Transition	0.022	Transition versus Active	-0.83%(-11.01%,10.51%)	0.880	0.270
	Active	0.022	Pre versus Active	-12.33%(-19.85%,-4.10%)	0.004	0.908
Prescription Stimulants	Pre	0.192	Pre versus Transition	-7.46%(-14.65%,0.33%)	0.060	0.522
	Transition	0.178	Transition versus Active	-9.65%(-16.96%,-1.71%)	0.018	0.843
	Active	0.160	Pre versus Active	-16.40%(-22.17%,-10.19%)	<.001	0.640

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids pediatric unintentional general exposure dosing units rate decreased 2.08% between the Pre-Implementation and Transition time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure dosing units rate decreased 11.59% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the pediatric unintentional general exposure dosing units rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.273).

The mean prescription stimulants pediatric unintentional general exposure dosing units rate decreased 7.46% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the pediatric unintentional general exposure dosing units rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.522).

The mean ER/LA REMS opioids pediatric unintentional general exposure dosing units rate decreased 11.34% between the Transition and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure dosing units rate decreased 0.83% between the Transition and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure dosing units rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.270$).

The mean prescription stimulants pediatric unintentional general exposure dosing units rate decreased 9.65% between the Transition and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure dosing units rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.843$).

The mean ER/LA REMS opioids pediatric unintentional general exposure dosing units rate decreased 13.18% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure dosing units rate decreased 12.33% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure dosing units rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.908$).

The mean prescription stimulants pediatric unintentional general exposure dosing units rate decreased 16.40% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure dosing units rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.640$).

Figure 5.4.5.4 through Figure 5.4.5.6 display the mean pediatric (≤ 5 years) unintentional general exposure rate percent change from the pre-implementation average population-, prescription dispensed-, and dosing unit- adjusted rates for ER/LA REMS opioids and comparator drugs.

Figure 5.4.5.4
The RADARS System Poison Center Program
Pediatric Unintentional General Exposures
Percent Change from Average Pre-Implementation Population Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

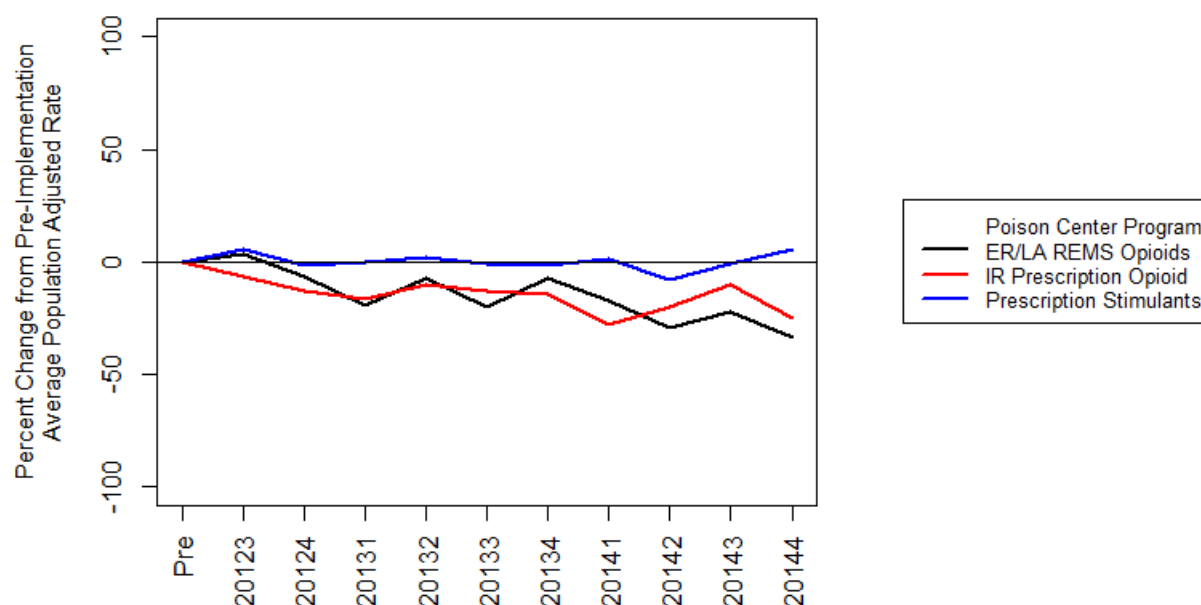


Figure 5.4.5.5

The RADARS System Poison Center Program
Pediatric Unintentional General Exposures
Percent Change from Average Pre-Implementation Prescription Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

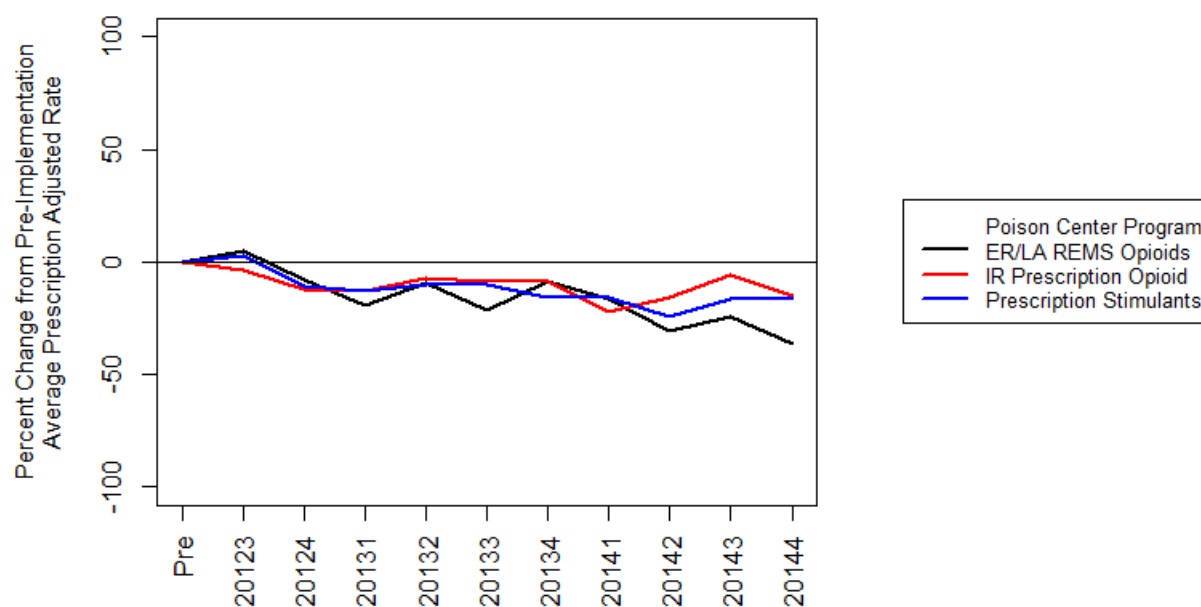
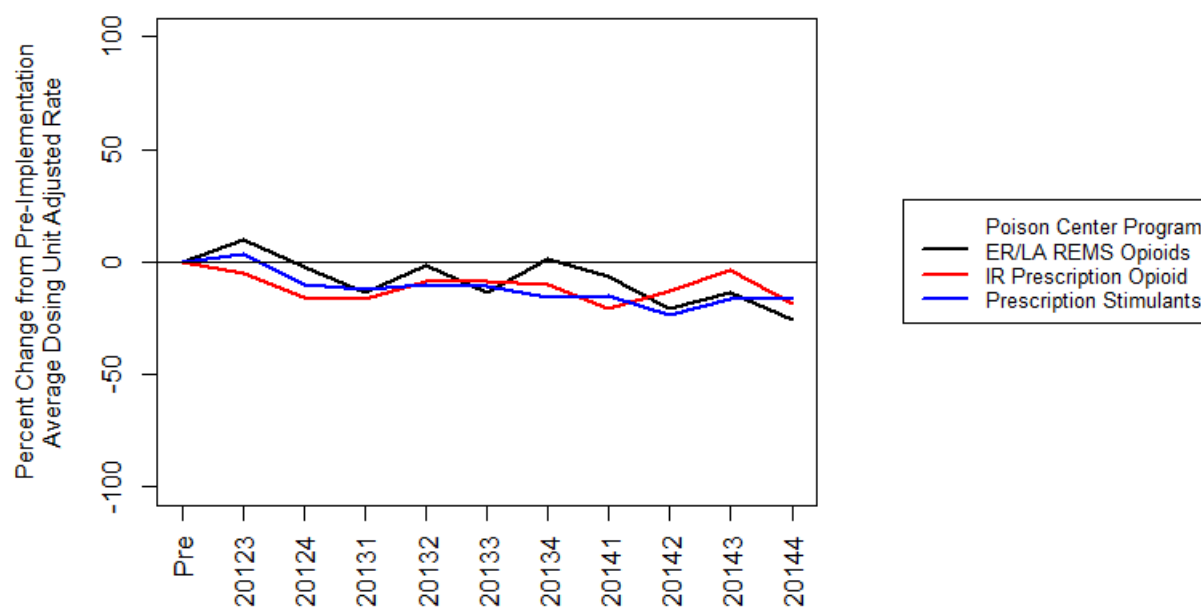


Figure 5.4.5.6

The RADARS System Poison Center Program
Pediatric Unintentional General Exposures
Percent Change from Average Pre-Implementation Dosing Unit Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014



5.4.6. Pediatric Unintentional General Exposures Resulting in a Major Medical Outcome, Hospitalization or Death from the RADARS System Poison Center Program

Figure 5.4.6.1 through Figure 5.4.6.3 show the observed and predicted population, prescription dispensed, and dosing unit mean pediatric (≤ 5 years) unintentional general exposure major medical outcome, hospitalization, or death rates and 95% confidence intervals for ER/LA REMS opioids and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 5.4.6.1

The RADARS System Poison Center Program
Pediatric Unintentional General Exposure Major Medical Outcome, Hospitalization or Death Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

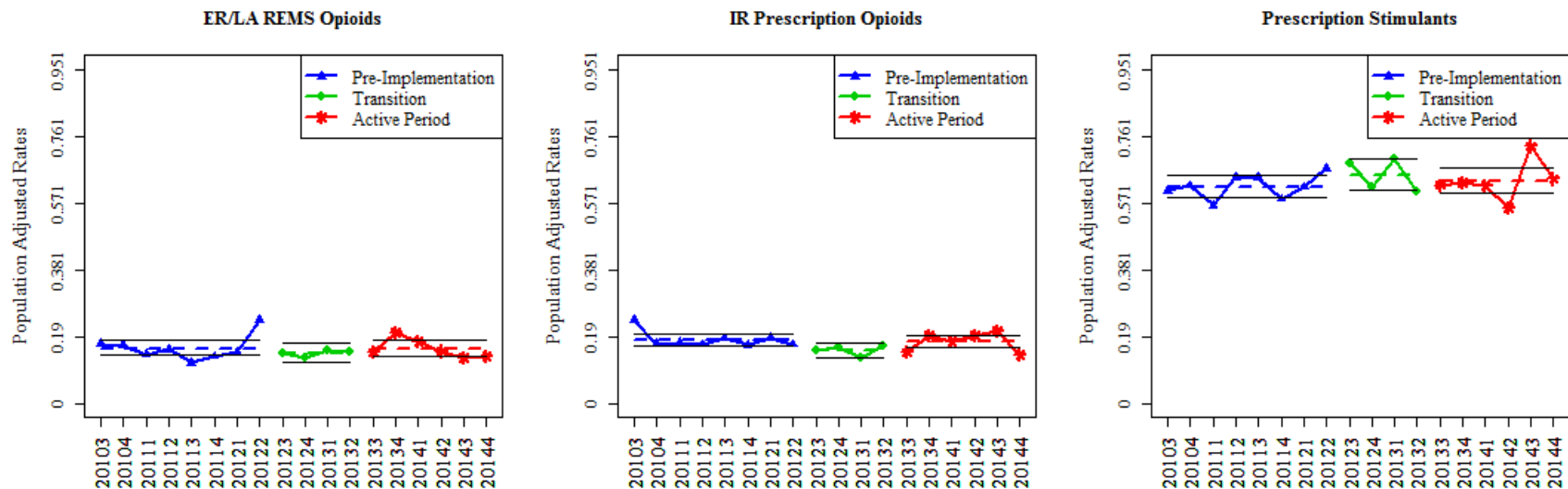


Table 5.4.6.1

The RADARS System Poison Center Program
**Pediatric Unintentional General Exposure Major Medical Outcome, Hospitalization or
Death Rates per 100,000 Population**
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.158	Pre versus Transition	-9.77%(-28.63%,14.08%)	0.390	.
	Transition	0.142	Transition versus Active	10.19%(-13.65%,40.62%)	0.435	.
	Active	0.157	Pre versus Active	-0.57%(-18.56%,21.39%)	0.955	.
IR Prescription Opioids	Pre	0.182	Pre versus Transition	-17.43%(-30.30%,-2.17%)	0.027	0.548
	Transition	0.150	Transition versus Active	17.12%(-1.85%,39.76%)	0.080	0.691
	Active	0.176	Pre versus Active	-3.29%(-16.01%,11.36%)	0.642	0.824
Prescription Stimulants	Pre	0.618	Pre versus Transition	5.08%(-3.54%,14.47%)	0.256	0.232
	Transition	0.649	Transition versus Active	-2.47%(-10.76%,6.58%)	0.580	0.356
	Active	0.633	Pre versus Active	2.48%(-5.02%,10.57%)	0.527	0.781

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids pediatric unintentional general exposure major medical outcome, hospitalization, or death population rate decreased 9.77% between the Pre-Implementation and Transition time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure major medical outcome, hospitalization, or death population rate decreased 17.43% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the pediatric unintentional general exposure major medical outcome, hospitalization, or death population rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure major medical outcome, hospitalization, or death population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.548).

The mean prescription stimulants pediatric unintentional general exposure major medical outcome, hospitalization, or death population rate increased 5.08% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the pediatric unintentional general exposure major medical outcome, hospitalization, or death population rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure major medical outcome, hospitalization, or death population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.232).

The mean ER/LA REMS opioids pediatric unintentional general exposure major medical outcome, hospitalization, or death population rate increased 10.19% between the Transition and Active Period time periods. This increase is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure major medical outcome, hospitalization, or death population rate increased 17.12% between the Transition and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure major medical outcome, hospitalization, or death population rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure major medical outcome, hospitalization, or death population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.691$).

The mean prescription stimulants pediatric unintentional general exposure major medical outcome, hospitalization, or death population rate decreased 2.47% between the Transition and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure major medical outcome, hospitalization, or death population rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure major medical outcome, hospitalization, or death population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.356$).

The mean ER/LA REMS opioids pediatric unintentional general exposure major medical outcome, hospitalization, or death population rate decreased 0.57% between the Pre-Implementation and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure major medical outcome, hospitalization, or death population rate decreased 3.29% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure major medical outcome, hospitalization, or death population rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure major medical outcome, hospitalization, or death population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.824$).

The mean prescription stimulants pediatric unintentional general exposure major medical outcome, hospitalization, or death population rate increased 2.48% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure major medical outcome, hospitalization, or death population rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure major medical outcome, hospitalization, or death population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.781$).

Figure 5.4.6.2

The RADARS System Poison Center Program
Pediatric Unintentional General Exposure Major Medical Outcome, Hospitalization or Death Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

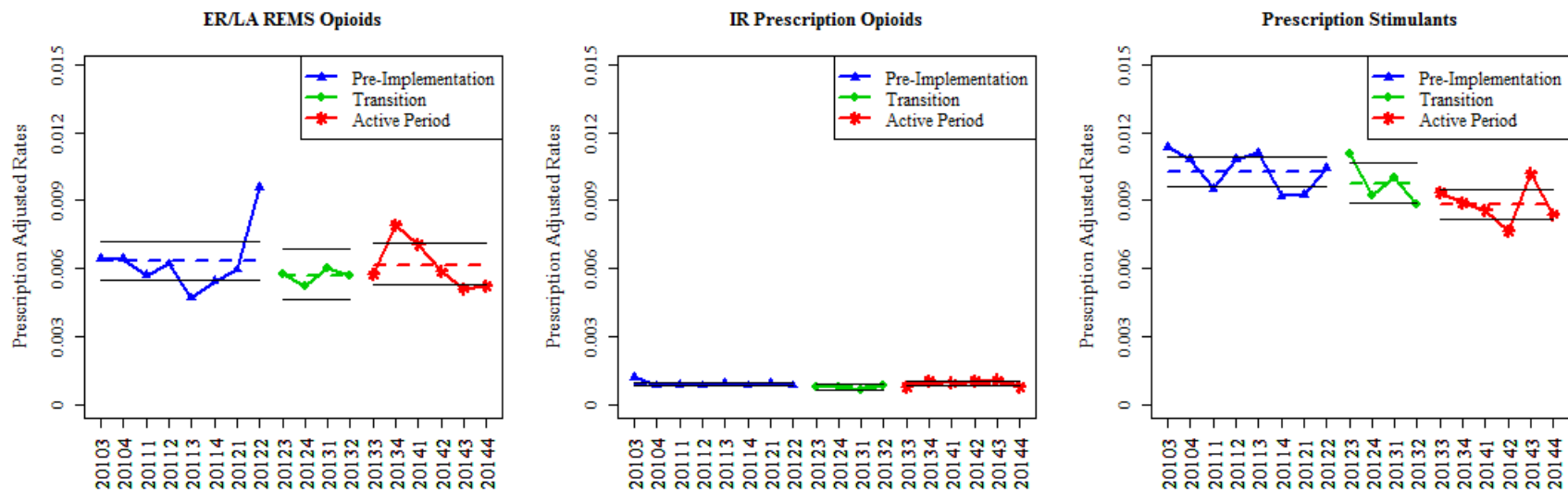


Table 5.4.6.2

The RADARS System Poison Center Program
**Pediatric Unintentional General Exposure Major Medical Outcome, Hospitalization or
Death Rates per 1,000 Prescriptions Dispensed**
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.006	Pre versus Transition	-10.17%(-29.05%,13.73%)	0.373	.
	Transition	0.006	Transition versus Active	8.41%(-15.17%,38.55%)	0.519	.
	Active	0.006	Pre versus Active	-2.61%(-20.33%,19.03%)	0.796	.
IR Prescription Opioids	Pre	<.001	Pre versus Transition	-15.24%(-28.41%,0.36%)	0.055	0.695
	Transition	<.001	Transition versus Active	22.13%(2.42%,45.65%)	0.026	0.439
	Active	<.001	Pre versus Active	3.53%(-10.04%,19.14%)	0.629	0.625
Prescription Stimulants	Pre	0.010	Pre versus Transition	-4.92%(-14.84%,6.15%)	0.369	0.669
	Transition	0.010	Transition versus Active	-9.52%(-19.29%,1.43%)	0.086	0.190
	Active	0.009	Pre versus Active	-13.97%(-21.99%,-5.14%)	0.003	0.276

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids pediatric unintentional general exposure major medical outcome, hospitalization, or death prescriptions dispensed rate decreased 10.17% between the Pre-Implementation and Transition time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure major medical outcome, hospitalization, or death prescriptions dispensed rate decreased 15.24% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the pediatric unintentional general exposure major medical outcome, hospitalization, or death prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure major medical outcome, hospitalization, or death prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.695).

The mean prescription stimulants pediatric unintentional general exposure major medical outcome, hospitalization, or death prescriptions dispensed rate decreased 4.92% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the pediatric unintentional general exposure major medical outcome, hospitalization, or death prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure major medical outcome, hospitalization, or death prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.669).

The mean ER/LA REMS opioids pediatric unintentional general exposure major medical outcome, hospitalization, or death prescriptions dispensed rate increased 8.41% between the Transition and Active Period time periods. This increase is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure major medical outcome, hospitalization, or death prescriptions dispensed rate increased 22.13% between the Transition and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure major medical outcome, hospitalization, or death prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure major medical outcome, hospitalization, or death prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.439$).

The mean prescription stimulants pediatric unintentional general exposure major medical outcome, hospitalization, or death prescriptions dispensed rate decreased 9.52% between the Transition and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure major medical outcome, hospitalization, or death prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure major medical outcome, hospitalization, or death prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.190$).

The mean ER/LA REMS opioids pediatric unintentional general exposure major medical outcome, hospitalization, or death prescriptions dispensed rate decreased 2.61% between the Pre-Implementation and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure major medical outcome, hospitalization, or death prescriptions dispensed rate increased 3.53% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure major medical outcome, hospitalization, or death prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure major medical outcome, hospitalization, or death prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.625$).

The mean prescription stimulants pediatric unintentional general exposure major medical outcome, hospitalization, or death prescriptions dispensed rate decreased 13.97% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure major medical outcome, hospitalization, or death prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure major medical outcome, hospitalization, or death prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.276$).

Figure 5.4.6.3

The RADARS System Poison Center Program

Pediatric Unintentional General Exposure Major Medical Outcome, Hospitalization or Death Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

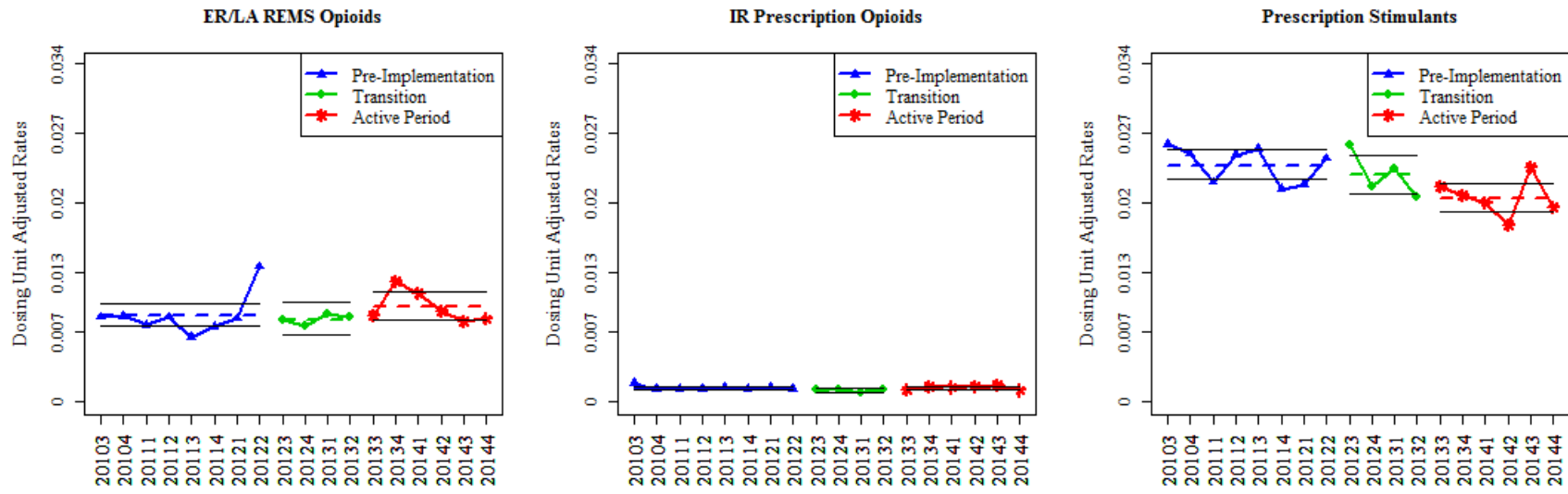


Table 5.4.6.3

The RADARS System Poison Center Program
**Pediatric Unintentional General Exposure Major Medical Outcome, Hospitalization or
Death Rates per 100,000 Dosing Units**
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.009	Pre versus Transition	-4.38%(-24.83%,21.63%)	0.715	.
	Transition	0.008	Transition versus Active	15.06%(-10.41%,47.77%)	0.272	.
	Active	0.009	Pre versus Active	10.02%(-10.35%,35.02%)	0.361	.
IR Prescription Opioids	Pre	0.001	Pre versus Transition	-17.54%(-31.43%,-0.84%)	0.040	0.338
	Transition	0.001	Transition versus Active	25.81%(3.80%,52.49%)	0.019	0.579
	Active	0.001	Pre versus Active	3.74%(-11.02%,20.95%)	0.639	0.653
Prescription Stimulants	Pre	0.024	Pre versus Transition	-4.18%(-13.77%,6.48%)	0.427	0.988
	Transition	0.023	Transition versus Active	-9.96%(-19.29%,0.45%)	0.060	0.078
	Active	0.020	Pre versus Active	-13.73%(-21.44%,-5.26%)	0.002	0.034

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids pediatric unintentional general exposure major medical outcome, hospitalization, or death dosing units rate decreased 4.38% between the Pre-Implementation and Transition time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure major medical outcome, hospitalization, or death dosing units rate decreased 17.54% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the pediatric unintentional general exposure major medical outcome, hospitalization, or death dosing units rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure major medical outcome, hospitalization, or death dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.338).

The mean prescription stimulants pediatric unintentional general exposure major medical outcome, hospitalization, or death dosing units rate decreased 4.18% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the pediatric unintentional general exposure major medical outcome, hospitalization, or death dosing units rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure major medical outcome, hospitalization, or death dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.988).

The mean ER/LA REMS opioids pediatric unintentional general exposure major medical outcome, hospitalization, or death dosing units rate increased 15.06% between the Transition and Active Period time periods. This increase is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure major medical outcome, hospitalization, or death dosing units rate increased 25.81% between the Transition and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure major medical outcome, hospitalization, or death dosing units rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure major medical outcome, hospitalization, or death dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.579$).

The mean prescription stimulants pediatric unintentional general exposure major medical outcome, hospitalization, or death dosing units rate decreased 9.96% between the Transition and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure major medical outcome, hospitalization, or death dosing units rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure major medical outcome, hospitalization, or death dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.078$).

The mean ER/LA REMS opioids pediatric unintentional general exposure major medical outcome, hospitalization, or death dosing units rate increased 10.02% between the Pre-Implementation and Active Period time periods. This increase is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure major medical outcome, hospitalization, or death dosing units rate increased 3.74% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure major medical outcome, hospitalization, or death dosing units rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure major medical outcome, hospitalization, or death dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.653$).

The mean prescription stimulants pediatric unintentional general exposure major medical outcome, hospitalization, or death dosing units rate decreased 13.73% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure major medical outcome, hospitalization, or death dosing units rate is statistically significant, indicating that the mean difference in pediatric unintentional general exposure major medical outcome, hospitalization, or death dosing units rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p=0.034$).

Figure 5.4.6.4 through Figure 5.4.6.6 display the mean pediatric (≤ 5 years) unintentional general exposure major medical outcome, hospitalization or death rate percent change from the pre-implementation average population-, prescription dispensed-, and dosing unit- adjusted rates for ER/LA REMS opioids and comparator drugs.

Figure 5.4.6.4

The RADARS System Poison Center Program
Pediatric Unintentional General Exposure Major Medical Outcome, Hospitalization or Deaths
Percent Change from Average Pre-Implementation Population Adjusted Rates
 From Third Quarter 2010 to Fourth Quarter 2014

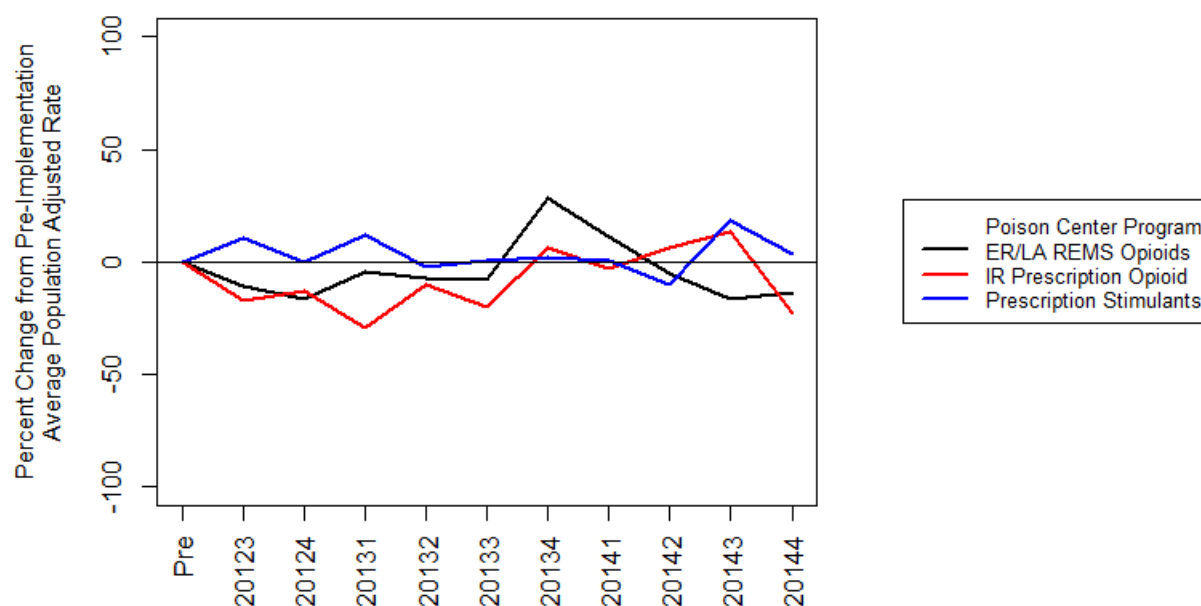


Figure 5.4.6.5

The RADARS System Poison Center Program
Pediatric Unintentional General Exposure Major Medical Outcome, Hospitalization or Deaths
Percent Change from Average Pre-Implementation Prescription Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

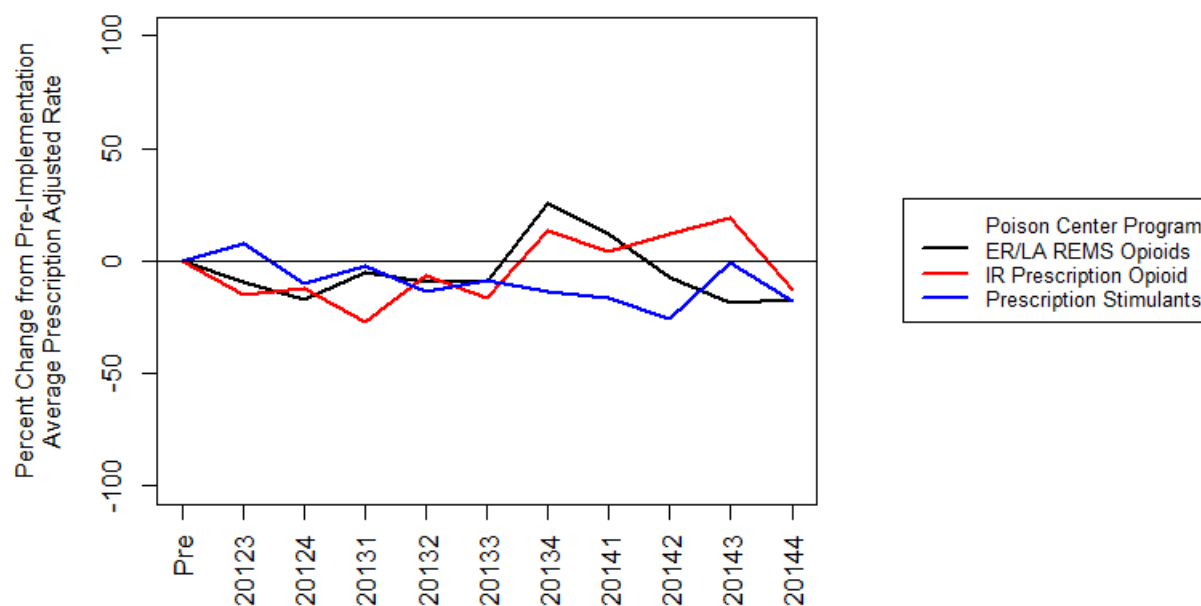
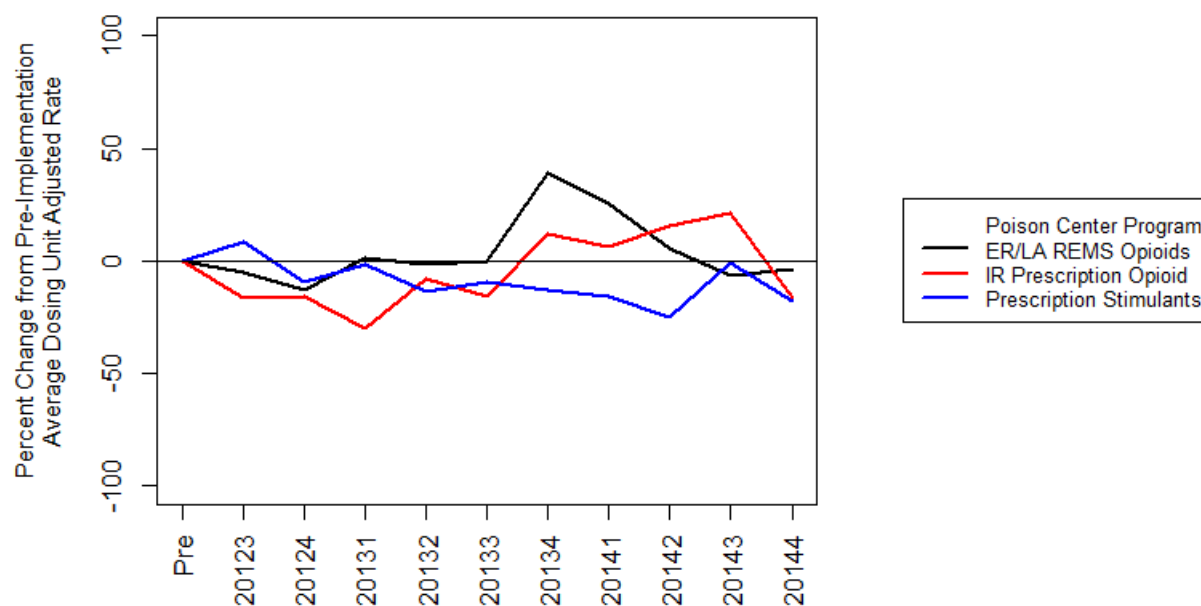


Figure 5.4.6.6

The RADARS System Poison Center Program
Pediatric Unintentional General Exposure Major Medical Outcome, Hospitalization or Deaths
Percent Change from Average Pre-Implementation Dosing Unit Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014



5.4.7. Pediatric Unintentional General Exposures Treated/Evaluated and Released from the RADARS System Poison Center Program

Figure 5.4.7.1 through Figure 5.4.7.3 show the observed and predicted population, prescription dispensed, and dosing unit mean pediatric (≤ 5 years) unintentional general exposure treated/evaluated and released rates and 95% confidence intervals for ER/LA REMS opioids and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 5.4.7.1

The RADARS System Poison Center Program
Pediatric Unintentional General Exposure Treated/Evaluated and Released Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

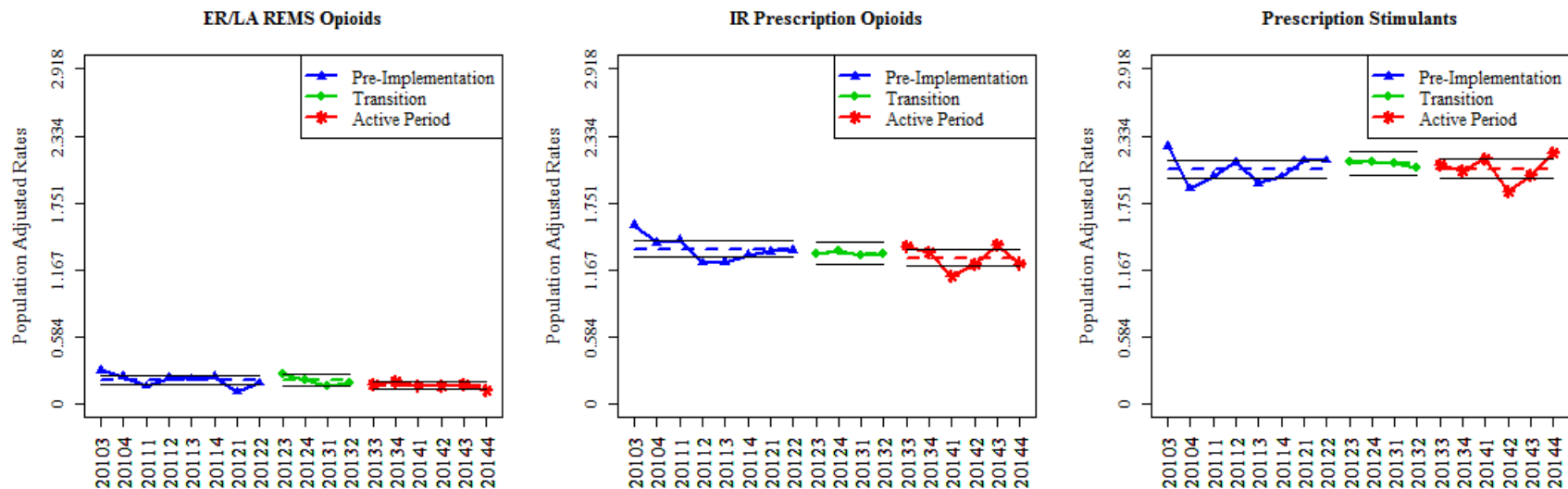


Table 5.4.7.1

The RADARS System Poison Center Program
**Pediatric Unintentional General Exposure Treated/Evaluated and Released Rates per
100,000 Population**
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.203	Pre versus Transition	-1.76%(-25.97%,30.37%)	0.902	.
	Transition	0.199	Transition versus Active	-20.65%(-41.82%,8.23%)	0.144	.
	Active	0.158	Pre versus Active	-22.04%(-40.25%,1.72%)	0.067	.
IR Prescription Opioids	Pre	1.349	Pre versus Transition	-3.05%(-11.19%,5.83%)	0.489	0.930
	Transition	1.307	Transition versus Active	-2.81%(-11.38%,6.59%)	0.546	0.220
	Active	1.271	Pre versus Active	-5.77%(-12.81%,1.83%)	0.133	0.180
Prescription Stimulants	Pre	2.043	Pre versus Transition	2.41%(-3.88%,9.12%)	0.461	0.779
	Transition	2.092	Transition versus Active	-2.21%(-8.46%,4.47%)	0.508	0.197
	Active	2.046	Pre versus Active	0.15%(-5.32%,5.94%)	0.958	0.071

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids pediatric unintentional general exposure treated/ evaluated and released population rate decreased 1.76% between the Pre-Implementation and Transition time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure treated/ evaluated and released population rate decreased 3.05% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the pediatric unintentional general exposure treated/ evaluated and released population rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure treated/ evaluated and released population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.930).

The mean prescription stimulants pediatric unintentional general exposure treated/ evaluated and released population rate increased 2.41% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the pediatric unintentional general exposure treated/ evaluated and released population rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure treated/ evaluated and released population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.779).

The mean ER/LA REMS opioids pediatric unintentional general exposure treated/ evaluated and

released population rate decreased 20.65% between the Transition and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure treated/ evaluated and released population rate decreased 2.81% between the Transition and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure treated/ evaluated and released population rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure treated/ evaluated and released population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.220$).

The mean prescription stimulants pediatric unintentional general exposure treated/ evaluated and released population rate decreased 2.21% between the Transition and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure treated/ evaluated and released population rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure treated/ evaluated and released population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.197$).

The mean ER/LA REMS opioids pediatric unintentional general exposure treated/ evaluated and released population rate decreased 22.04% between the Pre-Implementation and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure treated/ evaluated and released population rate decreased 5.77% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure treated/ evaluated and released population rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure treated/ evaluated and released population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.180$).

The mean prescription stimulants pediatric unintentional general exposure treated/ evaluated and released population rate increased 0.15% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure treated/ evaluated and released population rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure treated/ evaluated and released population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.071$).

Figure 5.4.7.2

The RADARS System Poison Center Program
Pediatric Unintentional General Exposure Treated/Evaluated and Released Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

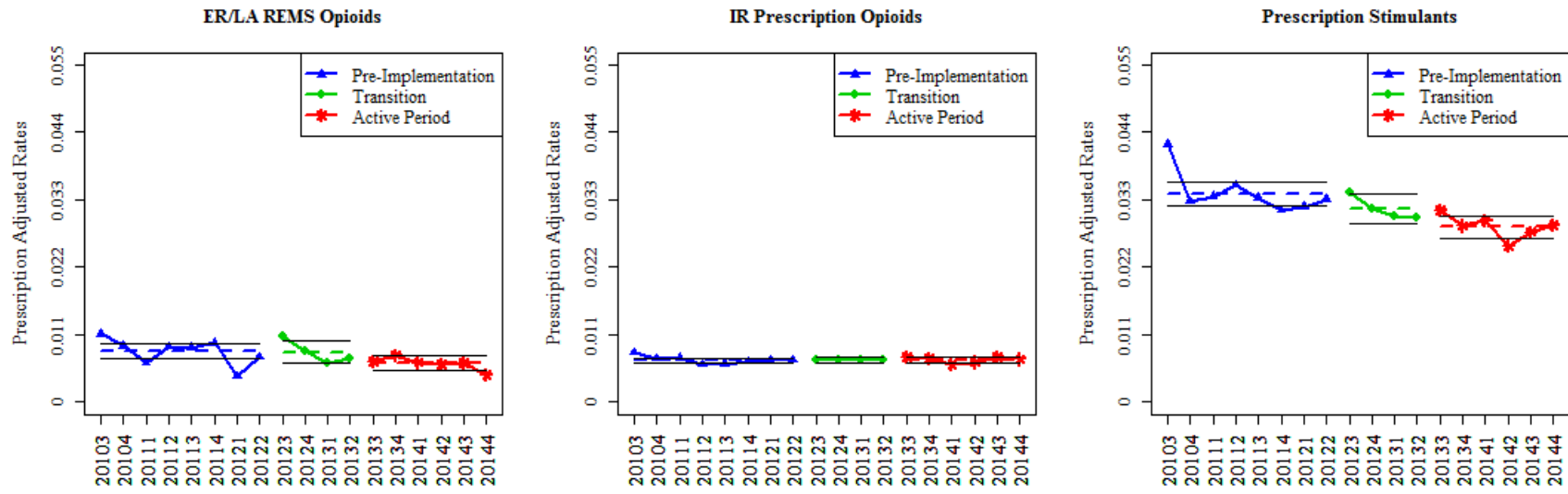


Table 5.4.7.2

The RADARS System Poison Center Program
**Pediatric Unintentional General Exposure Treated/Evaluated and Released Rates per 1,000
Prescriptions Dispensed**
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.008	Pre versus Transition	-2.20%(-25.70%,28.73%)	0.874	.
	Transition	0.008	Transition versus Active	-21.93%(-42.24%,5.54%)	0.108	.
	Active	0.006	Pre versus Active	-23.64%(-41.03%,-1.13%)	0.041	.
IR Prescription Opioids	Pre	0.007	Pre versus Transition	-0.48%(-9.00%,8.84%)	0.916	0.906
	Transition	0.007	Transition versus Active	1.35%(-7.76%,11.37%)	0.780	0.105
	Active	0.007	Pre versus Active	0.87%(-6.81%,9.18%)	0.831	0.043
Prescription Stimulants	Pre	0.034	Pre versus Transition	-7.34%(-15.83%,2.01%)	0.120	0.716
	Transition	0.031	Transition versus Active	-9.27%(-17.92%,0.28%)	0.057	0.354
	Active	0.029	Pre versus Active	-15.93%(-22.79%,-8.46%)	<.001	0.488

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids pediatric unintentional general exposure treated/ evaluated and released prescriptions dispensed rate decreased 2.20% between the Pre-Implementation and Transition time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure treated/ evaluated and released prescriptions dispensed rate decreased 0.48% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the pediatric unintentional general exposure treated/ evaluated and released prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure treated/ evaluated and released prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.906).

The mean prescription stimulants pediatric unintentional general exposure treated/ evaluated and released prescriptions dispensed rate decreased 7.34% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the pediatric unintentional general exposure treated/ evaluated and released prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure treated/ evaluated and released prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.716).

The mean ER/LA REMS opioids pediatric unintentional general exposure treated/ evaluated and

released prescriptions dispensed rate decreased 21.93% between the Transition and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure treated/ evaluated and released prescriptions dispensed rate increased 1.35% between the Transition and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure treated/ evaluated and released prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure treated/ evaluated and released prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.105$).

The mean prescription stimulants pediatric unintentional general exposure treated/ evaluated and released prescriptions dispensed rate decreased 9.27% between the Transition and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure treated/ evaluated and released prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure treated/ evaluated and released prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.354$).

The mean ER/LA REMS opioids pediatric unintentional general exposure treated/ evaluated and released prescriptions dispensed rate decreased 23.64% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure treated/ evaluated and released prescriptions dispensed rate increased 0.87% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure treated/ evaluated and released prescriptions dispensed rate is statistically significant, indicating that the mean difference in pediatric unintentional general exposure treated/ evaluated and released prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids ($p=0.043$).

The mean prescription stimulants pediatric unintentional general exposure treated/ evaluated and released prescriptions dispensed rate decreased 15.93% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure treated/ evaluated and released prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure treated/ evaluated and released prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.488$).

Figure 5.4.7.3

The RADARS System Poison Center Program
Pediatric Unintentional General Exposure Treated/Evaluated and Released Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

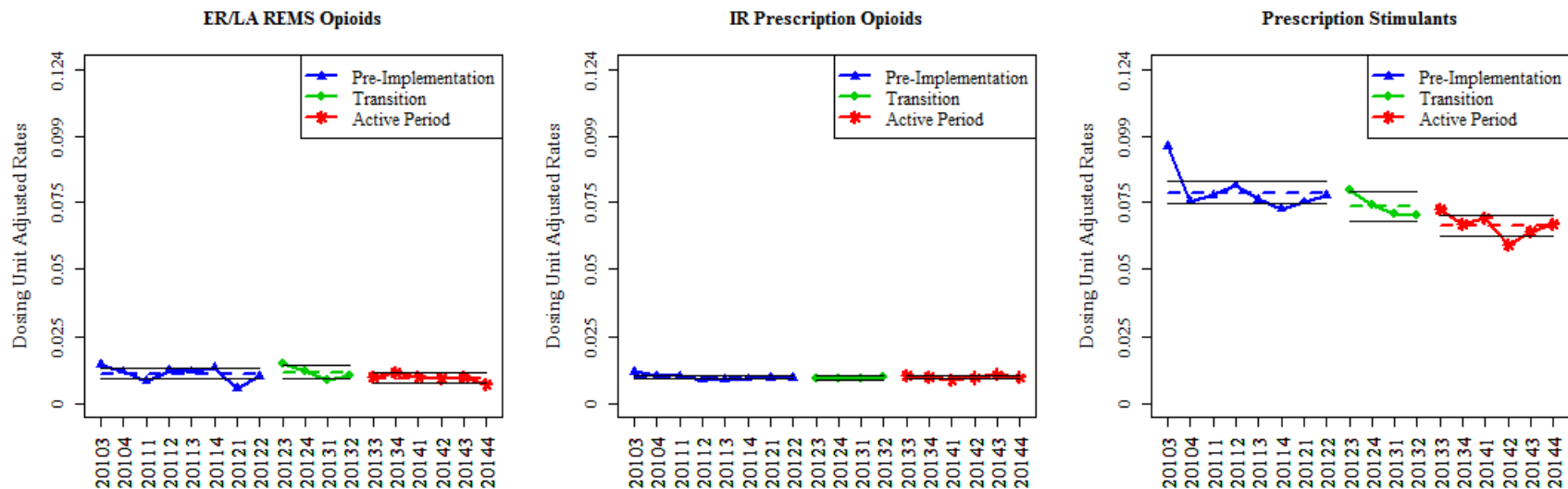


Table 5.4.7.3

The RADARS System Poison Center Program
**Pediatric Unintentional General Exposure Treated/Evaluated and Released Rates per
100,000 Dosing Units**
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.011	Pre versus Transition	4.11%(-19.71%,35.00%)	0.761	.
	Transition	0.012	Transition versus Active	-17.14%(-37.69%,10.19%)	0.196	.
	Active	0.010	Pre versus Active	-13.74%(-32.43%,10.13%)	0.236	.
IR Prescription Opioids	Pre	0.010	Pre versus Transition	-3.19%(-11.88%,6.37%)	0.500	0.606
	Transition	0.009	Transition versus Active	4.40%(-5.45%,15.28%)	0.394	0.133
	Active	0.010	Pre versus Active	1.08%(-7.00%,9.86%)	0.801	0.229
Prescription Stimulants	Pre	0.078	Pre versus Transition	-6.62%(-14.74%,2.28%)	0.141	0.439
	Transition	0.073	Transition versus Active	-9.72%(-17.88%,-0.74%)	0.035	0.576
	Active	0.066	Pre versus Active	-15.69%(-22.22%,-8.61%)	<.001	0.862

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids pediatric unintentional general exposure treated/ evaluated and released dosing units rate increased 4.11% between the Pre-Implementation and Transition time periods. This increase is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure treated/ evaluated and released dosing units rate decreased 3.19% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the pediatric unintentional general exposure treated/ evaluated and released dosing units rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure treated/ evaluated and released dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.606).

The mean prescription stimulants pediatric unintentional general exposure treated/ evaluated and released dosing units rate decreased 6.62% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the pediatric unintentional general exposure treated/ evaluated and released dosing units rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure treated/ evaluated and released dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.439).

The mean ER/LA REMS opioids pediatric unintentional general exposure treated/ evaluated and

released dosing units rate decreased 17.14% between the Transition and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure treated/ evaluated and released dosing units rate increased 4.40% between the Transition and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure treated/ evaluated and released dosing units rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure treated/ evaluated and released dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.133$).

The mean prescription stimulants pediatric unintentional general exposure treated/ evaluated and released dosing units rate decreased 9.72% between the Transition and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure treated/ evaluated and released dosing units rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure treated/ evaluated and released dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.576$).

The mean ER/LA REMS opioids pediatric unintentional general exposure treated/ evaluated and released dosing units rate decreased 13.74% between the Pre-Implementation and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure treated/ evaluated and released dosing units rate increased 1.08% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure treated/ evaluated and released dosing units rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure treated/ evaluated and released dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.229$).

The mean prescription stimulants pediatric unintentional general exposure treated/ evaluated and released dosing units rate decreased 15.69% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure treated/ evaluated and released dosing units rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure treated/ evaluated and released dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.862$).

Figure 5.4.7.4 through Figure 5.4.7.6 display the mean pediatric (≤ 5 years) unintentional general exposure treated/evaluated and released rate percent change from the pre-implementation average population-, prescription dispensed-, and dosing unit- adjusted rates for ER/LA REMS opioids and comparator drugs.

Figure 5.4.7.4

The RADARS System Poison Center Program
Pediatric Unintentional General Exposure Treated/Evaluated and Released
Percent Change from Average Pre-Implementation Population Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

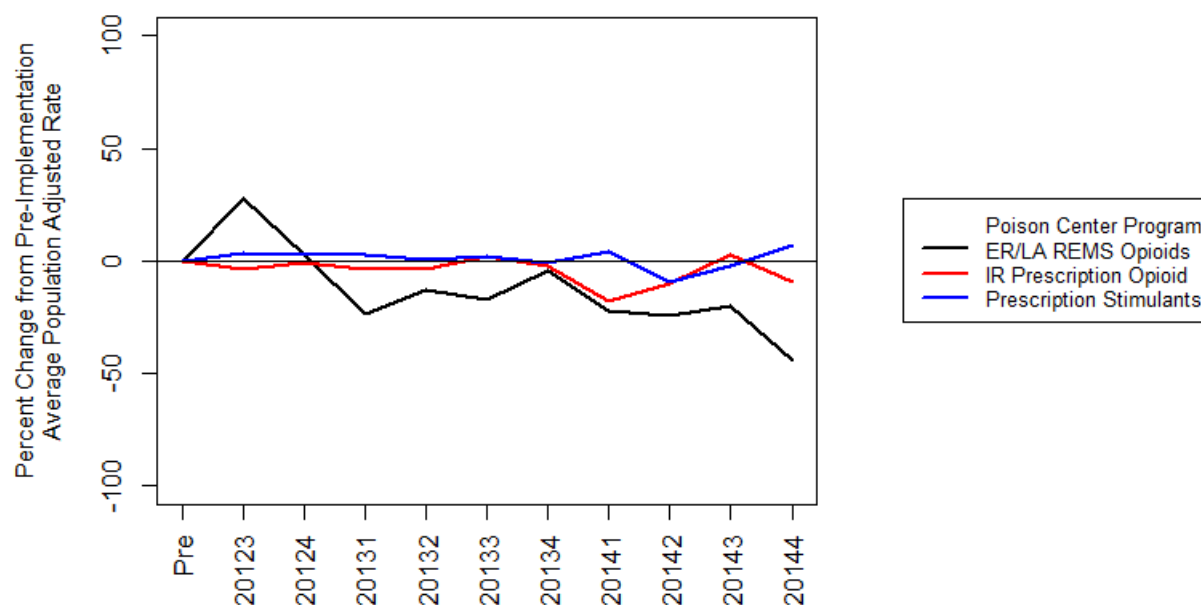


Figure 5.4.7.5

The RADARS System Poison Center Program
Pediatric Unintentional General Exposure Treated/Evaluated and Released
Percent Change from Average Pre-Implementation Prescription Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

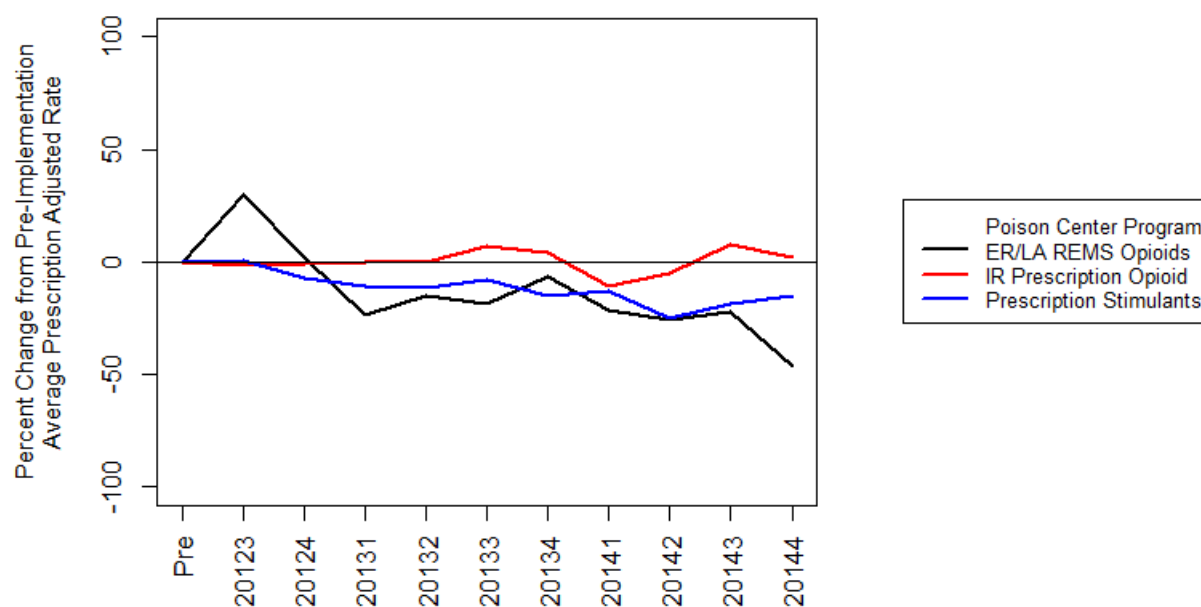
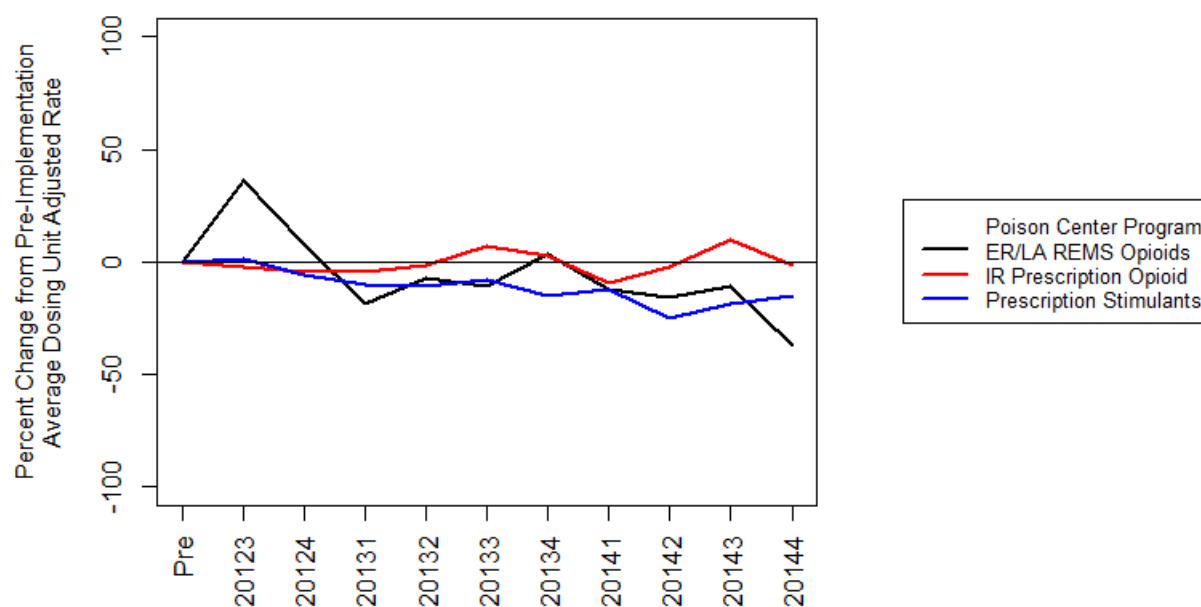


Figure 5.4.7.6

The RADARS System Poison Center Program
Pediatric Unintentional General Exposure Treated/Evaluated and Released
Percent Change from Average Pre-Implementation Dosing Unit Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014



5.4.8. Unintentional Therapeutic Errors from the RADARS System Poison Center Program

[Figure 5.4.8.1](#) through [Figure 5.4.8.3](#) show the observed and predicted population, prescription dispensed, and dosing unit mean unintentional therapeutic error rates and 95% confidence intervals for ER/LA REMS opioids and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 5.4.8.1

The RADARS System Poison Center Program
Unintentional Therapeutic Error Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

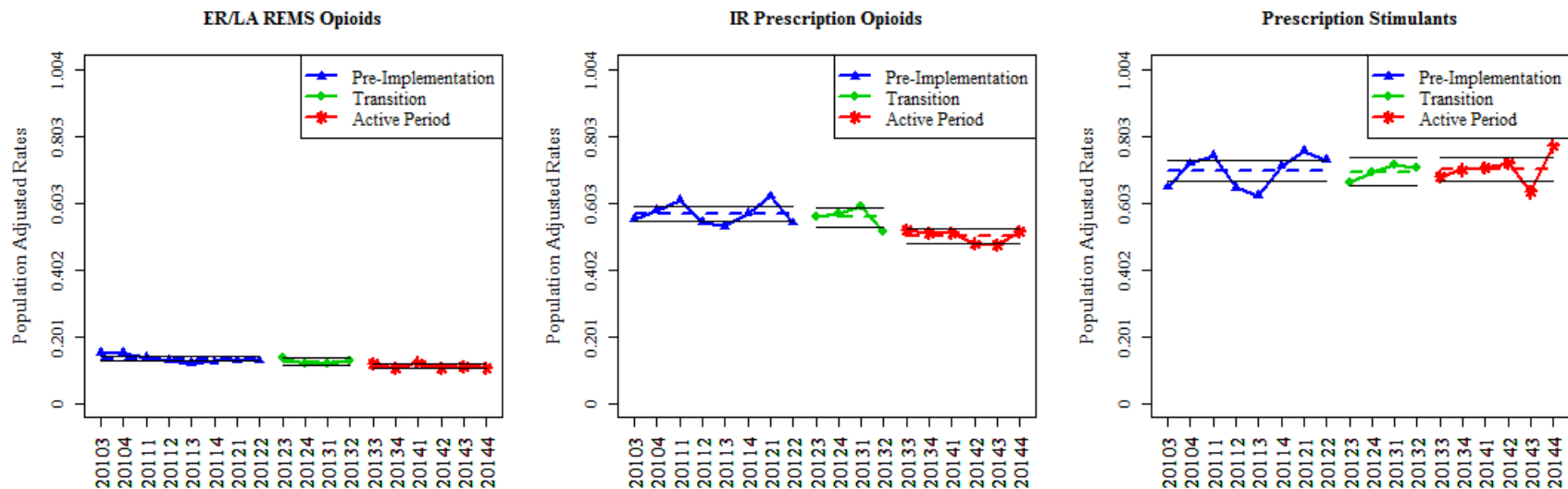


Table 5.4.8.1

The RADARS System Poison Center Program
Unintentional Therapeutic Error Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.134	Pre versus Transition	-5.98%(-14.07%,2.87%)	0.179	.
	Transition	0.126	Transition versus Active	-11.27%(-19.45%,-2.25%)	0.015	.
	Active	0.112	Pre versus Active	-16.57%(-23.10%,-9.49%)	<.001	.
IR Prescription Opioids	Pre	0.570	Pre versus Transition	-1.88%(-7.83%,4.44%)	0.551	0.445
	Transition	0.559	Transition versus Active	-10.13%(-15.92%,-3.95%)	0.002	0.832
	Active	0.502	Pre versus Active	-11.83%(-16.67%,-6.70%)	<.001	0.274
Prescription Stimulants	Pre	0.700	Pre versus Transition	-0.62%(-7.96%,7.31%)	0.874	0.358
	Transition	0.695	Transition versus Active	1.13%(-6.61%,9.52%)	0.781	0.041
	Active	0.703	Pre versus Active	0.51%(-6.02%,7.49%)	0.883	<.001

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids unintentional therapeutic error population rate decreased 5.98% between the Pre-Implementation and Transition time periods. This decrease is not statistically significant.

The mean IR prescription opioids unintentional therapeutic error population rate decreased 1.88% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the unintentional therapeutic error population rate is not statistically significant, indicating that the mean difference in unintentional therapeutic error population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.445).

The mean prescription stimulants unintentional therapeutic error population rate decreased 0.62% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the unintentional therapeutic error population rate is not statistically significant, indicating that the mean difference in unintentional therapeutic error population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.358).

The mean ER/LA REMS opioids unintentional therapeutic error population rate decreased 11.27% between the Transition and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids unintentional therapeutic error population rate decreased 10.13% between the Transition and Active Period time periods. The interaction of drug by time period for the unintentional therapeutic error population rate is not statistically significant, indicating that the mean difference in unintentional therapeutic error population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.832$).

The mean prescription stimulants unintentional therapeutic error population rate increased 1.13% between the Transition and Active Period time periods. The interaction of drug by time period for the unintentional therapeutic error population rate is statistically significant, indicating that the mean difference in unintentional therapeutic error population rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p=0.041$).

The mean ER/LA REMS opioids unintentional therapeutic error population rate decreased 16.57% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids unintentional therapeutic error population rate decreased 11.83% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the unintentional therapeutic error population rate is not statistically significant, indicating that the mean difference in unintentional therapeutic error population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.274$).

The mean prescription stimulants unintentional therapeutic error population rate increased 0.51% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the unintentional therapeutic error population rate is statistically significant, indicating that the mean difference in unintentional therapeutic error population rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p<.001$).

Figure 5.4.8.2

The RADARS System Poison Center Program
Unintentional Therapeutic Error Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

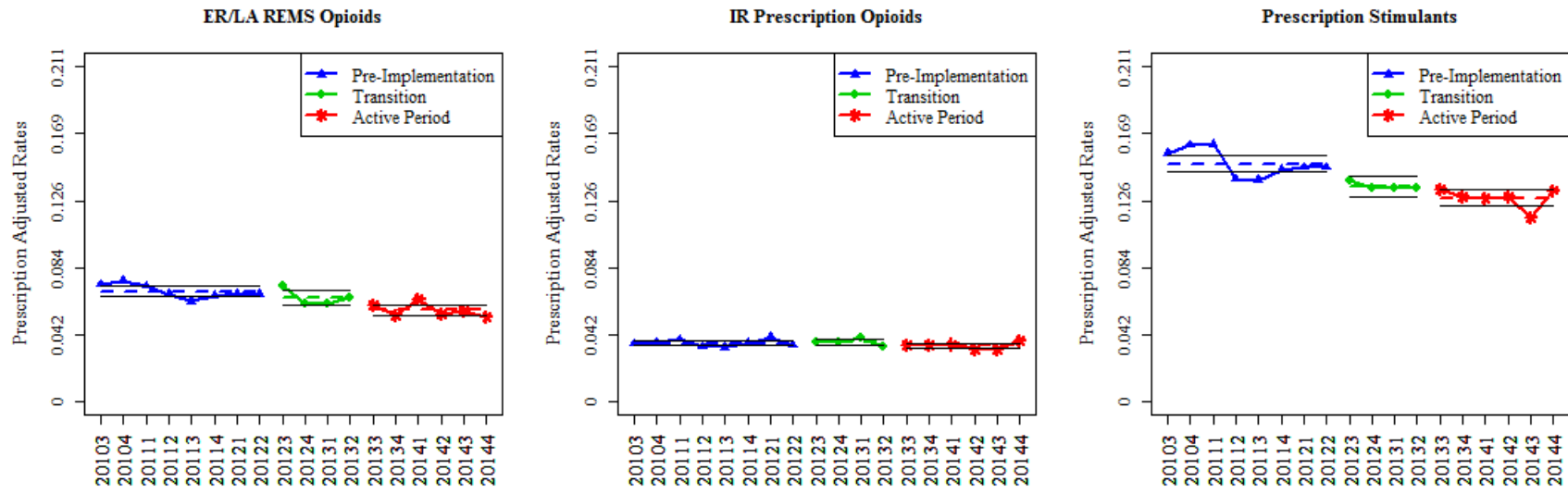


Table 5.4.8.2

The RADARS System Poison Center Program
Unintentional Therapeutic Error Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.069	Pre versus Transition	-5.67%(-13.13%,2.43%)	0.165	.
	Transition	0.065	Transition versus Active	-12.16%(-19.61%,-4.02%)	0.004	.
	Active	0.057	Pre versus Active	-17.14%(-23.11%,-10.72%)	<.001	.
IR Prescription Opioids	Pre	0.037	Pre versus Transition	1.50%(-5.23%,8.71%)	0.670	0.180
	Transition	0.037	Transition versus Active	-5.71%(-12.36%,1.43%)	0.115	0.227
	Active	0.035	Pre versus Active	-4.30%(-10.05%,1.83%)	0.165	0.004
Prescription Stimulants	Pre	0.150	Pre versus Transition	-9.38%(-14.68%,-3.74%)	0.001	0.442
	Transition	0.136	Transition versus Active	-5.60%(-11.33%,0.50%)	0.071	0.193
	Active	0.128	Pre versus Active	-14.45%(-18.85%,-9.81%)	<.001	0.493

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids unintentional therapeutic error prescriptions dispensed rate decreased 5.67% between the Pre-Implementation and Transition time periods. This decrease is not statistically significant.

The mean IR prescription opioids unintentional therapeutic error prescriptions dispensed rate increased 1.50% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the unintentional therapeutic error prescriptions dispensed rate is not statistically significant, indicating that the mean difference in unintentional therapeutic error prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.180).

The mean prescription stimulants unintentional therapeutic error prescriptions dispensed rate decreased 9.38% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the unintentional therapeutic error prescriptions dispensed rate is not statistically significant, indicating that the mean difference in unintentional therapeutic error prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.442).

The mean ER/LA REMS opioids unintentional therapeutic error prescriptions dispensed rate decreased 12.16% between the Transition and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids unintentional therapeutic error prescriptions dispensed rate decreased 5.71% between the Transition and Active Period time periods. The interaction of drug by time period for the unintentional therapeutic error prescriptions dispensed rate is not statistically significant, indicating that the mean difference in unintentional therapeutic error prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.227$).

The mean prescription stimulants unintentional therapeutic error prescriptions dispensed rate decreased 5.60% between the Transition and Active Period time periods. The interaction of drug by time period for the unintentional therapeutic error prescriptions dispensed rate is not statistically significant, indicating that the mean difference in unintentional therapeutic error prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.193$).

The mean ER/LA REMS opioids unintentional therapeutic error prescriptions dispensed rate decreased 17.14% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids unintentional therapeutic error prescriptions dispensed rate decreased 4.30% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the unintentional therapeutic error prescriptions dispensed rate is statistically significant, indicating that the mean difference in unintentional therapeutic error prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids ($p=0.004$).

The mean prescription stimulants unintentional therapeutic error prescriptions dispensed rate decreased 14.45% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the unintentional therapeutic error prescriptions dispensed rate is not statistically significant, indicating that the mean difference in unintentional therapeutic error prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.493$).

Figure 5.4.8.3

The RADARS System Poison Center Program
Unintentional Therapeutic Error Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

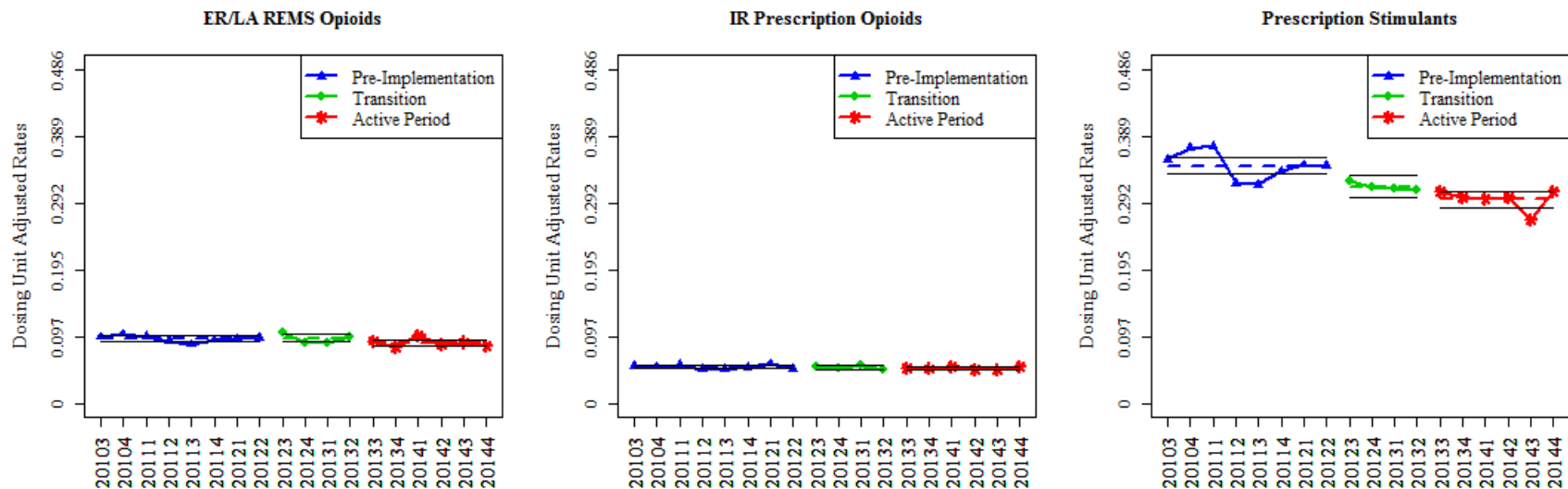


Table 5.4.8.3
The RADARS System Poison Center Program
Unintentional Therapeutic Error Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.094	Pre versus Transition	0.41%(-6.51%,7.84%)	0.911	.
	Transition	0.095	Transition versus Active	-6.78%(-13.67%,0.67%)	0.073	.
	Active	0.088	Pre versus Active	-6.39%(-12.26%,-0.13%)	0.045	.
IR Prescription Opioids	Pre	0.053	Pre versus Transition	-1.26%(-6.96%,4.80%)	0.677	0.724
	Transition	0.053	Transition versus Active	-2.87%(-8.84%,3.48%)	0.367	0.420
	Active	0.051	Pre versus Active	-4.10%(-9.12%,1.21%)	0.128	0.572
Prescription Stimulants	Pre	0.346	Pre versus Transition	-8.67%(-14.07%,-2.94%)	0.003	0.048
	Transition	0.316	Transition versus Active	-6.06%(-11.81%,0.07%)	0.053	0.880
	Active	0.297	Pre versus Active	-14.21%(-18.66%,-9.51%)	<.001	0.042

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids unintentional therapeutic error dosing units rate increased 0.41% between the Pre-Implementation and Transition time periods. This increase is not statistically significant.

The mean IR prescription opioids unintentional therapeutic error dosing units rate decreased 1.26% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the unintentional therapeutic error dosing units rate is not statistically significant, indicating that the mean difference in unintentional therapeutic error dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.724).

The mean prescription stimulants unintentional therapeutic error dosing units rate decreased 8.67% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the unintentional therapeutic error dosing units rate is statistically significant, indicating that the mean difference in unintentional therapeutic error dosing units rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants (p=0.048).

The mean ER/LA REMS opioids unintentional therapeutic error dosing units rate decreased 6.78% between the Transition and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids unintentional therapeutic error dosing units rate decreased 2.87% between the Transition and Active Period time periods. The interaction of drug by time period for the unintentional therapeutic error dosing units rate is not statistically significant, indicating that the mean difference in unintentional therapeutic error dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.420$).

The mean prescription stimulants unintentional therapeutic error dosing units rate decreased 6.06% between the Transition and Active Period time periods. The interaction of drug by time period for the unintentional therapeutic error dosing units rate is not statistically significant, indicating that the mean difference in unintentional therapeutic error dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.880$).

The mean ER/LA REMS opioids unintentional therapeutic error dosing units rate decreased 6.39% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids unintentional therapeutic error dosing units rate decreased 4.10% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the unintentional therapeutic error dosing units rate is not statistically significant, indicating that the mean difference in unintentional therapeutic error dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.572$).

The mean prescription stimulants unintentional therapeutic error dosing units rate decreased 14.21% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the unintentional therapeutic error dosing units rate is statistically significant, indicating that the mean difference in unintentional therapeutic error dosing units rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p=0.042$).

Figure 5.4.8.4 through Figure 5.4.8.6 display the mean unintentional therapeutic error rate percent change from the pre-implementation average population-, prescription dispensed-, and dosing unit- adjusted rates for ER/LA REMS opioids and comparator drugs.

Figure 5.4.8.4
The RADARS System Poison Center Program
Unintentional Therapeutic Errors
Percent Change from Average Pre-Implementation Population Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

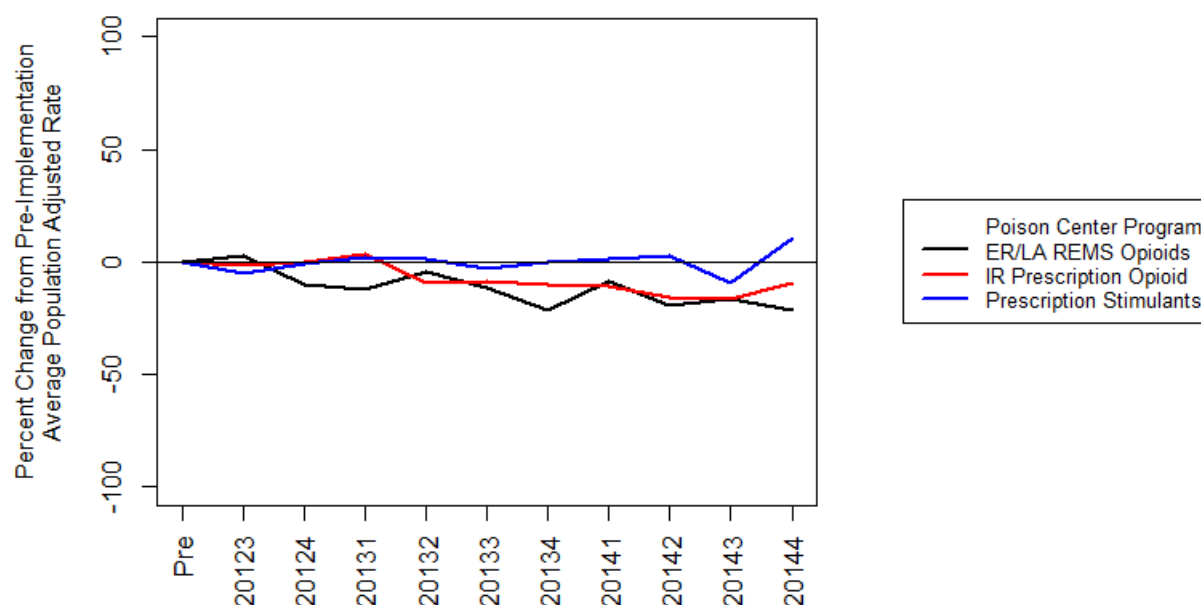


Figure 5.4.8.5

The RADARS System Poison Center Program
Unintentional Therapeutic Errors
Percent Change from Average Pre-Implementation Prescription Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

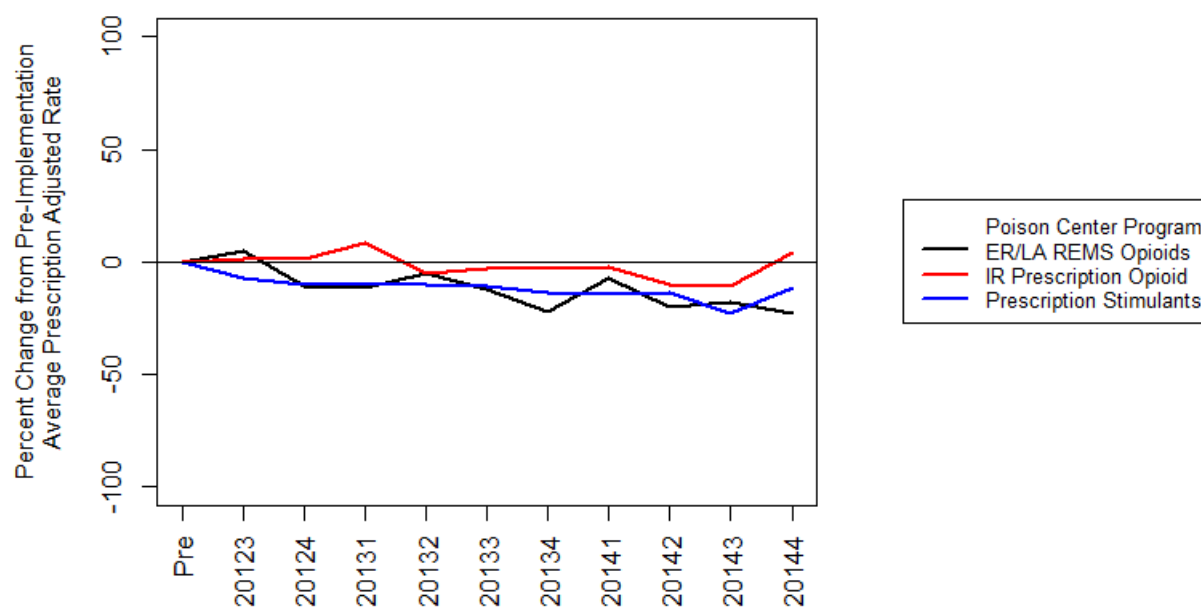
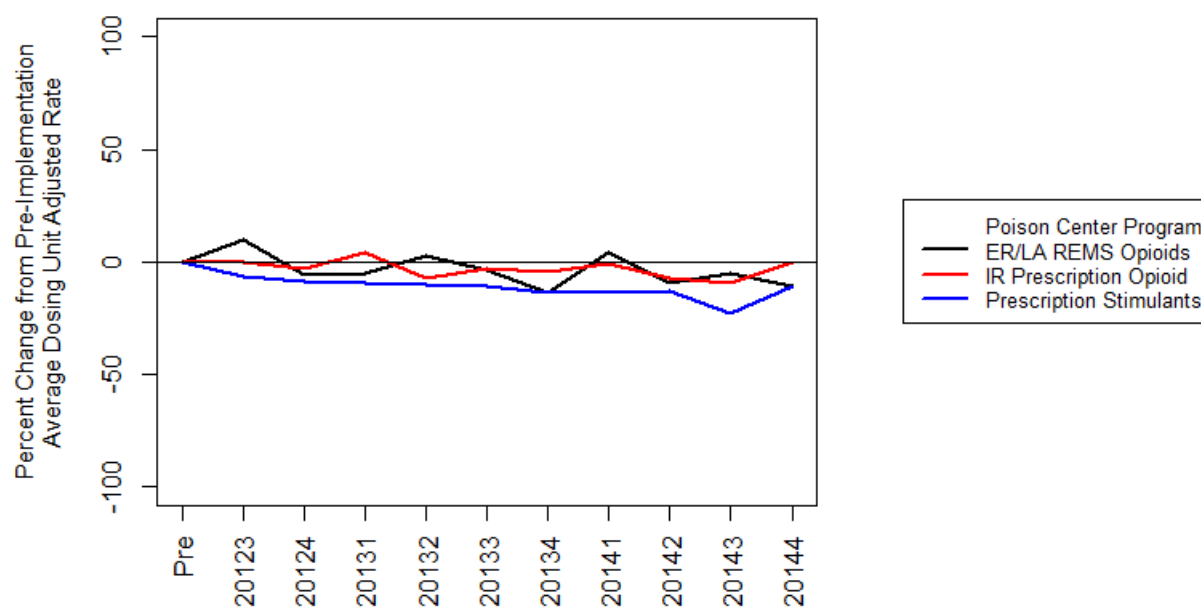


Figure 5.4.8.6

The RADARS System Poison Center Program
Unintentional Therapeutic Errors
Percent Change from Average Pre-Implementation Dosing Unit Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014



5.5. Deaths from the RADARS System Poison Center Program

5.5.1. Exposures Resulting in a Major Medical Outcome, Hospitalization or Death from the RADARS System Poison Center Program

Figure 5.5.1.1 through Figure 5.5.1.3 show the observed and predicted population, prescription dispensed, and dosing unit mean major medical outcome, hospitalization or death rates and 95% confidence intervals for ER/LA REMS opioids and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 5.5.1.1

The RADARS System Poison Center Program
Major Medical Outcome, Hospitalization or Death Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

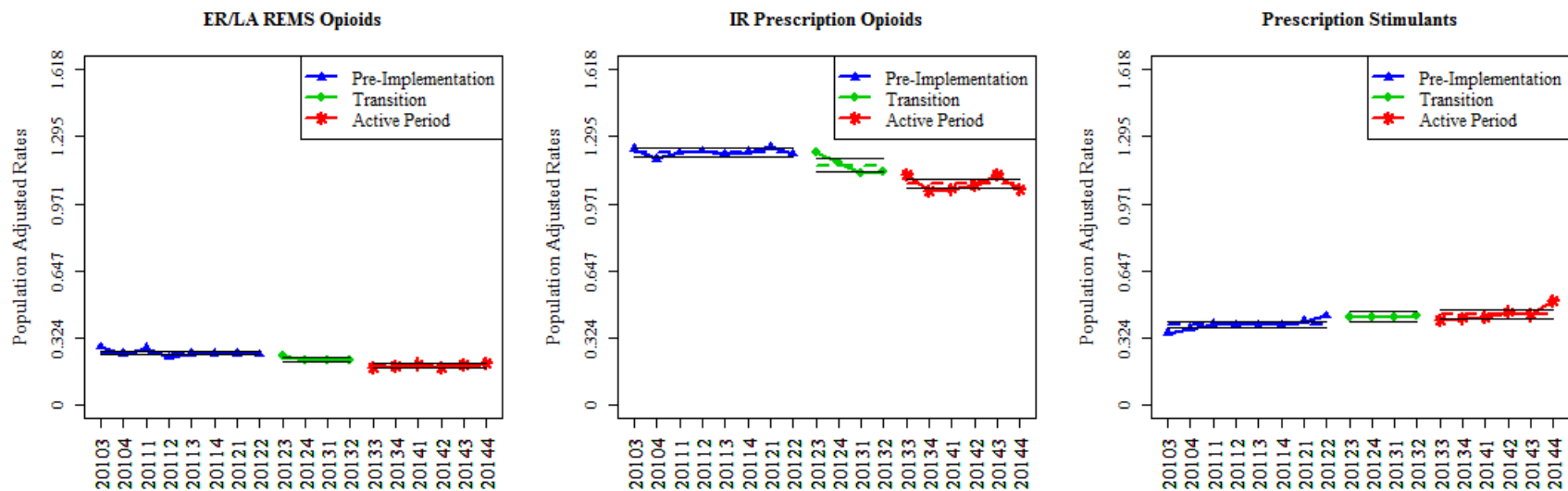


Table 5.5.1.1

The RADARS System Poison Center Program
Major Medical Outcome, Hospitalization or Death Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values *	Between Drug Interaction p-values #
ER/LA REMS Opioids	Pre	0.250	Pre versus Transition	-12.08%(-17.76%,-6.02%)	<.001	.
	Transition	0.220	Transition versus Active	-14.56%(-20.58%,-8.07%)	<.001	.
	Active	0.188	Pre versus Active	-24.88%(-29.33%,-20.15%)	<.001	.
IR Prescription Opioids	Pre	1.220	Pre versus Transition	-5.06%(-8.13%,-1.88%)	0.002	0.043
	Transition	1.158	Transition versus Active	-7.81%(-10.99%,-4.52%)	<.001	0.066
	Active	1.068	Pre versus Active	-12.47%(-15.02%,-9.85%)	<.001	<.001
Prescription Stimulants	Pre	0.387	Pre versus Transition	9.71%(1.78%,18.27%)	0.016	<.001
	Transition	0.424	Transition versus Active	3.36%(-4.23%,11.54%)	0.396	<.001
	Active	0.438	Pre versus Active	13.39%(6.19%,21.09%)	<.001	<.001

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids major medical outcome, hospitalization, or death population rate decreased 12.08% between the Pre-Implementation and Transition time periods. This decrease is statistically significant.

The mean IR prescription opioids major medical outcome, hospitalization, or death population rate decreased 5.06% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the major medical outcome, hospitalization, or death population rate is statistically significant, indicating that the mean difference in major medical outcome, hospitalization, or death population rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids (p=0.043).

The mean prescription stimulants major medical outcome, hospitalization, or death population rate increased 9.71% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the major medical outcome, hospitalization, or death population rate is statistically significant, indicating that the mean difference in major medical outcome, hospitalization, or death population rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants (p<.001).

The mean ER/LA REMS opioids major medical outcome, hospitalization, or death population rate decreased 14.56% between the Transition and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids major medical outcome, hospitalization, or death population

rate decreased 7.81% between the Transition and Active Period time periods. The interaction of drug by time period for the major medical outcome, hospitalization, or death population rate is not statistically significant, indicating that the mean difference in major medical outcome, hospitalization, or death population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.066$).

The mean prescription stimulants major medical outcome, hospitalization, or death population rate increased 3.36% between the Transition and Active Period time periods. The interaction of drug by time period for the major medical outcome, hospitalization, or death population rate is statistically significant, indicating that the mean difference in major medical outcome, hospitalization, or death population rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p<.001$).

The mean ER/LA REMS opioids major medical outcome, hospitalization, or death population rate decreased 24.88% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids major medical outcome, hospitalization, or death population rate decreased 12.47% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the major medical outcome, hospitalization, or death population rate is statistically significant, indicating that the mean difference in major medical outcome, hospitalization, or death population rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids ($p<.001$).

The mean prescription stimulants major medical outcome, hospitalization, or death population rate increased 13.39% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the major medical outcome, hospitalization, or death population rate is statistically significant, indicating that the mean difference in major medical outcome, hospitalization, or death population rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p<.001$).

Figure 5.5.1.2

The RADARS System Poison Center Program
Major Medical Outcome, Hospitalization or Death Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

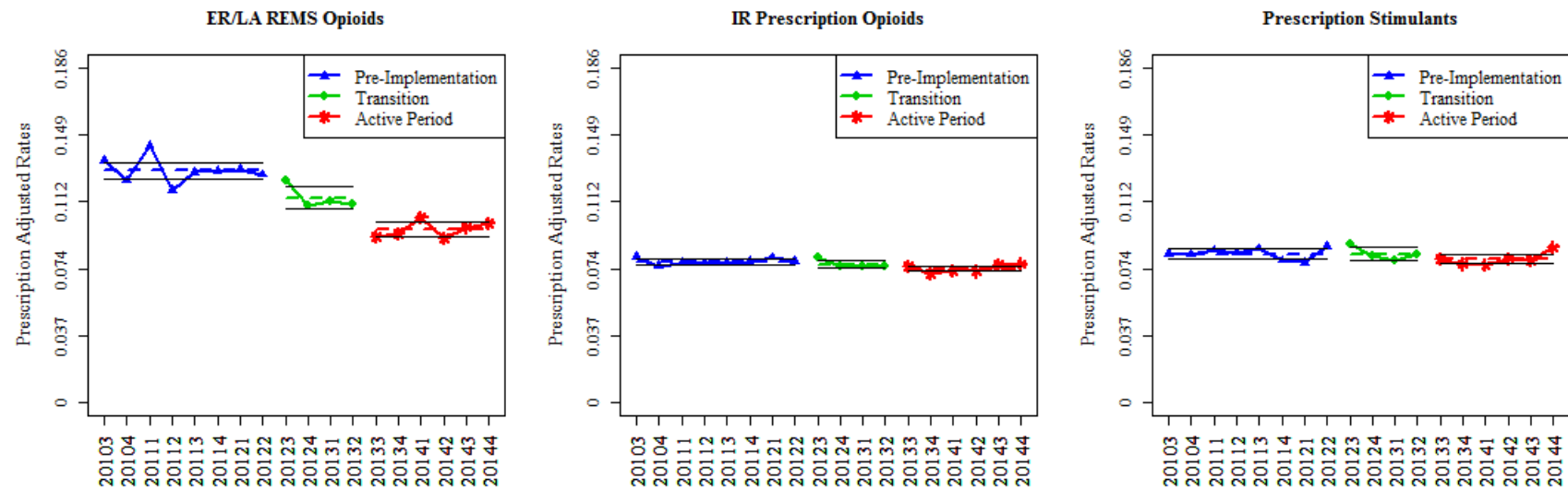


Table 5.5.1.2

The RADARS System Poison Center Program
Major Medical Outcome, Hospitalization or Death Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.129	Pre versus Transition	-11.80%(-17.32%,-5.91%)	<.001	.
	Transition	0.114	Transition versus Active	-15.42%(-21.20%,-9.21%)	<.001	.
	Active	0.096	Pre versus Active	-25.40%(-29.68%,-20.85%)	<.001	.
IR Prescription Opioids	Pre	0.078	Pre versus Transition	-1.78%(-4.82%,1.36%)	0.263	0.003
	Transition	0.077	Transition versus Active	-3.27%(-6.46%,0.02%)	0.051	<.001
	Active	0.074	Pre versus Active	-4.99%(-7.63%,-2.28%)	<.001	<.001
Prescription Stimulants	Pre	0.083	Pre versus Transition	0.04%(-4.96%,5.31%)	0.987	0.003
	Transition	0.083	Transition versus Active	-3.52%(-8.42%,1.63%)	0.177	0.003
	Active	0.080	Pre versus Active	-3.48%(-7.72%,0.95%)	0.122	<.001

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids major medical outcome, hospitalization, or death prescriptions dispensed rate decreased 11.80% between the Pre-Implementation and Transition time periods. This decrease is statistically significant.

The mean IR prescription opioids major medical outcome, hospitalization, or death prescriptions dispensed rate decreased 1.78% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the major medical outcome, hospitalization, or death prescriptions dispensed rate is statistically significant, indicating that the mean difference in major medical outcome, hospitalization, or death prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids (p=0.003).

The mean prescription stimulants major medical outcome, hospitalization, or death prescriptions dispensed rate increased 0.04% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the major medical outcome, hospitalization, or death prescriptions dispensed rate is statistically significant, indicating that the mean difference in major medical outcome, hospitalization, or death prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants (p=0.003).

The mean ER/LA REMS opioids major medical outcome, hospitalization, or death prescriptions dispensed rate decreased 15.42% between the Transition and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids major medical outcome, hospitalization, or death prescriptions dispensed rate decreased 3.27% between the Transition and Active Period time periods. The interaction of drug by time period for the major medical outcome, hospitalization, or death prescriptions dispensed rate is statistically significant, indicating that the mean difference in major medical outcome, hospitalization, or death prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids ($p < .001$).

The mean prescription stimulants major medical outcome, hospitalization, or death prescriptions dispensed rate decreased 3.52% between the Transition and Active Period time periods. The interaction of drug by time period for the major medical outcome, hospitalization, or death prescriptions dispensed rate is statistically significant, indicating that the mean difference in major medical outcome, hospitalization, or death prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p = 0.003$).

The mean ER/LA REMS opioids major medical outcome, hospitalization, or death prescriptions dispensed rate decreased 25.40% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids major medical outcome, hospitalization, or death prescriptions dispensed rate decreased 4.99% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the major medical outcome, hospitalization, or death prescriptions dispensed rate is statistically significant, indicating that the mean difference in major medical outcome, hospitalization, or death prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids ($p < .001$).

The mean prescription stimulants major medical outcome, hospitalization, or death prescriptions dispensed rate decreased 3.48% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the major medical outcome, hospitalization, or death prescriptions dispensed rate is statistically significant, indicating that the mean difference in major medical outcome, hospitalization, or death prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p < .001$).

Figure 5.5.1.3

The RADARS System Poison Center Program
Major Medical Outcome, Hospitalization or Death Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

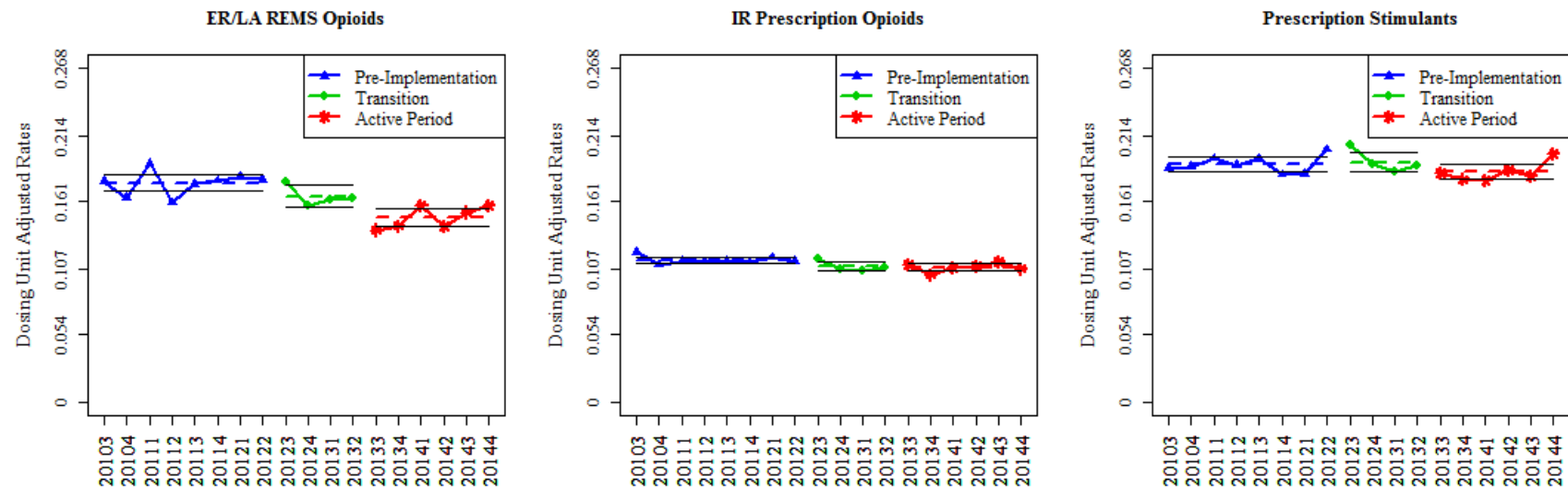


Table 5.5.1.3
The RADARS System Poison Center Program
Major Medical Outcome, Hospitalization or Death Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.176	Pre versus Transition	-6.11% (-12.08%, 0.27%)	0.060	.
	Transition	0.165	Transition versus Active	-10.23% (-16.47%, -3.53%)	0.003	.
	Active	0.148	Pre versus Active	-15.72% (-20.63%, -10.49%)	<.001	.
IR Prescription Opioids	Pre	0.114	Pre versus Transition	-4.45% (-8.07%, -0.68%)	0.021	0.653
	Transition	0.109	Transition versus Active	-0.36% (-4.38%, 3.83%)	0.863	0.014
	Active	0.108	Pre versus Active	-4.80% (-8.04%, -1.44%)	0.005	<.001
Prescription Stimulants	Pre	0.191	Pre versus Transition	0.82% (-4.05%, 5.94%)	0.747	0.090
	Transition	0.193	Transition versus Active	-3.99% (-8.70%, 0.96%)	0.112	0.134
	Active	0.185	Pre versus Active	-3.21% (-7.31%, 1.08%)	0.141	<.001

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids major medical outcome, hospitalization, or death dosing units rate decreased 6.11% between the Pre-Implementation and Transition time periods. This decrease is not statistically significant.

The mean IR prescription opioids major medical outcome, hospitalization, or death dosing units rate decreased 4.45% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the major medical outcome, hospitalization, or death dosing units rate is not statistically significant, indicating that the mean difference in major medical outcome, hospitalization, or death dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.653).

The mean prescription stimulants major medical outcome, hospitalization, or death dosing units rate increased 0.82% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the major medical outcome, hospitalization, or death dosing units rate is not statistically significant, indicating that the mean difference in major medical outcome, hospitalization, or death dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.090).

The mean ER/LA REMS opioids major medical outcome, hospitalization, or death dosing units rate decreased 10.23% between the Transition and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids major medical outcome, hospitalization, or death dosing units rate decreased 0.36% between the Transition and Active Period time periods. The interaction of drug by time period for the major medical outcome, hospitalization, or death dosing units rate is statistically significant, indicating that the mean difference in major medical outcome, hospitalization, or death dosing units rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids ($p=0.014$).

The mean prescription stimulants major medical outcome, hospitalization, or death dosing units rate decreased 3.99% between the Transition and Active Period time periods. The interaction of drug by time period for the major medical outcome, hospitalization, or death dosing units rate is not statistically significant, indicating that the mean difference in major medical outcome, hospitalization, or death dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.134$).

The mean ER/LA REMS opioids major medical outcome, hospitalization, or death dosing units rate decreased 15.72% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids major medical outcome, hospitalization, or death dosing units rate decreased 4.80% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the major medical outcome, hospitalization, or death dosing units rate is statistically significant, indicating that the mean difference in major medical outcome, hospitalization, or death dosing units rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids ($p<.001$).

The mean prescription stimulants major medical outcome, hospitalization, or death dosing units rate decreased 3.21% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the major medical outcome, hospitalization, or death dosing units rate is statistically significant, indicating that the mean difference in major medical outcome, hospitalization, or death dosing units rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p<.001$).

Figure 5.5.1.4 through Figure 5.5.1.6 display the mean major medical outcome, hospitalization or death rate percent change from the pre-implementation average population-, prescription dispensed-, and dosing unit- adjusted rates for ER/LA REMS opioids and comparator drugs.

Figure 5.5.1.4
The RADARS System Poison Center Program
Major Medical Outcome, Hospitalization or Deaths
Percent Change from Average Pre-Implementation Population Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

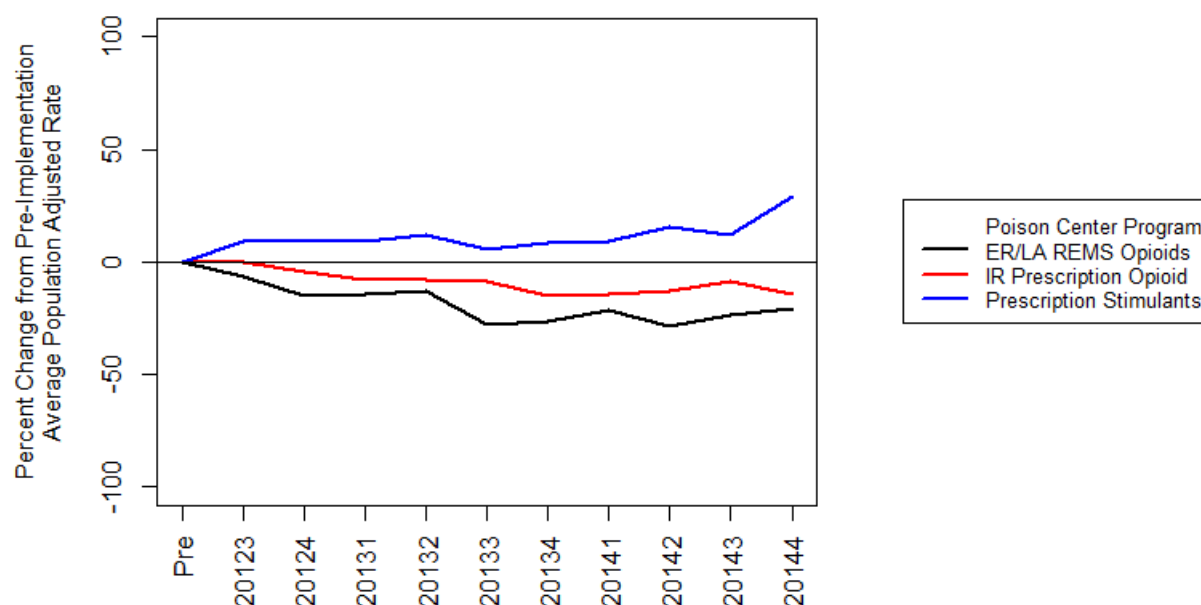


Figure 5.5.1.5

The RADARS System Poison Center Program
Major Medical Outcome, Hospitalization or Deaths
Percent Change from Average Pre-Implementation Prescription Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

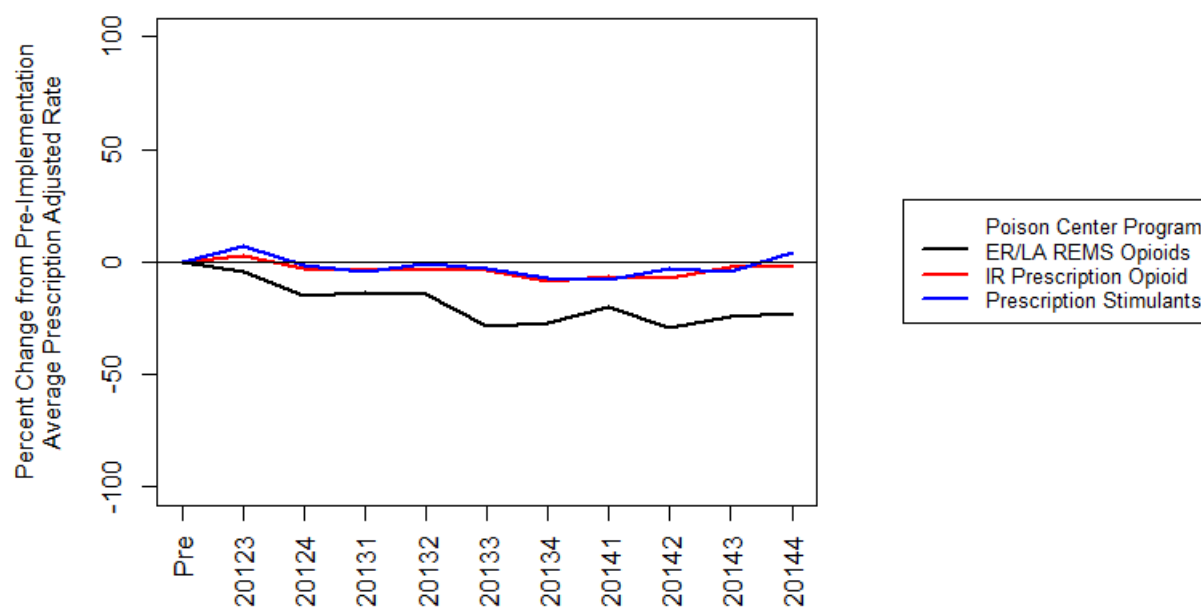
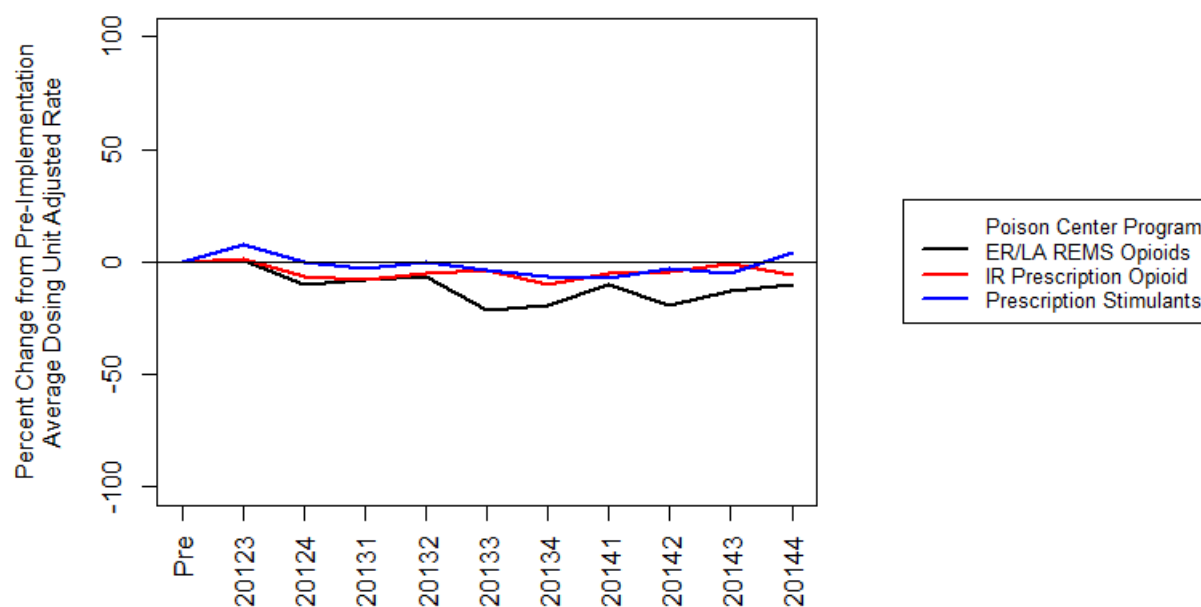


Figure 5.5.1.6

The RADARS System Poison Center Program
Major Medical Outcome, Hospitalization or Deaths
Percent Change from Average Pre-Implementation Dosing Unit Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014



5.5.2. Exposures Resulting in a Death from the RADARS System Poison Center Program

[Figure 5.5.2.1](#) through [Figure 5.5.2.3](#) show the observed and predicted population, prescription dispensed, and dosing unit mean death rates and 95% confidence intervals for ER/LA REMS opioids and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 5.5.2.1

The RADARS System Poison Center Program
Death Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

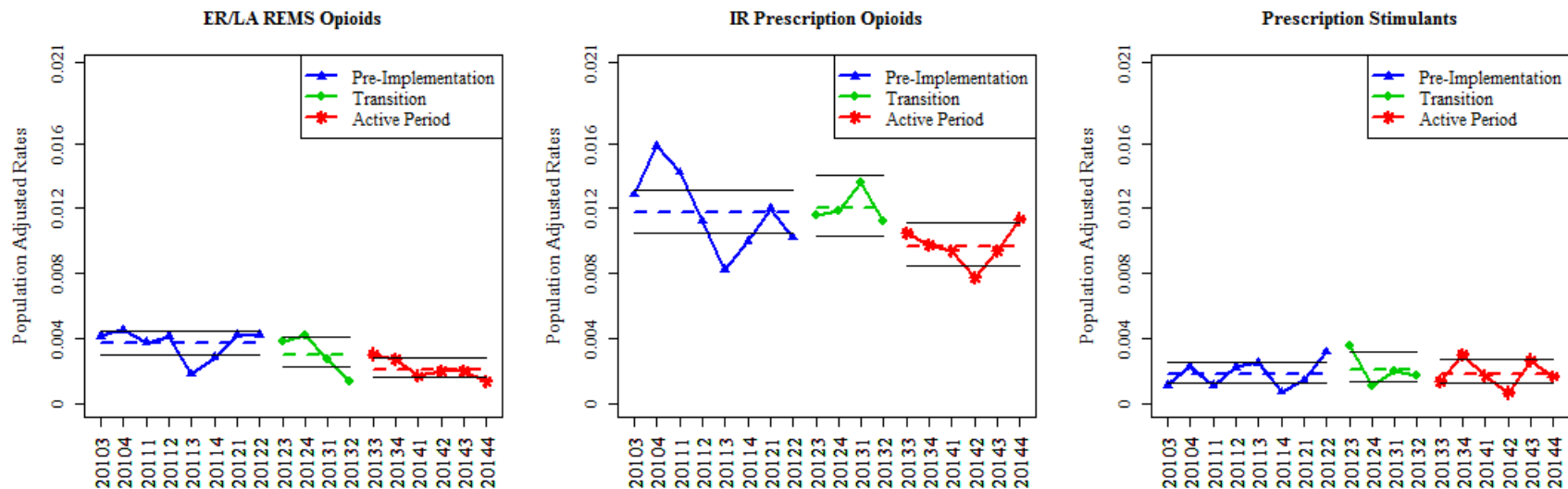


Table 5.5.2.1
The RADARS System Poison Center Program
Death Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.004	Pre versus Transition	-18.36% (-42.79%, 16.50%)	0.264	.
	Transition	0.003	Transition versus Active	-29.43% (-53.25%, 6.52%)	0.097	.
	Active	0.002	Pre versus Active	-42.39% (-59.22%, -18.61%)	0.002	.
IR Prescription Opioids	Pre	0.012	Pre versus Transition	2.53% (-15.27%, 24.06%)	0.798	0.268
	Transition	0.012	Transition versus Active	-19.69% (-34.67%, -1.27%)	0.037	0.582
	Active	0.010	Pre versus Active	-17.66% (-31.11%, -1.57%)	0.033	0.072
Prescription Stimulants	Pre	0.002	Pre versus Transition	13.36% (-35.07%, 97.94%)	0.659	0.330
	Transition	0.002	Transition versus Active	-10.63% (-49.92%, 59.47%)	0.704	0.515
	Active	0.002	Pre versus Active	1.31% (-39.02%, 68.31%)	0.960	0.072

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids death population rate decreased 18.36% between the Pre-Implementation and Transition time periods. This decrease is not statistically significant.

The mean IR prescription opioids death population rate increased 2.53% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the death population rate is not statistically significant, indicating that the mean difference in death population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.268).

The mean prescription stimulants death population rate increased 13.36% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the death population rate is not statistically significant, indicating that the mean difference in death population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.330).

The mean ER/LA REMS opioids death population rate decreased 29.43% between the Transition and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids death population rate decreased 19.69% between the Transition and Active Period time periods. The interaction of drug by time period for the death

population rate is not statistically significant, indicating that the mean difference in death population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.582$).

The mean prescription stimulants death population rate decreased 10.63% between the Transition and Active Period time periods. The interaction of drug by time period for the death population rate is not statistically significant, indicating that the mean difference in death population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.515$).

The mean ER/LA REMS opioids death population rate decreased 42.39% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids death population rate decreased 17.66% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the death population rate is not statistically significant, indicating that the mean difference in death population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.072$).

The mean prescription stimulants death population rate increased 1.31% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the death population rate is not statistically significant, indicating that the mean difference in death population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.072$).

Figure 5.5.2.2

The RADARS System Poison Center Program
Death Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

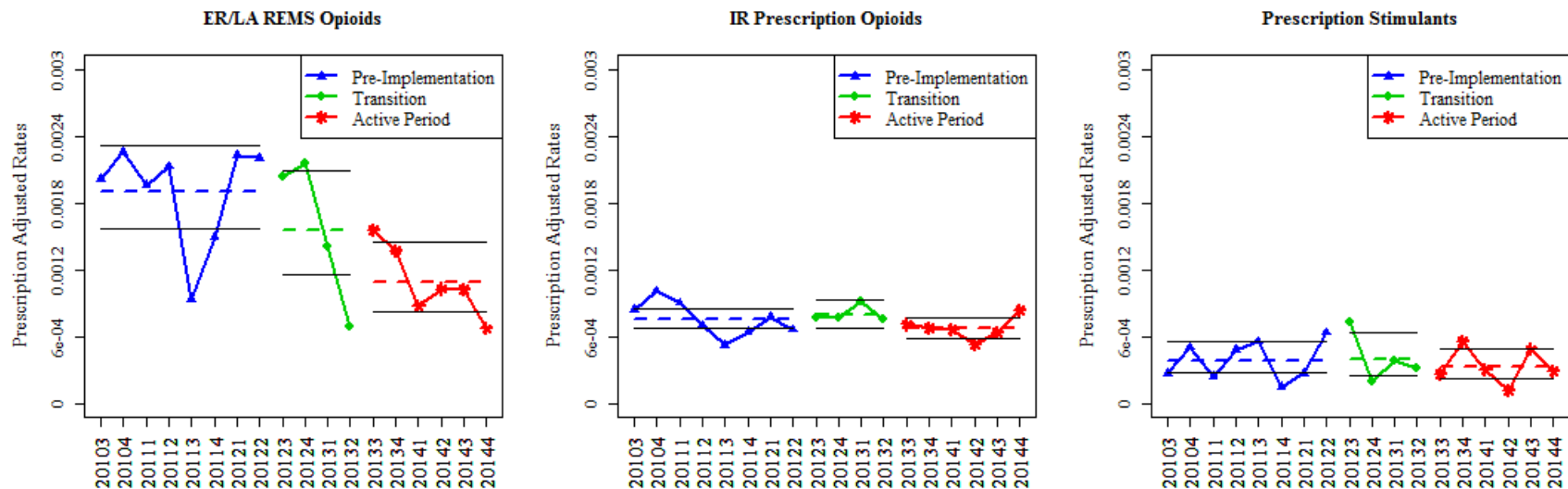


Table 5.5.2.2

The RADARS System Poison Center Program
Death Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.002	Pre versus Transition	-18.09% (-42.50%, 16.67%)	0.269	.
	Transition	0.002	Transition versus Active	-30.15% (-53.63%, 5.23%)	0.086	.
	Active	0.001	Pre versus Active	-42.78% (-59.43%, -19.30%)	0.001	.
IR Prescription Opioids	Pre	<.001	Pre versus Transition	6.07% (-12.85%, 29.08%)	0.557	0.211
	Transition	<.001	Transition versus Active	-15.73% (-31.88%, 4.24%)	0.115	0.426
	Active	<.001	Pre versus Active	-10.62% (-25.63%, 7.42%)	0.231	0.025
Prescription Stimulants	Pre	<.001	Pre versus Transition	3.37% (-41.62%, 83.03%)	0.909	0.497
	Transition	<.001	Transition versus Active	-16.58% (-53.93%, 51.03%)	0.549	0.630
	Active	<.001	Pre versus Active	-13.77% (-48.75%, 45.10%)	0.577	0.197

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids death prescriptions dispensed rate decreased 18.09% between the Pre-Implementation and Transition time periods. This decrease is not statistically significant.

The mean IR prescription opioids death prescriptions dispensed rate increased 6.07% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the death prescriptions dispensed rate is not statistically significant, indicating that the mean difference in death prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.211).

The mean prescription stimulants death prescriptions dispensed rate increased 3.37% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the death prescriptions dispensed rate is not statistically significant, indicating that the mean difference in death prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.497).

The mean ER/LA REMS opioids death prescriptions dispensed rate decreased 30.15% between the Transition and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids death prescriptions dispensed rate decreased 15.73% between the Transition and Active Period time periods. The interaction of drug by time period for the

death prescriptions dispensed rate is not statistically significant, indicating that the mean difference in death prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.426$).

The mean prescription stimulants death prescriptions dispensed rate decreased 16.58% between the Transition and Active Period time periods. The interaction of drug by time period for the death prescriptions dispensed rate is not statistically significant, indicating that the mean difference in death prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.630$).

The mean ER/LA REMS opioids death prescriptions dispensed rate decreased 42.78% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids death prescriptions dispensed rate decreased 10.62% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the death prescriptions dispensed rate is statistically significant, indicating that the mean difference in death prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids ($p=0.025$).

The mean prescription stimulants death prescriptions dispensed rate decreased 13.77% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the death prescriptions dispensed rate is not statistically significant, indicating that the mean difference in death prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.197$).

Figure 5.5.2.3
The RADARS System Poison Center Program
Death Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

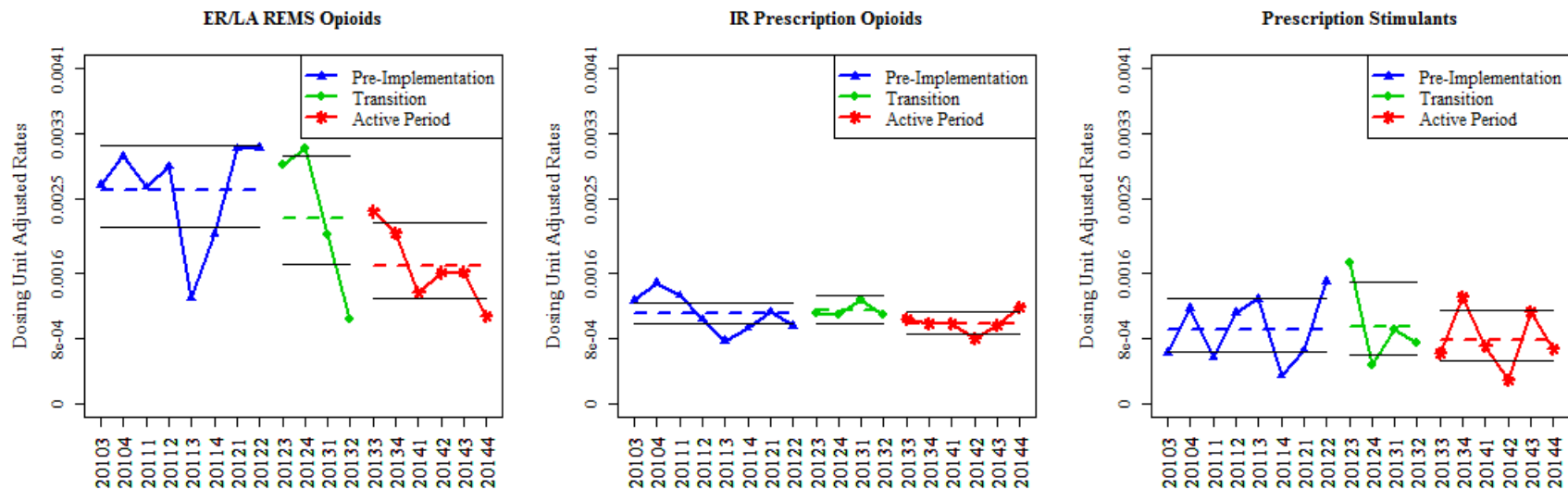


Table 5.5.2.3
The RADARS System Poison Center Program
Death Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.003	Pre versus Transition	-12.81%(-38.22%,23.04%)	0.435	.
	Transition	0.002	Transition versus Active	-25.86%(-50.25%,10.48%)	0.141	.
	Active	0.002	Pre versus Active	-35.36%(-53.75%,-9.66%)	0.011	.
IR Prescription Opioids	Pre	0.001	Pre versus Transition	3.18%(-14.79%,24.93%)	0.748	0.402
	Transition	0.001	Transition versus Active	-13.20%(-29.44%,6.78%)	0.181	0.492
	Active	<.001	Pre versus Active	-10.44%(-25.12%,7.13%)	0.228	0.092
Prescription Stimulants	Pre	<.001	Pre versus Transition	4.18%(-41.17%,84.47%)	0.888	0.601
	Transition	<.001	Transition versus Active	-16.99%(-54.15%,50.31%)	0.539	0.757
	Active	<.001	Pre versus Active	-13.52%(-48.61%,45.52%)	0.584	0.357

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids death dosing units rate decreased 12.81% between the Pre-Implementation and Transition time periods. This decrease is not statistically significant.

The mean IR prescription opioids death dosing units rate increased 3.18% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the death dosing units rate is not statistically significant, indicating that the mean difference in death dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.402).

The mean prescription stimulants death dosing units rate increased 4.18% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the death dosing units rate is not statistically significant, indicating that the mean difference in death dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.601).

The mean ER/LA REMS opioids death dosing units rate decreased 25.86% between the Transition and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids death dosing units rate decreased 13.20% between the Transition and Active Period time periods. The interaction of drug by time period for the death dosing units rate is not statistically significant, indicating that the mean difference in death dosing units rates for ER/LA REMS opioids is not significantly different than the mean

difference observed for IR prescription opioids ($p=0.492$).

The mean prescription stimulants death dosing units rate decreased 16.99% between the Transition and Active Period time periods. The interaction of drug by time period for the death dosing units rate is not statistically significant, indicating that the mean difference in death dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.757$).

The mean ER/LA REMS opioids death dosing units rate decreased 35.36% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids death dosing units rate decreased 10.44% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the death dosing units rate is not statistically significant, indicating that the mean difference in death dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.092$).

The mean prescription stimulants death dosing units rate decreased 13.52% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the death dosing units rate is not statistically significant, indicating that the mean difference in death dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.357$).

Figure 5.5.2.4 through Figure 5.5.2.6 display the mean death rate percent change from the pre-implementation average population-, prescription dispensed-, and dosing unit- adjusted rates for ER/LA REMS opioids and comparator drugs.

Figure 5.5.2.4
The RADARS System Poison Center Program
Deaths
Percent Change from Average Pre-Implementation Population Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

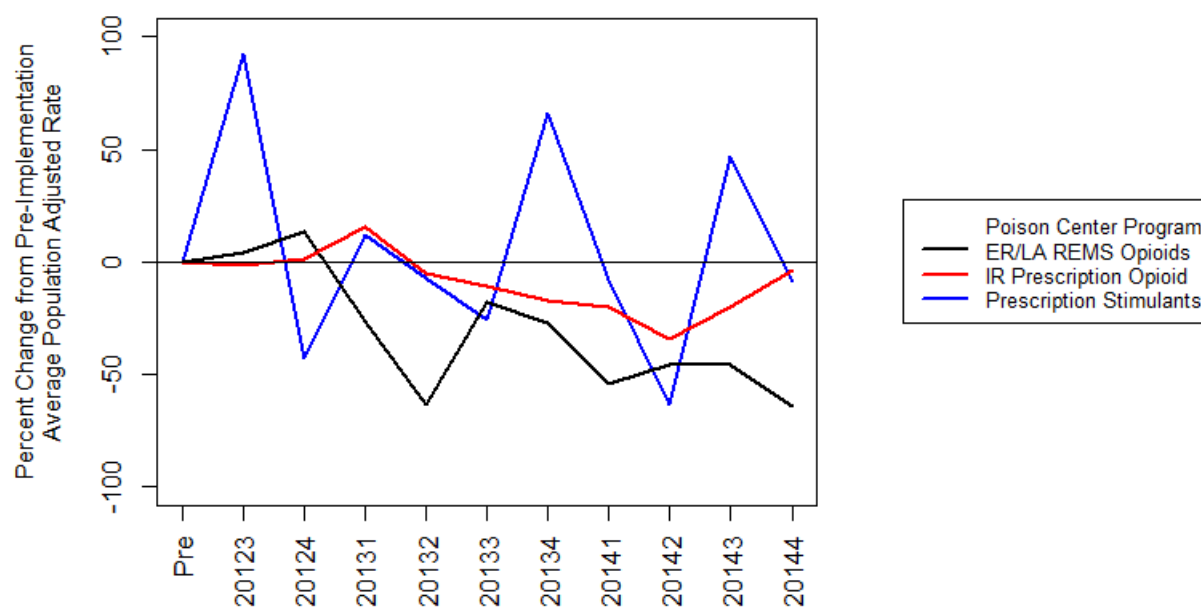


Figure 5.5.2.5
The RADARS System Poison Center Program
Deaths
Percent Change from Average Pre-Implementation Prescription Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

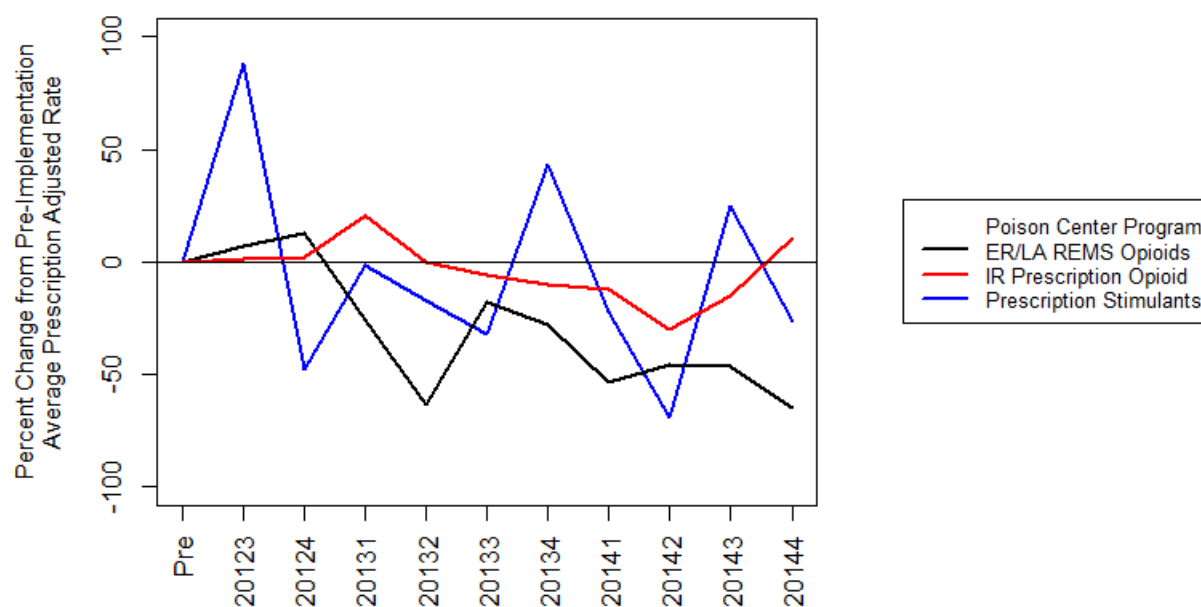
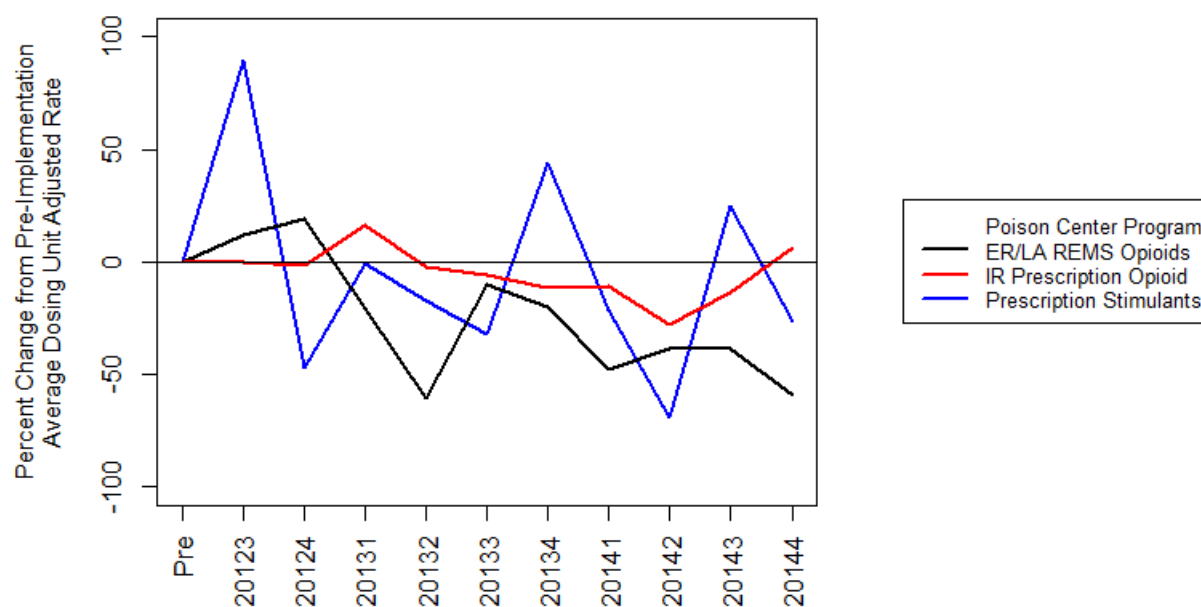


Figure 5.5.2.6
The RADARS System Poison Center Program
Deaths
Percent Change from Average Pre-Implementation Dosing Unit Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014



5.6. Abuse from the RADARS System Treatment Center Programs Combined

5.6.1. Abuse from the RADARS System Treatment Center Programs Combined

Figure 5.7.1.1 through Figure 5.7.1.3 show the observed and predicted population, prescription dispensed, and dosing unit mean past 30 day use to get high (abuse) mention rates and 95% confidence intervals for ER/LA REMS opioids and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 5.6.1.1

The RADARS System Treatment Center Programs Combined
Mean Past 30 Day Mention Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

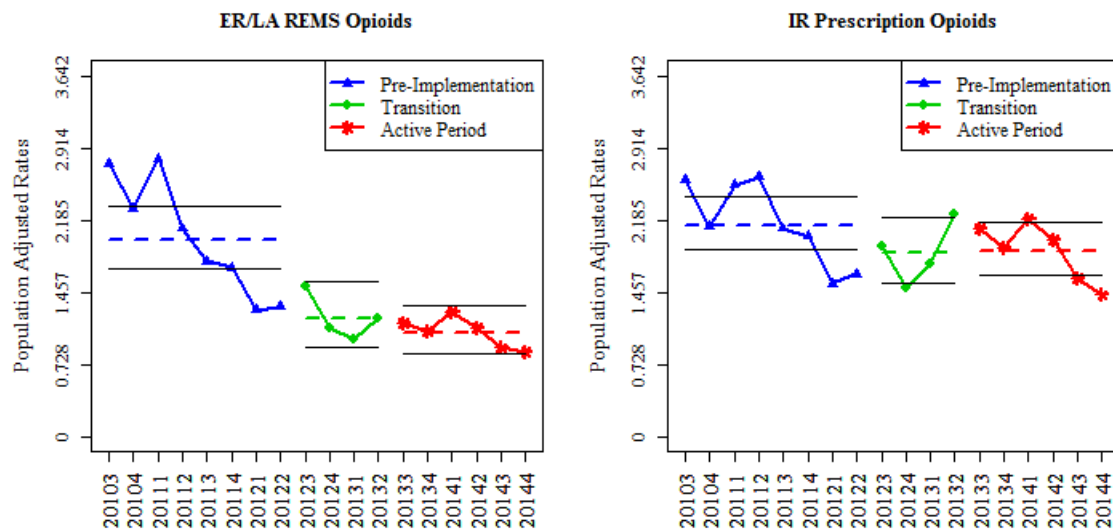


Table 5.6.1.1

The RADARS System Treatment Center Programs Combined
Mean Past 30 Day Mention Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	1.987	Pre versus Transition	-40.02% (-56.09%, -18.06%)	0.001	.
	Transition	1.192	Transition versus Active	-11.67% (-38.18%, 26.21%)	0.496	.
	Active	1.053	Pre versus Active	-47.02% (-60.00%, -29.81%)	<.001	.
IR Prescription Opioids	Pre	2.133	Pre versus Transition	-13.01% (-29.97%, 8.06%)	0.208	0.055
	Transition	1.855	Transition versus Active	1.07% (-19.60%, 27.03%)	0.928	0.533
	Active	1.875	Pre versus Active	-12.09% (-27.31%, 6.32%)	0.184	0.003

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids past 30 day mention population rate decreased 40.02% between the Pre-Implementation and Transition time periods. This decrease is statistically significant.

The mean IR prescription opioids past 30 day mention population rate decreased 13.01% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the past 30 day mention population rate is not statistically significant, indicating that the mean difference in past 30 day mention population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.055).

The mean ER/LA REMS opioids past 30 day mention population rate decreased 11.67% between the Transition and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids past 30 day mention population rate increased 1.07% between the Transition and Active Period time periods. The interaction of drug by time period for the past 30 day mention population rate is not statistically significant, indicating that the mean difference in past 30 day mention population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.533).

The mean ER/LA REMS opioids past 30 day mention population rate decreased 47.02% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids past 30 day mention population rate decreased 12.09% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the past 30 day mention population rate is statistically significant, indicating that the mean difference in past 30 day mention population rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids (p=0.003).

Figure 5.6.1.2

The RADARS System Treatment Center Programs Combined
Mean Past 30 Day Mention Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

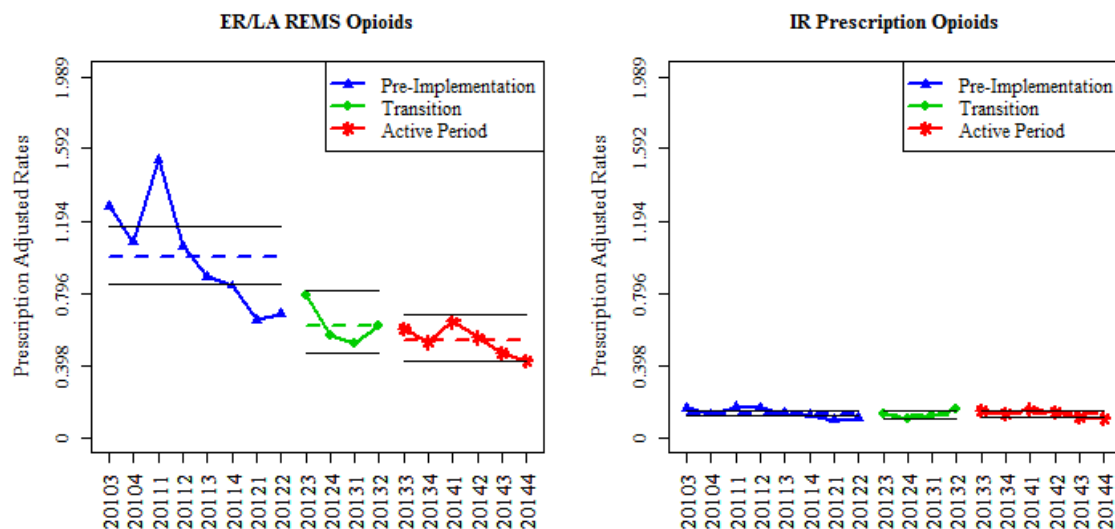


Table 5.6.1.2

The RADARS System Treatment Center Programs Combined
Mean Past 30 Day Mention Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.994	Pre versus Transition	-37.88%(-54.69%,-14.82%)	0.003	.
	Transition	0.618	Transition versus Active	-13.57%(-39.76%,24.01%)	0.429	.
	Active	0.534	Pre versus Active	-46.31%(-59.60%,-28.64%)	<.001	.
IR Prescription Opioids	Pre	0.135	Pre versus Transition	-6.62%(-24.39%,15.34%)	0.525	0.035
	Transition	0.126	Transition versus Active	4.65%(-16.23%,30.75%)	0.689	0.377
	Active	0.132	Pre versus Active	-2.27%(-18.78%,17.60%)	0.808	<.001

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids past 30 day mention prescriptions dispensed rate decreased 37.88% between the Pre-Implementation and Transition time periods. This decrease is

statistically significant.

The mean IR prescription opioids past 30 day mention prescriptions dispensed rate decreased 6.62% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the past 30 day mention prescriptions dispensed rate is statistically significant, indicating that the mean difference in past 30 day mention prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids ($p=0.035$).

The mean ER/LA REMS opioids past 30 day mention prescriptions dispensed rate decreased 13.57% between the Transition and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids past 30 day mention prescriptions dispensed rate increased 4.65% between the Transition and Active Period time periods. The interaction of drug by time period for the past 30 day mention prescriptions dispensed rate is not statistically significant, indicating that the mean difference in past 30 day mention prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.377$).

The mean ER/LA REMS opioids past 30 day mention prescriptions dispensed rate decreased 46.31% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids past 30 day mention prescriptions dispensed rate decreased 2.27% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the past 30 day mention prescriptions dispensed rate is statistically significant, indicating that the mean difference in past 30 day mention prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids ($p<.001$).

Figure 5.6.1.3

The RADARS System Treatment Center Programs Combined
Mean Past 30 Day Mention Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

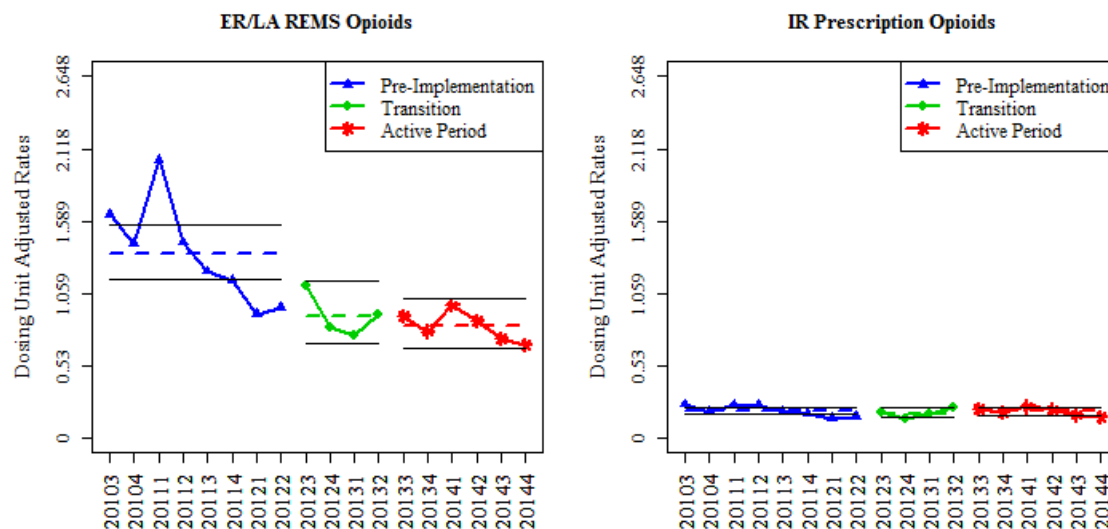


Table 5.6.1.3

The RADARS System Treatment Center Programs Combined
Mean Past 30 Day Mention Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	1.347	Pre versus Transition	-33.89%(-50.61%,-11.52%)	0.005	.
	Transition	0.890	Transition versus Active	-8.08%(-34.14%,28.29%)	0.620	.
	Active	0.818	Pre versus Active	-39.24%(-53.27%,-20.98%)	<.001	.
IR Prescription Opioids	Pre	0.196	Pre versus Transition	-8.42%(-26.73%,14.48%)	0.440	0.082
	Transition	0.180	Transition versus Active	7.29%(-15.21%,35.74%)	0.558	0.458
	Active	0.193	Pre versus Active	-1.74%(-19.20%,19.48%)	0.860	0.004

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.

#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids past 30 day mention dosing units rate decreased 33.89% between the Pre-Implementation and Transition time periods. This decrease is statistically significant.

The mean IR prescription opioids past 30 day mention dosing units rate decreased 8.42% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the past 30 day mention dosing units rate is not statistically significant, indicating that the mean difference in past 30 day mention dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.082$).

The mean ER/LA REMS opioids past 30 day mention dosing units rate decreased 8.08% between the Transition and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids past 30 day mention dosing units rate increased 7.29% between the Transition and Active Period time periods. The interaction of drug by time period for the past 30 day mention dosing units rate is not statistically significant, indicating that the mean difference in past 30 day mention dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.458$).

The mean ER/LA REMS opioids past 30 day mention dosing units rate decreased 39.24% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids past 30 day mention dosing units rate decreased 1.74% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the past 30 day mention dosing units rate is statistically significant, indicating that the mean difference in past 30 day mention dosing units rates for ER/LA REMS opioids is significantly different than the mean difference observed for IR prescription opioids ($p=0.004$).

Figure 5.7.1.4 through Figure 5.7.1.6 display the mean past 30 day mention rate percent change from the pre-implementation average population-, prescription dispensed-, and dosing unit-adjusted rates for ER/LA REMS opioids and comparator drugs.

Figure 5.6.1.4
The RADARS System Treatment Center Programs Combined
Mean Past 30 Day Mention Rates
Percent Change from Average Pre-Implementation Population Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

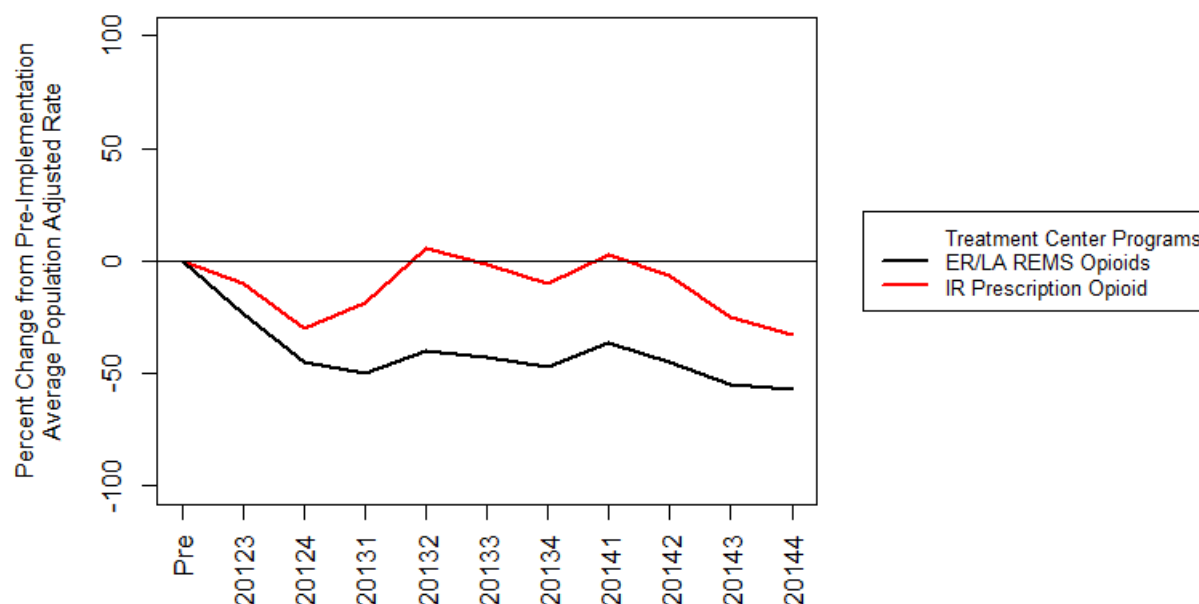


Figure 5.6.1.5

The RADARS System Treatment Center Programs Combined
Mean Past 30 Day Mention Rates
Percent Change from Average Pre-Implementation Prescription Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

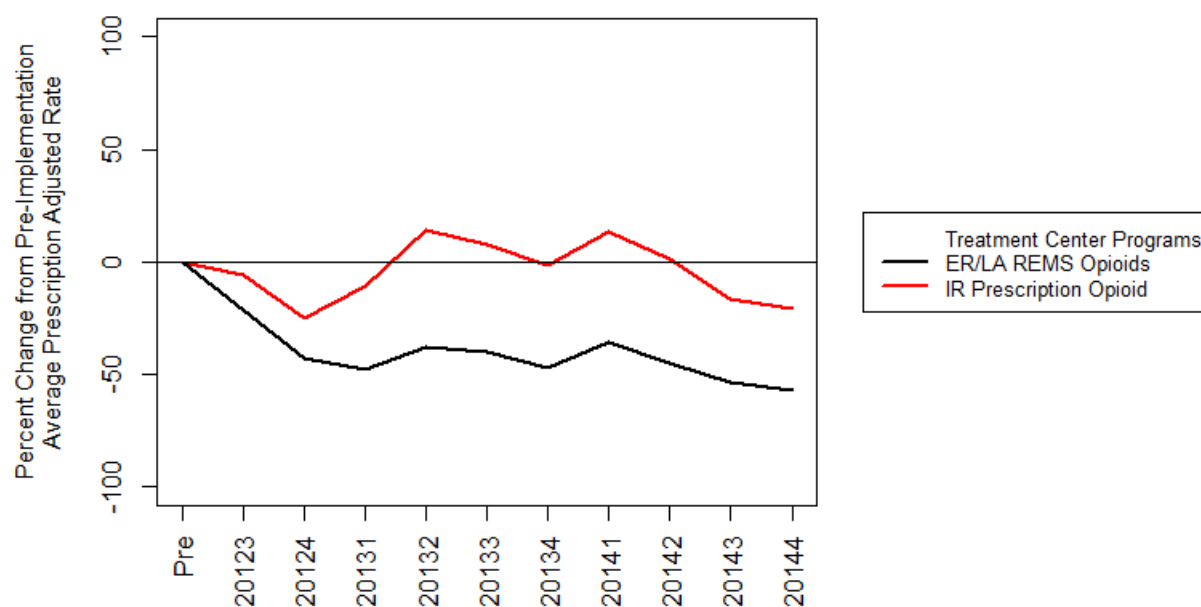
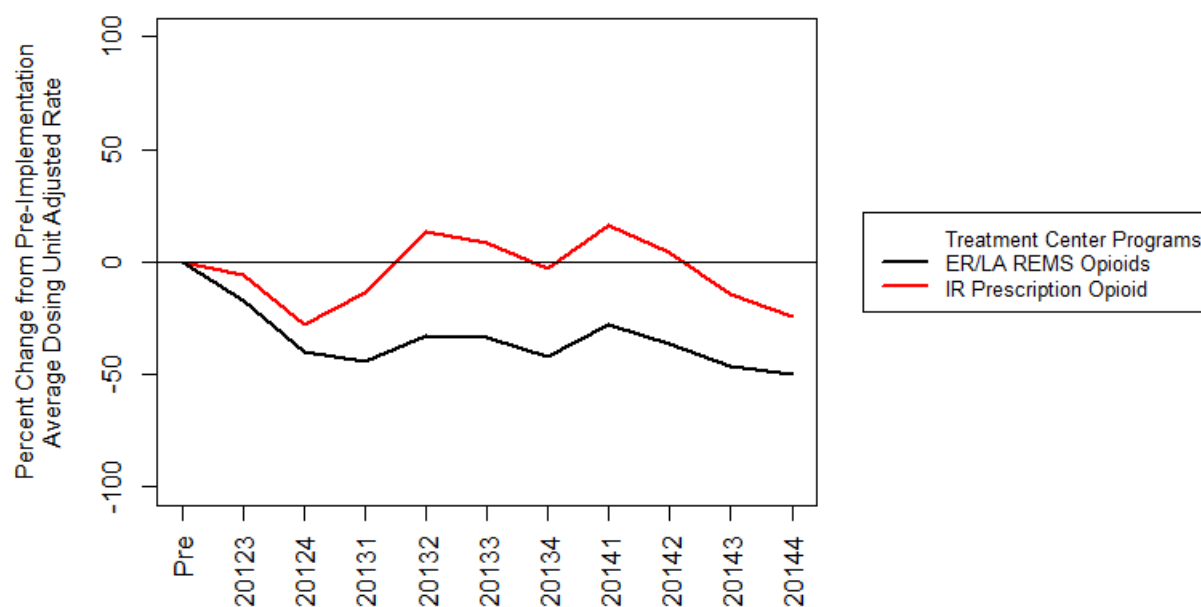


Figure 5.6.1.6

The RADARS System Treatment Center Programs Combined
Mean Past 30 Day Mention Rates
Percent Change from Average Pre-Implementation Dosing Unit Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014



5.7. Abuse from the RADARS System College Survey Program

5.7.1. Abuse from the RADARS System College Survey Program

Figure 5.7.1.1 through Figure 5.7.1.3 display the observed and predicted population, prescription dispensed, and dosing unit mean past 90 day non-medical use (abuse) mention rates and 95% confidence intervals for ER/LA REMS opioids and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 5.7.1.1

The RADARS System College Survey Program
Mean Past 90 Day Abuse Mention Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

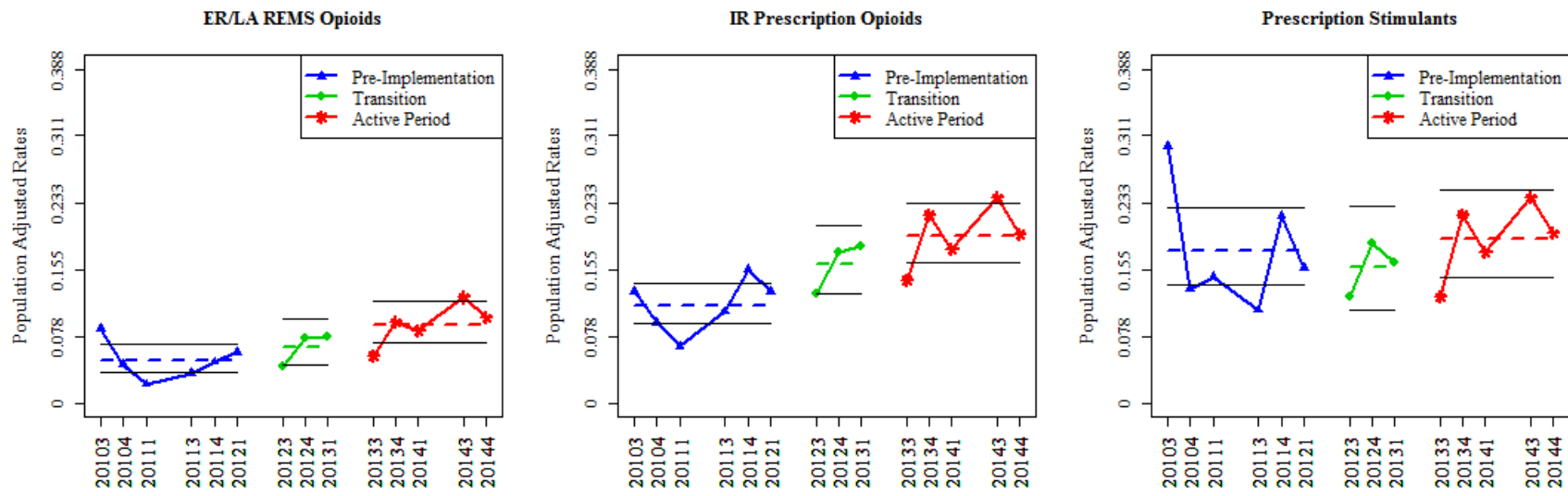


Table 5.7.1.1

The RADARS System College Survey Program
Mean Past 90 Day Abuse Mention Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.049	Pre versus Transition	33.51%(-19.68%,121.94%)	0.265	.
	Transition	0.066	Transition versus Active	38.45%(-13.47%,121.54%)	0.175	.
	Active	0.091	Pre versus Active	84.85%(22.07%,179.93%)	0.004	.
IR Prescription Opioids	Pre	0.114	Pre versus Transition	42.70%(3.69%,96.37%)	0.029	0.828
	Transition	0.162	Transition versus Active	20.13%(-10.82%,61.84%)	0.228	0.617
	Active	0.195	Pre versus Active	71.43%(30.88%,124.54%)	<.001	0.765
Prescription Stimulants	Pre	0.177	Pre versus Transition	-10.55%(-42.95%,40.23%)	0.627	0.247
	Transition	0.158	Transition versus Active	20.42%(-23.75%,90.19%)	0.425	0.677
	Active	0.191	Pre versus Active	7.72%(-25.25%,55.23%)	0.690	0.056

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids past 90 day mention population rate increased 33.51% between the Pre-Implementation and Transition time periods. This increase is not statistically significant.

The mean IR prescription opioids past 90 day mention population rate increased 42.70% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the past 90 day mention population rate is not statistically significant, indicating that the mean difference in past 90 day mention population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.828).

The mean prescription stimulants past 90 day mention population rate decreased 10.55% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the past 90 day mention population rate is not statistically significant, indicating that the mean difference in past 90 day mention population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.247).

The mean ER/LA REMS opioids past 90 day mention population rate increased 38.45% between the Transition and Active Period time periods. This increase is not statistically significant.

The mean IR prescription opioids past 90 day mention population rate increased 20.13% between the Transition and Active Period time periods. The interaction of drug by time period for the past 90 day mention population rate is not statistically significant, indicating that the mean difference

in past 90 day mention population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.617$).

The mean prescription stimulants past 90 day mention population rate increased 20.42% between the Transition and Active Period time periods. The interaction of drug by time period for the past 90 day mention population rate is not statistically significant, indicating that the mean difference in past 90 day mention population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.677$).

The mean ER/LA REMS opioids past 90 day mention population rate increased 84.85% between the Pre-Implementation and Active Period time periods. This increase is statistically significant.

The mean IR prescription opioids past 90 day mention population rate increased 71.43% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the past 90 day mention population rate is not statistically significant, indicating that the mean difference in past 90 day mention population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.765$).

The mean prescription stimulants past 90 day mention population rate increased 7.72% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the past 90 day mention population rate is not statistically significant, indicating that the mean difference in past 90 day mention population rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.056$).

Figure 5.7.1.2

The RADARS System College Survey Program
Mean Past 90 Day Abuse Mention Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

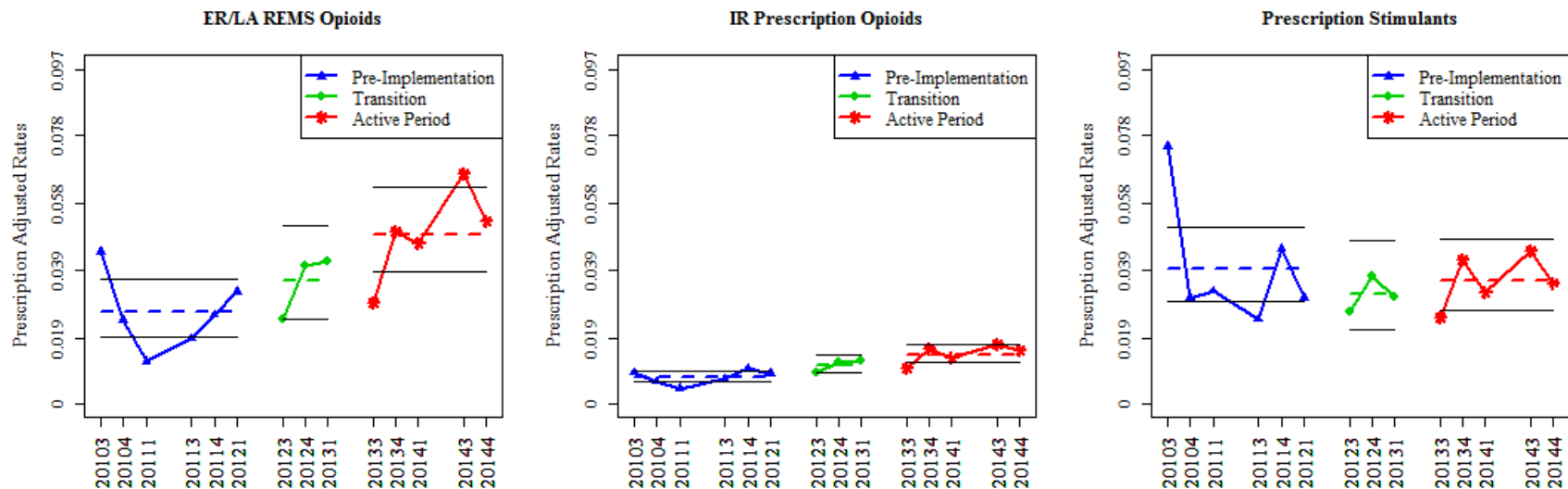


Table 5.7.1.2

The RADARS System College Survey Program
Mean Past 90 Day Abuse Mention Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.027	Pre versus Transition	34.37%(-17.43%,118.66%)	0.234	.
	Transition	0.036	Transition versus Active	37.76%(-12.20%,116.13%)	0.163	.
	Active	0.049	Pre versus Active	85.10%(24.37%,175.47%)	0.002	.
IR Prescription Opioids	Pre	0.008	Pre versus Transition	46.33%(6.49%,101.08%)	0.019	0.774
	Transition	0.011	Transition versus Active	28.15%(-4.75%,72.40%)	0.101	0.793
	Active	0.014	Pre versus Active	87.52%(43.34%,145.32%)	<.001	0.958
Prescription Stimulants	Pre	0.039	Pre versus Transition	-18.51%(-49.74%,32.14%)	0.407	0.153
	Transition	0.032	Transition versus Active	12.60%(-31.10%,84.03%)	0.636	0.553
	Active	0.036	Pre versus Active	-8.24%(-38.05%,35.90%)	0.668	0.014

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids past 90 day mention prescriptions dispensed rate increased 34.37% between the Pre-Implementation and Transition time periods. This increase is not statistically significant.

The mean IR prescription opioids past 90 day mention prescriptions dispensed rate increased 46.33% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the past 90 day mention prescriptions dispensed rate is not statistically significant, indicating that the mean difference in past 90 day mention prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.774).

The mean prescription stimulants past 90 day mention prescriptions dispensed rate decreased 18.51% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the past 90 day mention prescriptions dispensed rate is not statistically significant, indicating that the mean difference in past 90 day mention prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.153).

The mean ER/LA REMS opioids past 90 day mention prescriptions dispensed rate increased 37.76% between the Transition and Active Period time periods. This increase is not statistically significant.

The mean IR prescription opioids past 90 day mention prescriptions dispensed rate increased 28.15% between the Transition and Active Period time periods. The interaction of drug by time period for the past 90 day mention prescriptions dispensed rate is not statistically significant, indicating that the mean difference in past 90 day mention prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.793$).

The mean prescription stimulants past 90 day mention prescriptions dispensed rate increased 12.60% between the Transition and Active Period time periods. The interaction of drug by time period for the past 90 day mention prescriptions dispensed rate is not statistically significant, indicating that the mean difference in past 90 day mention prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.553$).

The mean ER/LA REMS opioids past 90 day mention prescriptions dispensed rate increased 85.10% between the Pre-Implementation and Active Period time periods. This increase is statistically significant.

The mean IR prescription opioids past 90 day mention prescriptions dispensed rate increased 87.52% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the past 90 day mention prescriptions dispensed rate is not statistically significant, indicating that the mean difference in past 90 day mention prescriptions dispensed rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.958$).

The mean prescription stimulants past 90 day mention prescriptions dispensed rate decreased 8.24% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the past 90 day mention prescriptions dispensed rate is statistically significant, indicating that the mean difference in past 90 day mention prescriptions dispensed rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p=0.014$).

Figure 5.7.1.3

The RADARS System College Survey Program
Mean Past 90 Day Abuse Mention Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

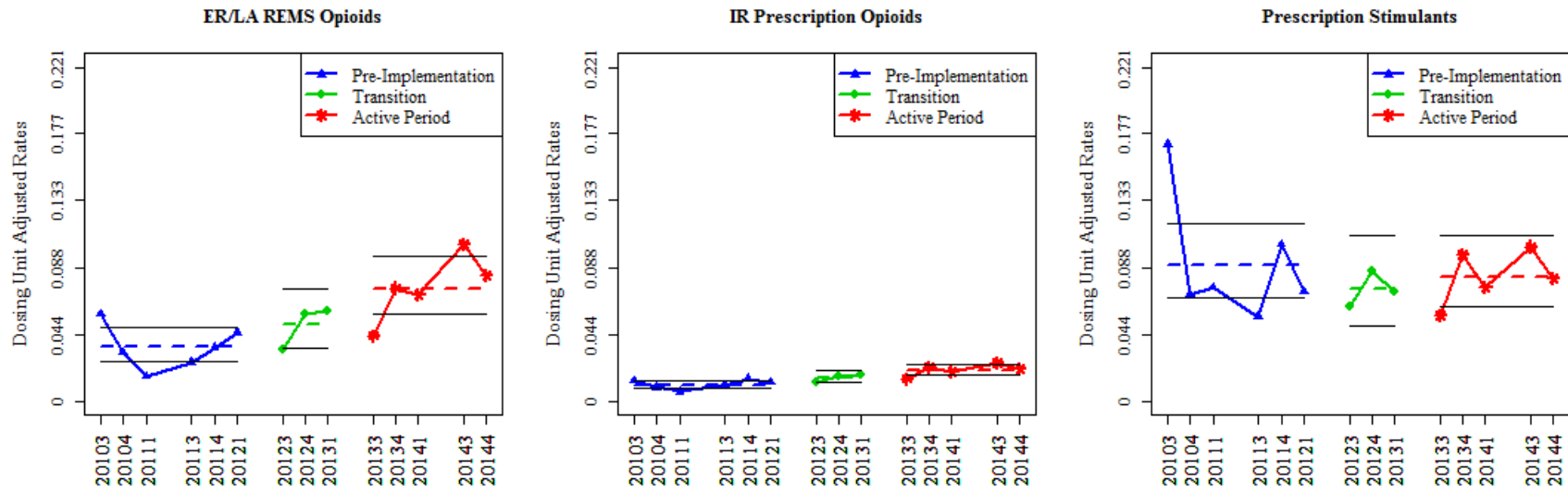


Table 5.7.1.3
The RADARS System College Survey Program
Mean Past 90 Day Abuse Mention Rates per 100,000 Dosing Units
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values *	Between Drug Interaction p-values #
ER/LA REMS Opioids	Pre	0.036	Pre versus Transition	42.55%(-13.06%,133.75%)	0.160	.
	Transition	0.051	Transition versus Active	46.89%(-7.03%,132.09%)	0.099	.
	Active	0.075	Pre versus Active	109.40%(39.83%,213.58%)	<.001	.
IR Prescription Opioids	Pre	0.011	Pre versus Transition	41.55%(3.51%,93.59%)	0.030	0.981
	Transition	0.016	Transition versus Active	31.98%(-1.46%,76.76%)	0.063	0.699
	Active	0.021	Pre versus Active	86.82%(43.38%,143.41%)	<.001	0.643
Prescription Stimulants	Pre	0.090	Pre versus Transition	-17.68%(-48.93%,32.70%)	0.425	0.117
	Transition	0.074	Transition versus Active	11.64%(-31.28%,81.38%)	0.656	0.420
	Active	0.083	Pre versus Active	-8.09%(-37.65%,35.47%)	0.670	0.004

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

The mean ER/LA REMS opioids past 90 day mention dosing units rate increased 42.55% between the Pre-Implementation and Transition time periods. This increase is not statistically significant.

The mean IR prescription opioids past 90 day mention dosing units rate increased 41.55% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the past 90 day mention dosing units rate is not statistically significant, indicating that the mean difference in past 90 day mention dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids (p=0.981).

The mean prescription stimulants past 90 day mention dosing units rate decreased 17.68% between the Pre-Implementation and Transition time periods. The interaction of drug by time period for the past 90 day mention dosing units rate is not statistically significant, indicating that the mean difference in past 90 day mention dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants (p=0.117).

The mean ER/LA REMS opioids past 90 day mention dosing units rate increased 46.89% between the Transition and Active Period time periods. This increase is not statistically significant.

The mean IR prescription opioids past 90 day mention dosing units rate increased 31.98%

between the Transition and Active Period time periods. The interaction of drug by time period for the past 90 day mention dosing units rate is not statistically significant, indicating that the mean difference in past 90 day mention dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.699$).

The mean prescription stimulants past 90 day mention dosing units rate increased 11.64% between the Transition and Active Period time periods. The interaction of drug by time period for the past 90 day mention dosing units rate is not statistically significant, indicating that the mean difference in past 90 day mention dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for prescription stimulants ($p=0.420$).

The mean ER/LA REMS opioids past 90 day mention dosing units rate increased 109.40% between the Pre-Implementation and Active Period time periods. This increase is statistically significant.

The mean IR prescription opioids past 90 day mention dosing units rate increased 86.82% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the past 90 day mention dosing units rate is not statistically significant, indicating that the mean difference in past 90 day mention dosing units rates for ER/LA REMS opioids is not significantly different than the mean difference observed for IR prescription opioids ($p=0.643$).

The mean prescription stimulants past 90 day mention dosing units rate decreased 8.09% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the past 90 day mention dosing units rate is statistically significant, indicating that the mean difference in past 90 day mention dosing units rates for ER/LA REMS opioids is significantly different than the mean difference observed for prescription stimulants ($p=0.004$).

Figure 5.7.1.4 through Figure 5.7.1.6 display the mean past 90 day non-medical use (abuse) mention rate percent change from the pre-implementation average population-, prescription dispensed-, and dosing unit- adjusted rates for ER/LA REMS opioids and comparator drugs.

Figure 5.7.1.4
 The RADARS System College Survey Program
Mean Past 90 Day Abuse Mention Rates
Percent Change from Average Pre-Implementation Population Adjusted Rates
 From Third Quarter 2010 to Fourth Quarter 2014

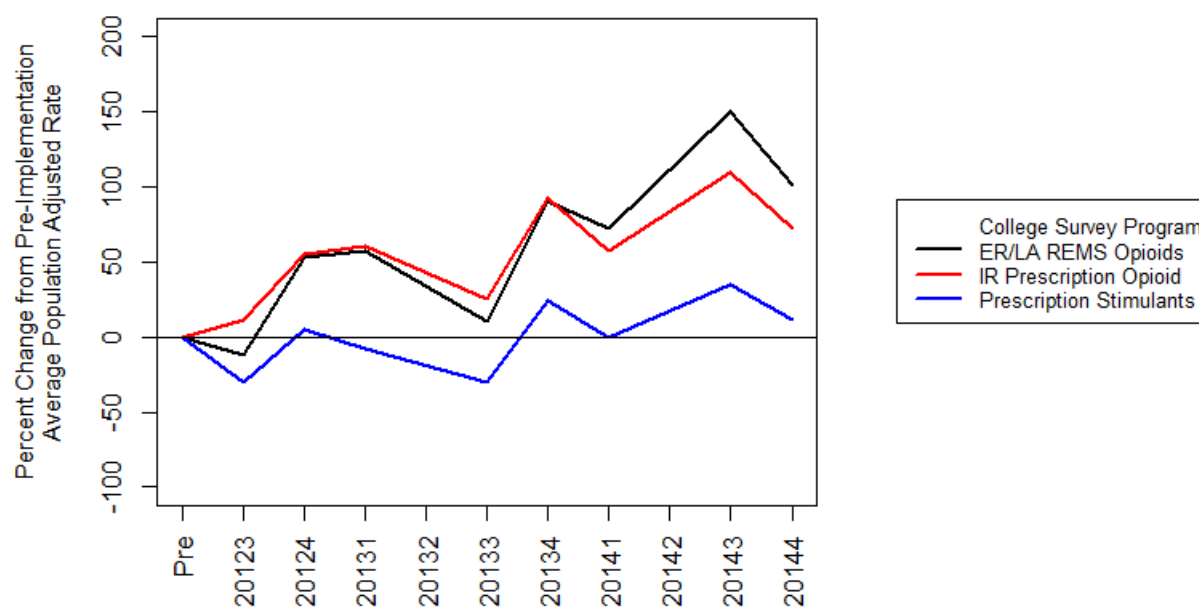


Figure 5.7.1.5

The RADARS System College Survey Program
Mean Past 90 Day Abuse Mention Rates
Percent Change from Average Pre-Implementation Prescription Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014

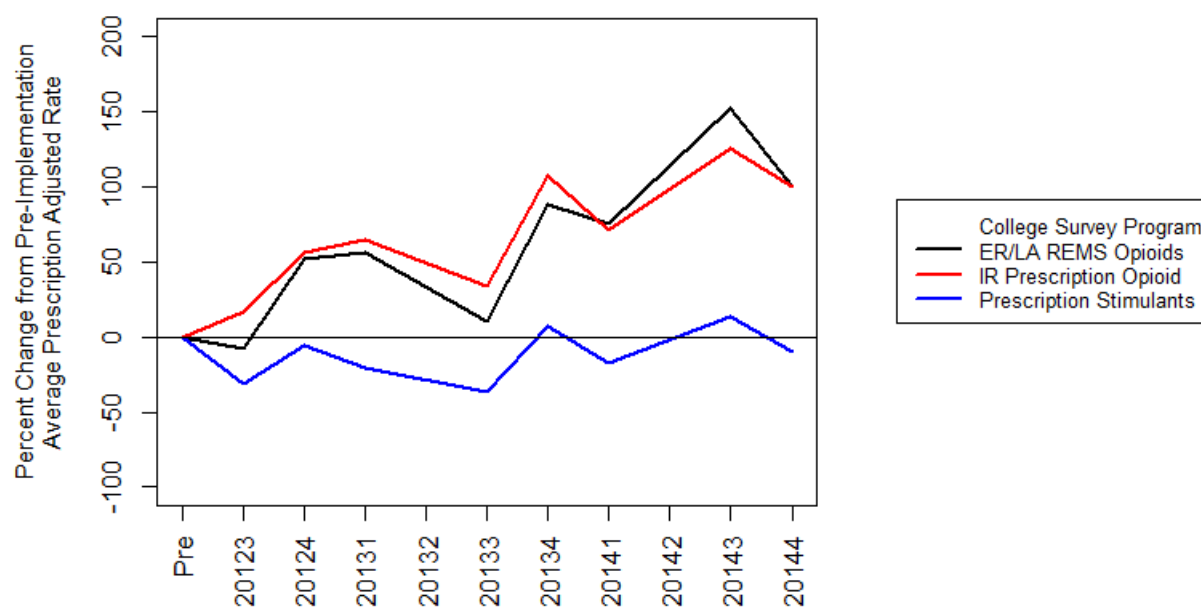
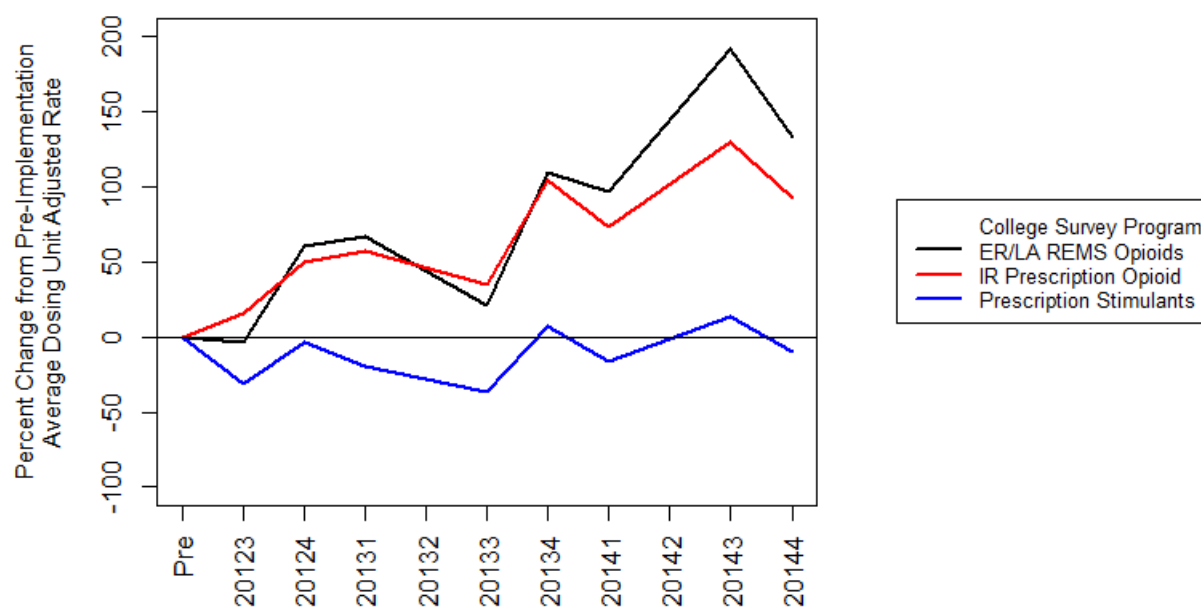


Figure 5.7.1.6

The RADARS System College Survey Program
Mean Past 90 Day Abuse Mention Rates
Percent Change from Average Pre-Implementation Dosing Unit Adjusted Rates
From Third Quarter 2010 to Fourth Quarter 2014



6. RESULTS EXCLUDING ABUSE DETERRENT FORMULATIONS

To explore the effect of ADFs on changes in abuse and misuse rates, data were reanalyzed after excluding currently available labeled ADF drugs (OxyContin, EMBEDA) and ADF drugs with no current FDA approved claim of abuse deterrent properties (Exalgo, Opana ER, OXAYDO, Nucynta ER, and Zohydro ER).

6.1. Emergency Department Visits from the RADARS System Poison Center Program

6.1.1. Under 20 Years Treated/Evaluated and Released from the RADARS System Poison Center Program

[Figure 6.1.1.1](#) through [Figure 6.1.1.2](#) show the observed and predicted population, prescription dispensed, and dosing unit mean under 20 years treated/ evaluated and released rates and 95% confidence intervals for ER/LA REMS opioids excluding ADFs and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 6.1.1.1
The RADARS System Poison Center Program
Under 20 Years Treated/Evaluated and Released Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

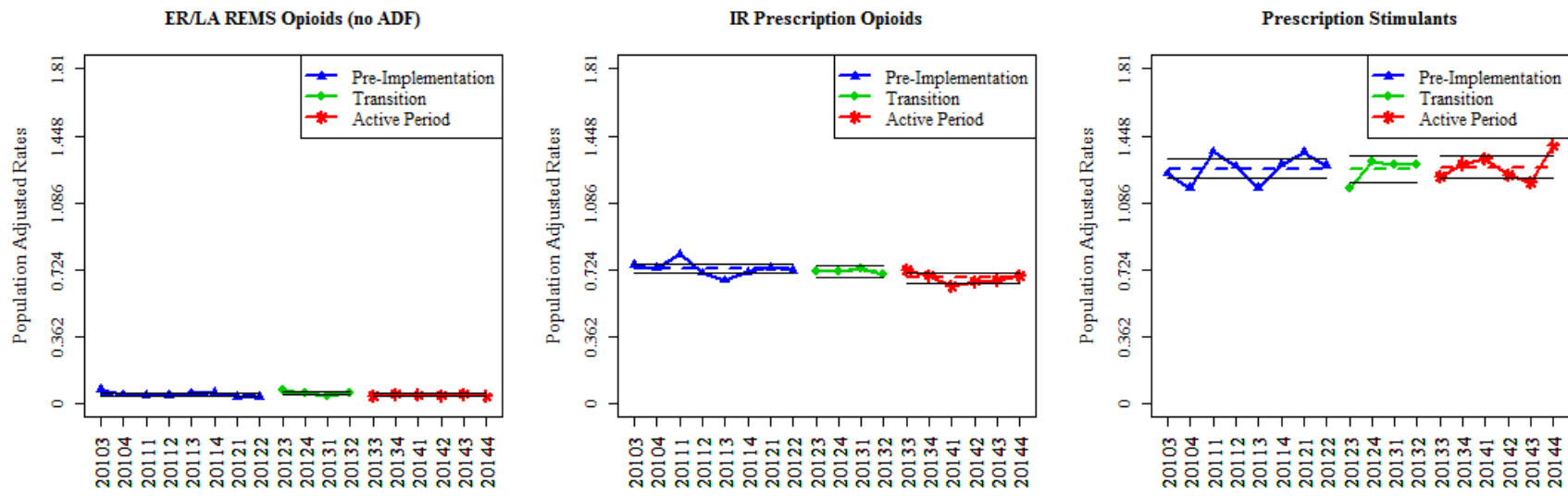


Figure 6.1.1.2

The RADARS System Poison Center Program
Under 20 Years Treated/Evaluated and Released Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

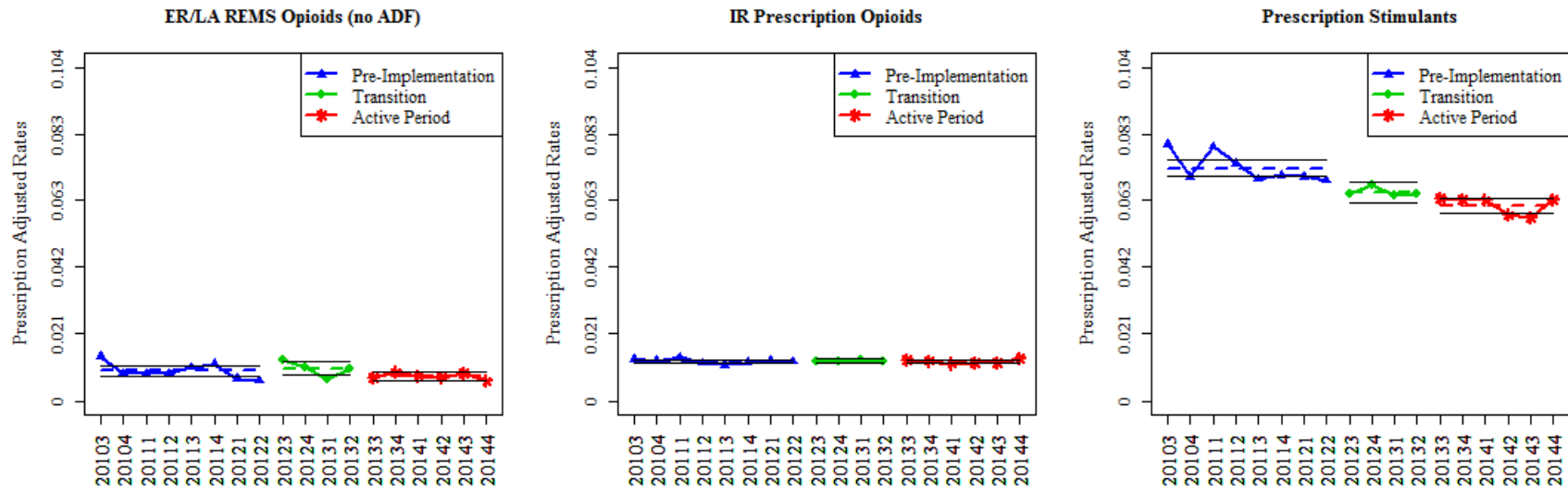


Table 6.1.1.1

The RADARS System Poison Center Program
**Under 20 Years Treated/Evaluated and Released Rates per 100,000 Population and per
1,000 Prescriptions Dispensed**
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Pre-Implementation Mean Exposure	Transition Mean Exposure	Active Period Mean Exposure	Active Period to Pre-Implementation % change (95% CI)	p-value for % change	p-value for interaction
Population Adjusted Rates/100,000						
ER/LA REMS Opioids (no ADF)	0.049	0.054	0.044	-10.55%(-30.35%,14.87%)	0.382	.
IR Prescription Opioids	0.727	0.714	0.677	-6.80%(-11.30%,-2.08%)	0.005	0.752
Prescription Stimulants	1.270	1.265	1.278	0.60%(-5.29%,6.86%)	0.846	0.371
Prescription Adjusted Rates/1,000						
ER/LA REMS Opioids (no ADF)	0.009	0.010	0.008	-17.41%(-35.54%,5.82%)	0.130	.
IR Prescription Opioids	0.013	0.013	0.012	-0.60%(-5.86%,4.96%)	0.828	0.152
Prescription Stimulants	0.073	0.065	0.061	-15.86%(-20.19%,-11.28%)	<.001	0.885

The mean ER/LA REMS opioids under 20 years treated/ evaluated and released population rate decreased 10.55% between the Pre-Implementation and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids under 20 years treated/ evaluated and released population rate decreased 6.80% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the under 20 years treated/ evaluated and released population rate is not statistically significant, indicating that the mean difference in under 20 years treated/ evaluated and released population rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for IR prescription opioids (p=0.752).

The mean stimulants under 20 years treated/ evaluated and released population rate increased 0.60% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the under 20 years treated/ evaluated and released population rate is not statistically significant, indicating that the mean difference in under 20 years treated/ evaluated and released population rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for stimulants (p=0.371).

The mean ER/LA REMS opioids under 20 years treated/ evaluated and released prescriptions dispensed rate decreased 17.41% between the Pre-Implementation and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids under 20 years treated/ evaluated and released prescriptions dispensed rate decreased 0.60% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the under 20 years treated/ evaluated and released prescriptions dispensed rate is not statistically significant, indicating that the mean difference in under 20 years treated/ evaluated and released prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for IR prescription opioids ($p=0.152$).

The mean stimulants under 20 years treated/ evaluated and released prescriptions dispensed rate decreased 15.86% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the under 20 years treated/ evaluated and released prescriptions dispensed rate is not statistically significant, indicating that the mean difference in under 20 years treated/ evaluated and released prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for stimulants ($p=0.885$).

6.1.2. Adult Treated/Evaluated and Released from the RADARS System Poison Center Program

Figure 6.1.2.1 through Figure 6.1.2.2 show the observed and predicted population, prescription dispensed, and dosing unit mean adult treated/ evaluated and released rates and 95% confidence intervals for ER/LA REMS opioids excluding ADFs and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 6.1.2.1

The RADARS System Poison Center Program
Adult Treated/Evaluated and Released Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

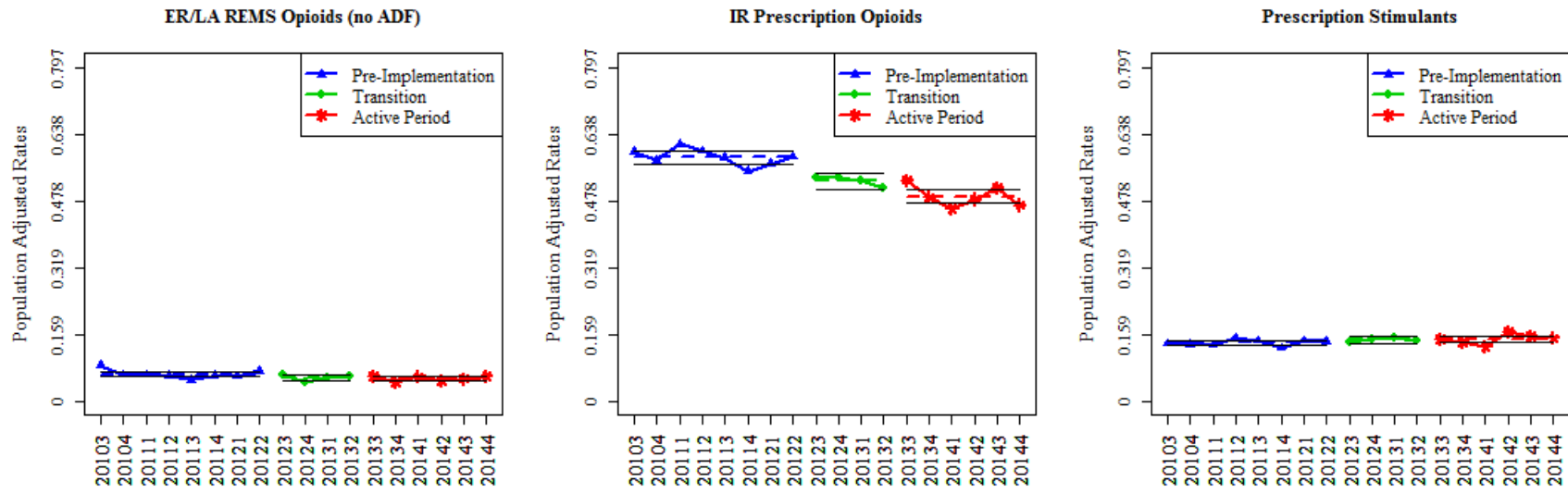


Figure 6.1.2.2

The RADARS System Poison Center Program
Adult Treated/Evaluated and Released Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

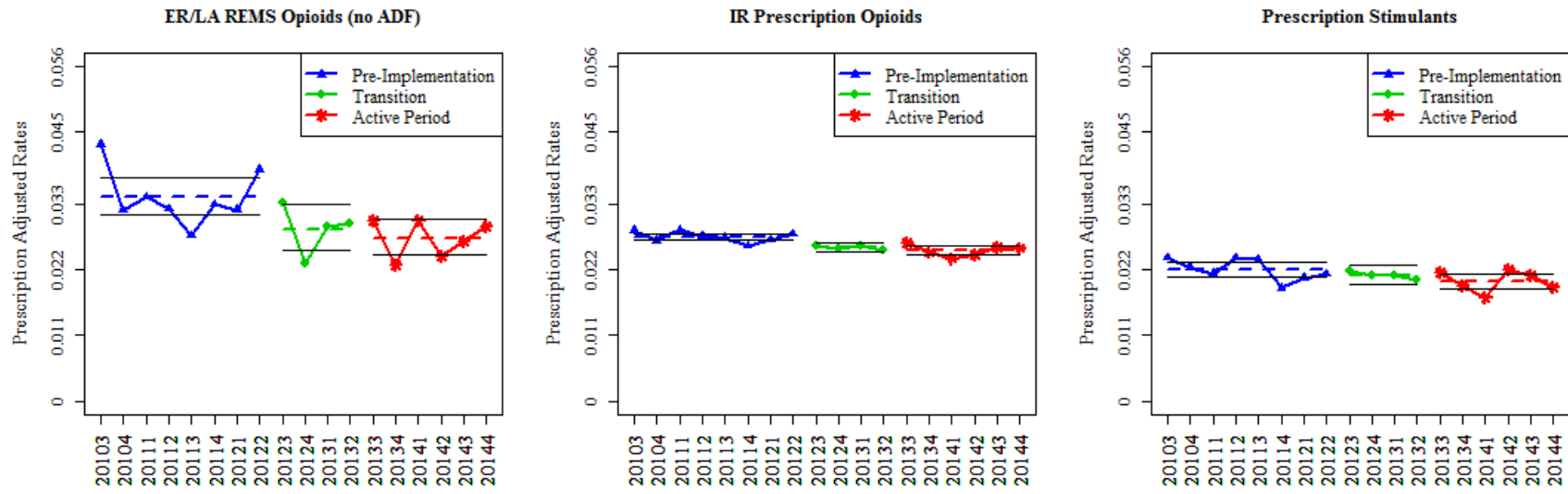


Table 6.1.2.1

The RADARS System Poison Center Program
**Adult Treated/Evaluated and Released Rates per 100,000 Population and per 1,000
Prescriptions Dispensed**
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Pre-Implementation Mean Exposure	Transition Mean Exposure	Active Period Mean Exposure	Active Period to Pre-Implementation % change (95% CI)	p-value for % change	p-value for interaction
Population Adjusted Rates/100,000						
ER/LA REMS Opioids (no ADF)	0.064	0.056	0.054	-15.71%(-27.54%,-1.94%)	0.027	.
IR Prescription Opioids	0.582	0.525	0.489	-16.01%(-19.44%,-12.42%)	<.001	0.965
Prescription Stimulants	0.140	0.146	0.149	6.55%(-0.40%,13.99%)	0.065	0.006
Prescription Adjusted Rates/1,000						
ER/LA REMS Opioids (no ADF)	0.034	0.029	0.027	-20.24%(-30.82%,-8.04%)	0.002	.
IR Prescription Opioids	0.027	0.026	0.025	-8.19%(-11.27%,-5.01%)	<.001	0.060
Prescription Stimulants	0.022	0.021	0.020	-8.66%(-15.85%,-0.87%)	0.030	0.106

The mean ER/LA REMS opioids adult treated/ evaluated and released population rate decreased 15.71% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids adult treated/ evaluated and released population rate decreased 16.01% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adult treated/ evaluated and released population rate is not statistically significant, indicating that the mean difference in adult treated/ evaluated and released population rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for IR prescription opioids (p=0.965).

The mean stimulants adult treated/ evaluated and released population rate increased 6.55% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adult treated/ evaluated and released population rate is statistically significant, indicating that the mean difference in adult treated/ evaluated and released population rates for ER/LA REMS opioids excluding ADFs is significantly different than the mean difference observed for stimulants (p=0.006).

The mean ER/LA REMS opioids adult treated/ evaluated and released prescriptions dispensed rate decreased 20.24% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids adult treated/ evaluated and released prescriptions dispensed rate decreased 8.19% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adult treated/ evaluated and released prescriptions dispensed rate is not statistically significant, indicating that the mean difference in adult treated/ evaluated and released prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for IR prescription opioids ($p=0.060$).

The mean stimulants adult treated/ evaluated and released prescriptions dispensed rate decreased 8.66% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adult treated/ evaluated and released prescriptions dispensed rate is not statistically significant, indicating that the mean difference in adult treated/ evaluated and released prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for stimulants ($p=0.106$).

6.2. Abuse from the RADARS System Poison Center Program

6.2.1. Intentional Abuse Exposures from the RADARS System Poison Center Program

Figure 6.2.1.1 through Figure 6.2.1.2 show the observed and predicted population, prescription dispensed, and dosing unit mean intentional abuse exposure rates and 95% confidence intervals for ER/LA REMS opioids excluding ADFs and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 6.2.1.1

The RADARS System Poison Center Program
Intentional Abuse Exposure Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

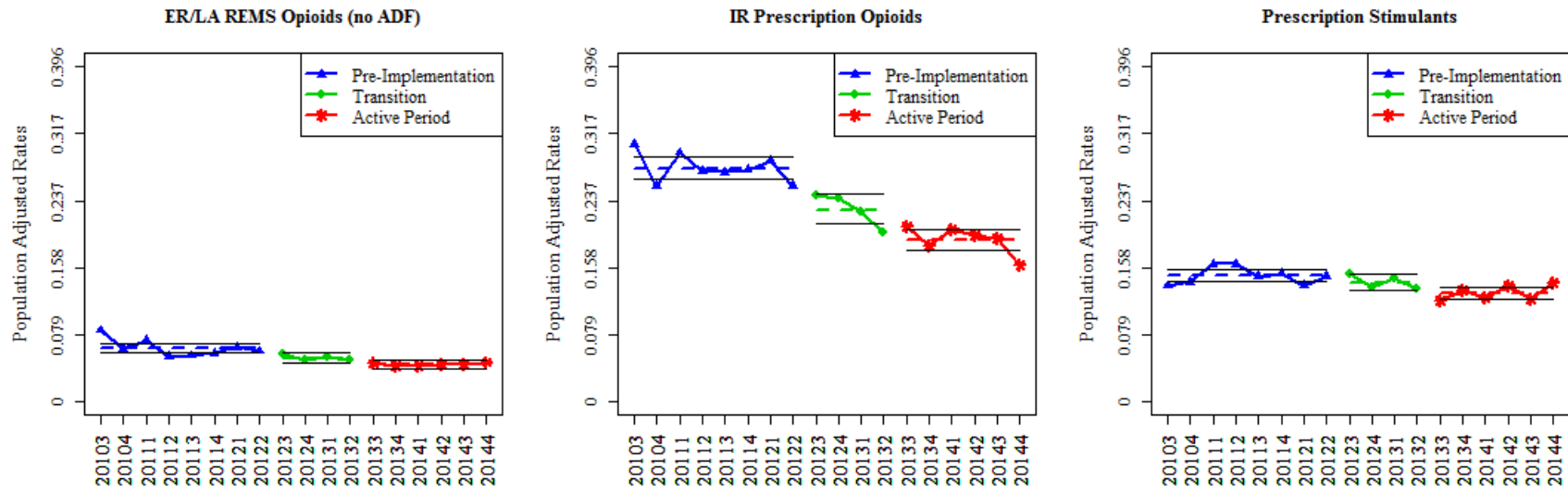


Figure 6.2.1.2
The RADARS System Poison Center Program
Intentional Abuse Exposure Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

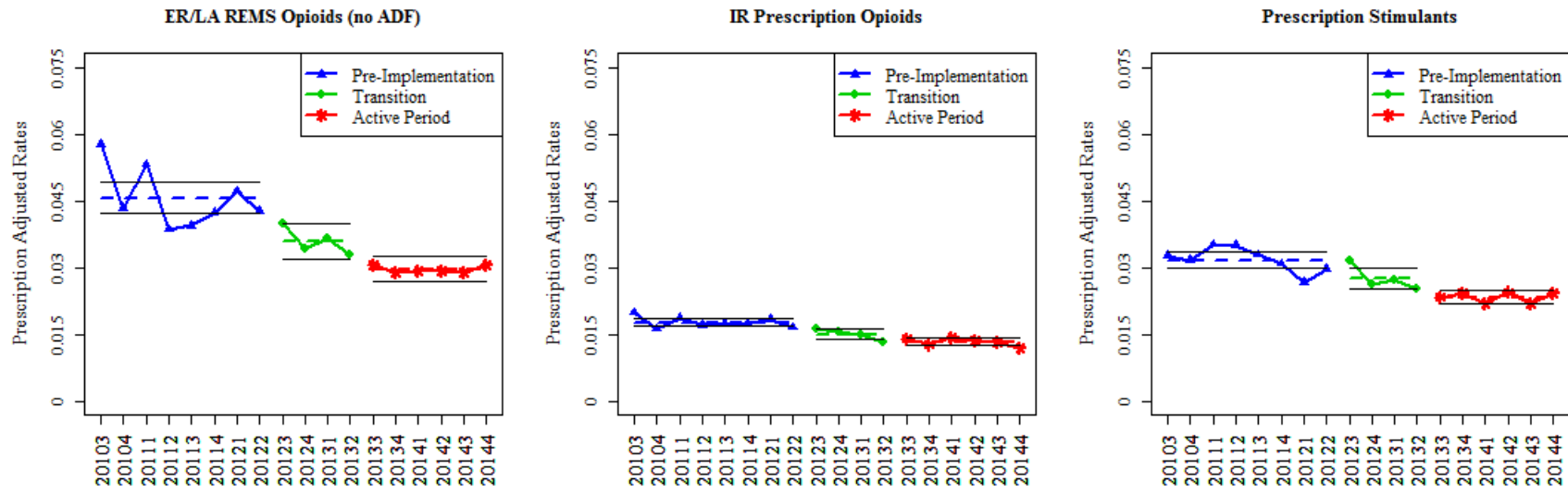


Table 6.2.1.1

The RADARS System Poison Center Program
**Intentional Abuse Exposure Rates per 100,000 Population and per 1,000 Prescriptions
Dispensed**
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Pre-Implementation Mean Exposure	Transition Mean Exposure	Active Period Mean Exposure	Active Period to Pre-Implementation % change (95% CI)	p-value for % change	p-value for interaction
Population Adjusted Rates/100,000						
ER/LA REMS Opioids (no ADF)	0.063	0.051	0.044	-30.77%(-39.35%,-20.97%)	<.001	.
IR Prescription Opioids	0.276	0.227	0.191	-30.89%(-36.40%,-24.90%)	<.001	0.983
Prescription Stimulants	0.148	0.141	0.129	-13.35%(-19.35%,-6.90%)	<.001	0.003
Prescription Adjusted Rates/1,000						
ER/LA REMS Opioids (no ADF)	0.046	0.036	0.030	-34.95%(-42.53%,-26.37%)	<.001	.
IR Prescription Opioids	0.018	0.015	0.013	-24.99%(-30.45%,-19.10%)	<.001	0.054
Prescription Stimulants	0.032	0.028	0.023	-26.25%(-32.50%,-19.41%)	<.001	0.106

The mean ER/LA REMS opioids intentional abuse exposure population rate decreased 30.77% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids intentional abuse exposure population rate decreased 30.89% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the intentional abuse exposure population rate is not statistically significant, indicating that the mean difference in intentional abuse exposure population rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for IR prescription opioids (p=0.983).

The mean stimulants intentional abuse exposure population rate decreased 13.35% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the intentional abuse exposure population rate is statistically significant, indicating that the mean difference in intentional abuse exposure population rates for ER/LA REMS opioids excluding ADFs is significantly different than the mean difference observed for stimulants (p=0.003).

The mean ER/LA REMS opioids intentional abuse exposure prescriptions dispensed rate decreased 34.95% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids intentional abuse exposure prescriptions dispensed rate decreased 24.99% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the intentional abuse exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in intentional abuse exposure prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for IR prescription opioids ($p=0.054$).

The mean stimulants intentional abuse exposure prescriptions dispensed rate decreased 26.25% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the intentional abuse exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in intentional abuse exposure prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for stimulants ($p=0.106$).

6.2.2. Adolescent Intentional Abuse Exposures from the RADARS System Poison Center Program

[Figure 6.2.2.1](#) through [Figure 6.2.2.2](#) show the observed and predicted population, prescription dispensed, and dosing unit mean adolescent intentional abuse exposure rates and 95% confidence intervals for ER/LA REMS opioids excluding ADFs and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 6.2.2.1

The RADARS System Poison Center Program
Adolescent Intentional Abuse Exposure Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

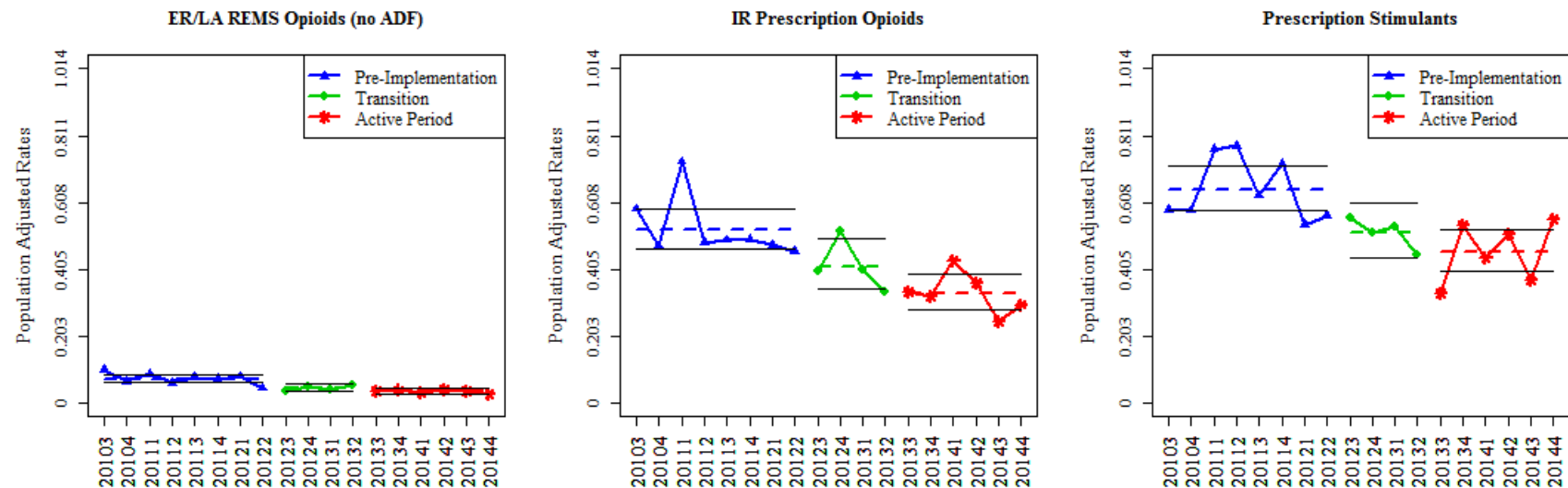


Figure 6.2.2.2

The RADARS System Poison Center Program
Adolescent Intentional Abuse Exposure Rates per 1,000 Prescriptions Dispensed and per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

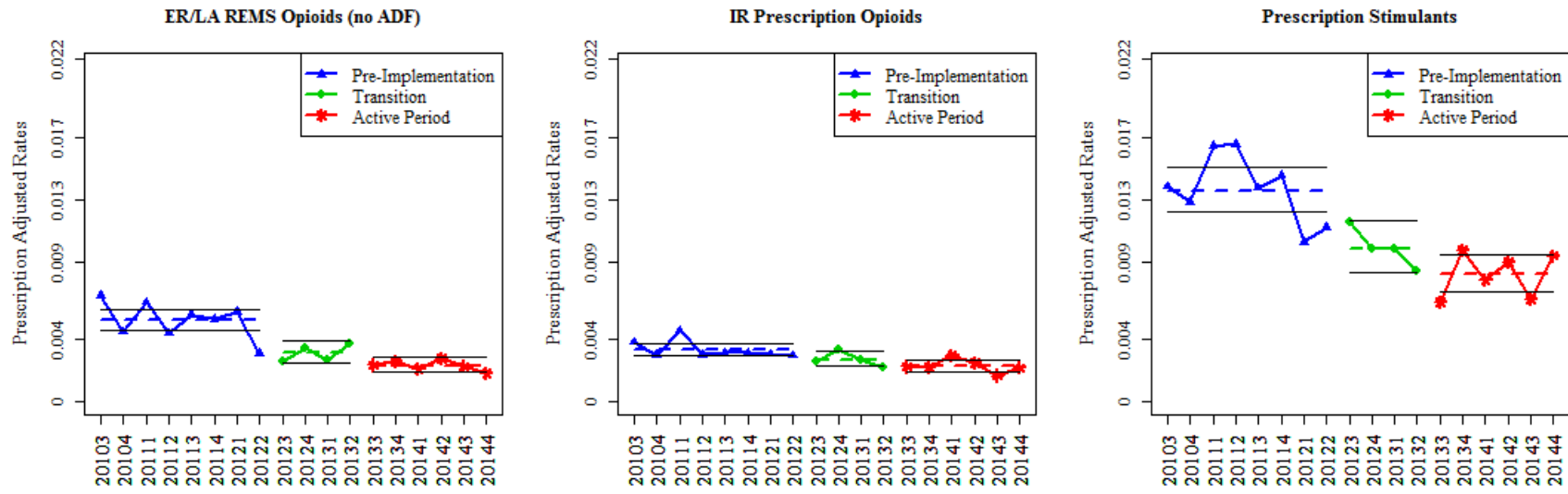


Table 6.2.2.1

The RADARS System Poison Center Program
Adolescent Intentional Abuse Exposure Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Pre-Implementation Mean Exposure	Transition Mean Exposure	Active Period Mean Exposure	Active Period to Pre-Implementation % change (95% CI)	p-value for % change	p-value for interaction
Population Adjusted Rates/100,000						
ER/LA REMS Opioids (no ADF)	0.073	0.045	0.034	-52.85% (-63.20%, -39.58%)	<.001	.
IR Prescription Opioids	0.525	0.415	0.333	-36.62% (-48.01%, -22.73%)	<.001	0.068
Prescription Stimulants	0.647	0.516	0.459	-28.99% (-40.15%, -15.74%)	<.001	0.008
Prescription Adjusted Rates/1,000						
ER/LA REMS Opioids (no ADF)	0.005	0.003	0.002	-55.91% (-65.41%, -43.78%)	<.001	.
IR Prescription Opioids	0.003	0.003	0.002	-31.53% (-43.67%, -16.77%)	<.001	0.006
Prescription Stimulants	0.014	0.010	0.008	-39.84% (-49.63%, -28.15%)	<.001	0.043

The mean ER/LA REMS opioids adolescent intentional abuse exposure population rate decreased 52.85% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids adolescent intentional abuse exposure population rate decreased 36.62% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adolescent intentional abuse exposure population rate is not statistically significant, indicating that the mean difference in adolescent intentional abuse exposure population rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for IR prescription opioids (p=0.068).

The mean stimulants adolescent intentional abuse exposure population rate decreased 28.99% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adolescent intentional abuse exposure population rate is statistically significant, indicating that the mean difference in adolescent intentional abuse exposure population rates for ER/LA REMS opioids excluding ADFs is significantly different than the mean difference observed for stimulants (p=0.008).

The mean ER/LA REMS opioids adolescent intentional abuse exposure prescriptions dispensed rate decreased 55.91% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids adolescent intentional abuse exposure prescriptions dispensed rate decreased 31.53% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adolescent intentional abuse exposure prescriptions dispensed rate is statistically significant, indicating that the mean difference in adolescent intentional abuse exposure prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is significantly different than the mean difference observed for IR prescription opioids ($p=0.006$).

The mean stimulants adolescent intentional abuse exposure prescriptions dispensed rate decreased 39.84% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adolescent intentional abuse exposure prescriptions dispensed rate is statistically significant, indicating that the mean difference in adolescent intentional abuse exposure prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is significantly different than the mean difference observed for stimulants ($p=0.043$).

6.3. Misuse from the RADARS System Poison Center Program

6.3.1. Misuse Exposures from the RADARS System Poison Center Program

Figure 6.3.1.1 through Figure 6.3.1.2 show the observed and predicted population, prescription dispensed, and dosing unit mean misuse exposure rates and 95% confidence intervals for ER/LA REMS opioids excluding ADFs and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 6.3.1.1

The RADARS System Poison Center Program
Misuse Exposure Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

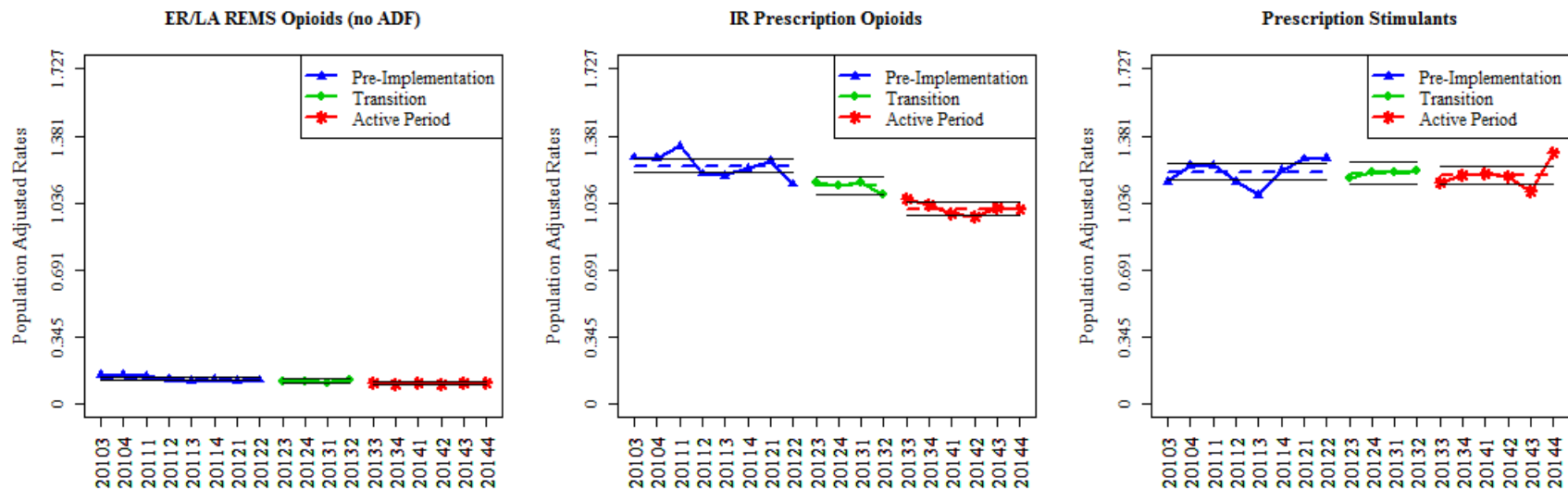


Figure 6.3.1.2

The RADARS System Poison Center Program
Misuse Exposure Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

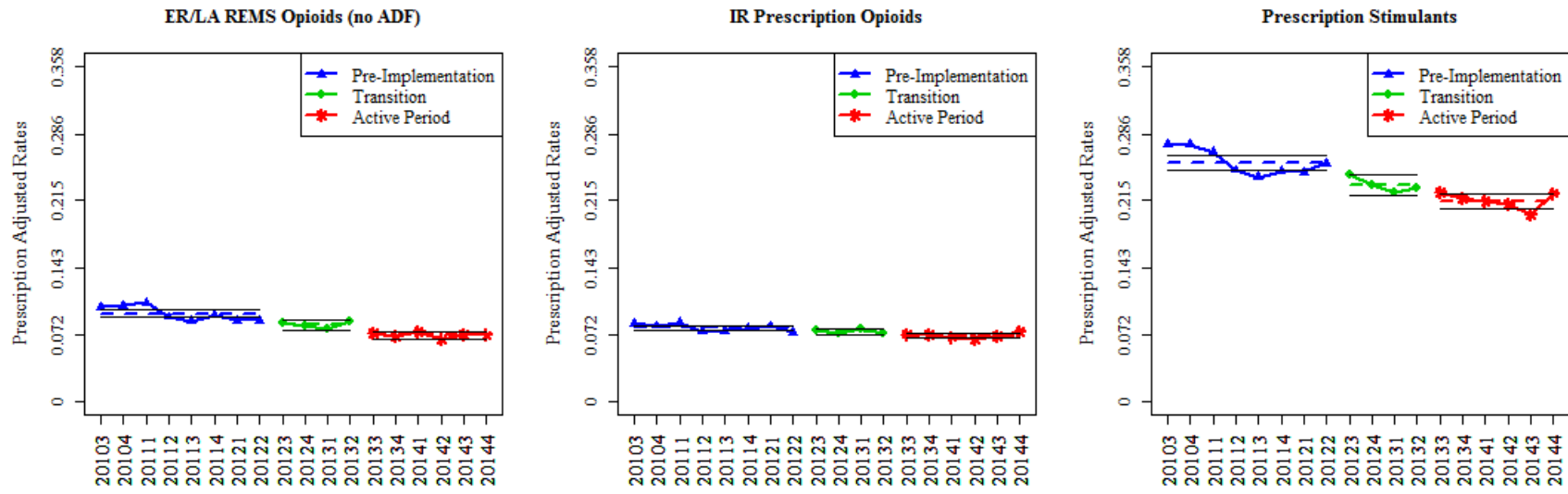


Table 6.3.1.1

The RADARS System Poison Center Program
Misuse Exposure Rates per 100,000 Population and per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Pre-Implementation Mean Exposure	Transition Mean Exposure	Active Period Mean Exposure	Active Period to Pre-Implementation % change (95% CI)	p-value for % change	p-value for interaction
Population Adjusted Rates/100,000						
ER/LA REMS Opioids (no ADF)	0.129	0.116	0.104	-19.94%(-26.29%,-13.04%)	<.001	.
IR Prescription Opioids	1.227	1.124	1.006	-17.94%(-21.54%,-14.19%)	<.001	0.608
Prescription Stimulants	1.195	1.186	1.177	-1.46%(-6.57%,3.94%)	0.589	<.001
Prescription Adjusted Rates/1,000						
ER/LA REMS Opioids (no ADF)	0.094	0.082	0.071	-24.78%(-29.96%,-19.21%)	<.001	.
IR Prescription Opioids	0.079	0.075	0.070	-10.94%(-14.98%,-6.71%)	<.001	<.001
Prescription Stimulants	0.256	0.231	0.214	-16.12%(-20.14%,-11.90%)	<.001	0.014

The mean ER/LA REMS opioids misuse exposure population rate decreased 19.94% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids misuse exposure population rate decreased 17.94% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the misuse exposure population rate is not statistically significant, indicating that the mean difference in misuse exposure population rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for IR prescription opioids (p=0.608).

The mean stimulants misuse exposure population rate decreased 1.46% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the misuse exposure population rate is statistically significant, indicating that the mean difference in misuse exposure population rates for ER/LA REMS opioids excluding ADFs is significantly different than the mean difference observed for stimulants (p<0.001).

The mean ER/LA REMS opioids misuse exposure prescriptions dispensed rate decreased 24.78% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids misuse exposure prescriptions dispensed rate decreased 10.94% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the misuse exposure prescriptions dispensed rate is statistically significant,

indicating that the mean difference in misuse exposure prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is significantly different than the mean difference observed for IR prescription opioids ($p < 0.001$).

The mean stimulants misuse exposure prescriptions dispensed rate decreased 16.12% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the misuse exposure prescriptions dispensed rate is statistically significant, indicating that the mean difference in misuse exposure prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is significantly different than the mean difference observed for stimulants ($p = 0.014$).

6.3.2. Adult Unintentional Exposures from the RADARS System Poison Center Program

Figure 6.3.2.1 through Figure 6.3.2.2 show the observed and predicted population, prescription dispensed, and dosing unit mean adult unintentional exposure rates and 95% confidence intervals for ER/LA REMS opioids excluding ADFs and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 6.3.2.1

The RADARS System Poison Center Program
Adult Unintentional Exposure Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

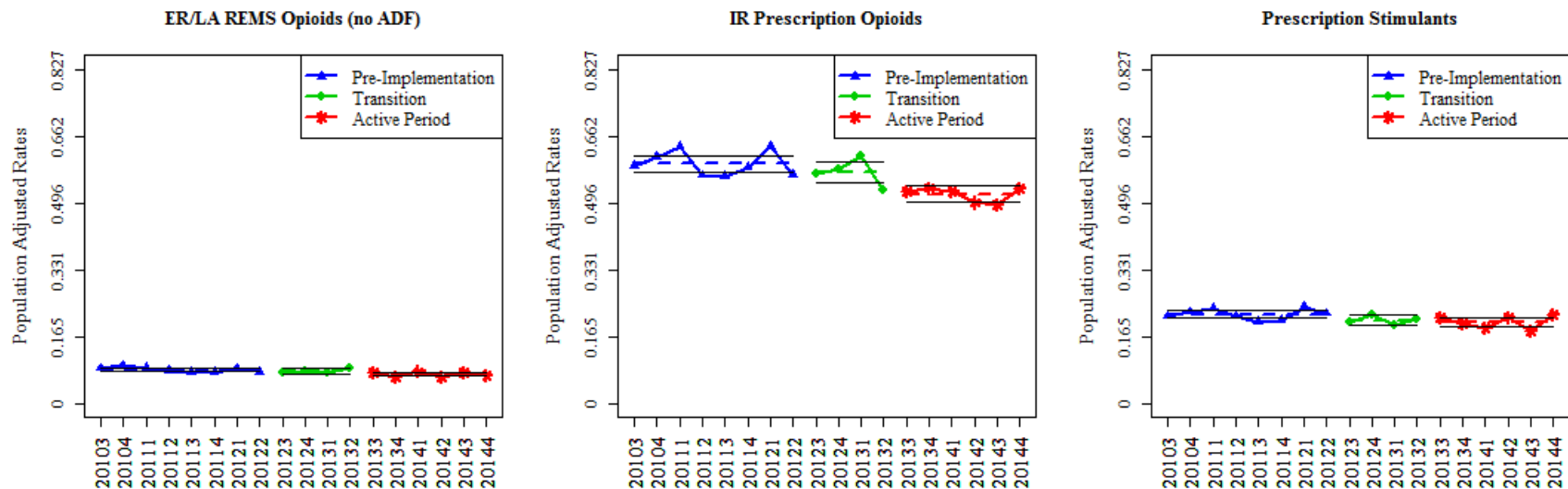


Figure 6.3.2.2
The RADARS System Poison Center Program
Adult Unintentional Exposure Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

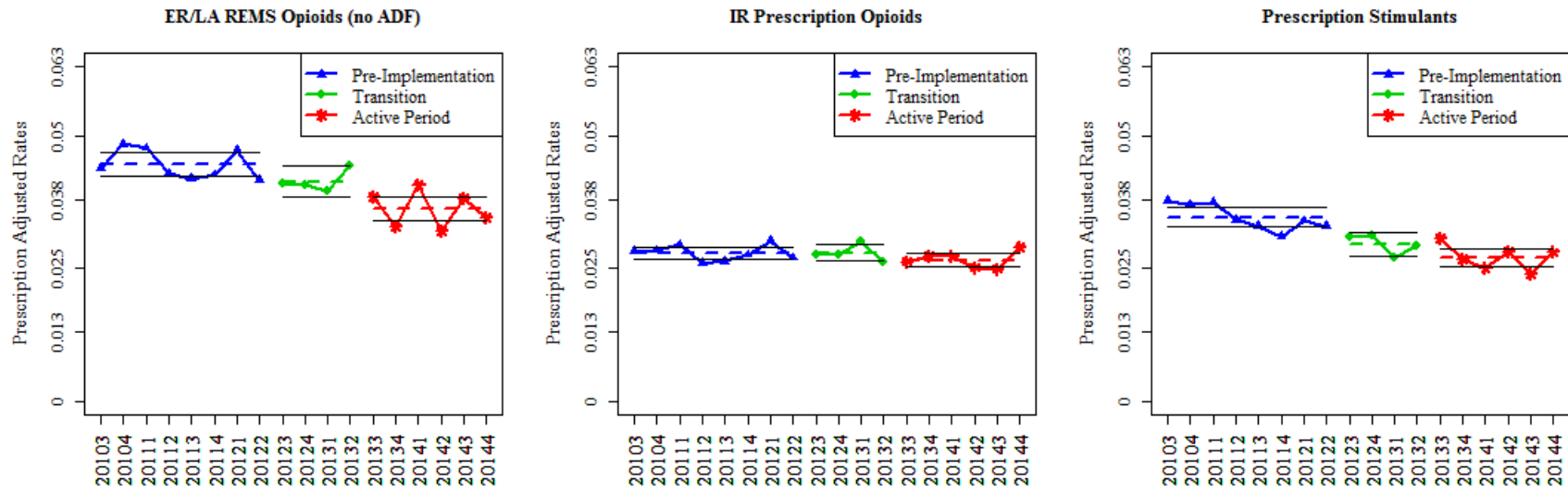


Table 6.3.2.1

The RADARS System Poison Center Program
**Adult Unintentional Exposure Rates per 100,000 Population and per 1,000 Prescriptions
Dispensed**
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Pre-Implementation Mean Exposure	Transition Mean Exposure	Active Period Mean Exposure	Active Period to Pre-Implementation % change (95% CI)	p-value for % change	p-value for interaction
Population Adjusted Rates/100,000						
ER/LA REMS Opioids (no ADF)	0.084	0.080	0.072	-14.15%(-21.02%,-6.69%)	<.001	.
IR Prescription Opioids	0.593	0.572	0.517	-12.77%(-17.19%,-8.13%)	<.001	0.750
Prescription Stimulants	0.221	0.206	0.202	-8.65%(-14.88%,-1.96%)	0.012	0.265
Prescription Adjusted Rates/1,000						
ER/LA REMS Opioids (no ADF)	0.045	0.042	0.036	-18.77%(-24.87%,-12.18%)	<.001	.
IR Prescription Opioids	0.028	0.028	0.027	-4.66%(-10.11%,1.13%)	0.112	0.001
Prescription Stimulants	0.035	0.030	0.027	-21.70%(-27.79%,-15.09%)	<.001	0.523

The mean ER/LA REMS opioids adult unintentional exposure population rate decreased 14.15% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids adult unintentional exposure population rate decreased 12.77% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adult unintentional exposure population rate is not statistically significant, indicating that the mean difference in adult unintentional exposure population rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for IR prescription opioids (p=0.750).

The mean stimulants adult unintentional exposure population rate decreased 8.65% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adult unintentional exposure population rate is not statistically significant, indicating that the mean difference in adult unintentional exposure population rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for stimulants (p=0.265).

The mean ER/LA REMS opioids adult unintentional exposure prescriptions dispensed rate decreased 18.77% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids adult unintentional exposure prescriptions dispensed rate decreased 4.66% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adult unintentional exposure prescriptions dispensed rate is statistically significant, indicating that the mean difference in adult unintentional exposure prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is significantly different than the mean difference observed for IR prescription opioids ($p=0.001$).

The mean stimulants adult unintentional exposure prescriptions dispensed rate decreased 21.70% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the adult unintentional exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in adult unintentional exposure prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for stimulants ($p=0.523$).

6.3.3. Child and Adolescent Unintentional Exposures from the RADARS System Poison Center Program

[Figure 6.3.3.1](#) through [Figure 6.3.3.2](#) show the observed and predicted population, prescription dispensed, and dosing unit mean child and adolescent unintentional exposure rates and 95% confidence intervals for ER/LA REMS opioids excluding ADFs and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 6.3.3.1

The RADARS System Poison Center Program
Child and Adolescent Unintentional Exposure Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

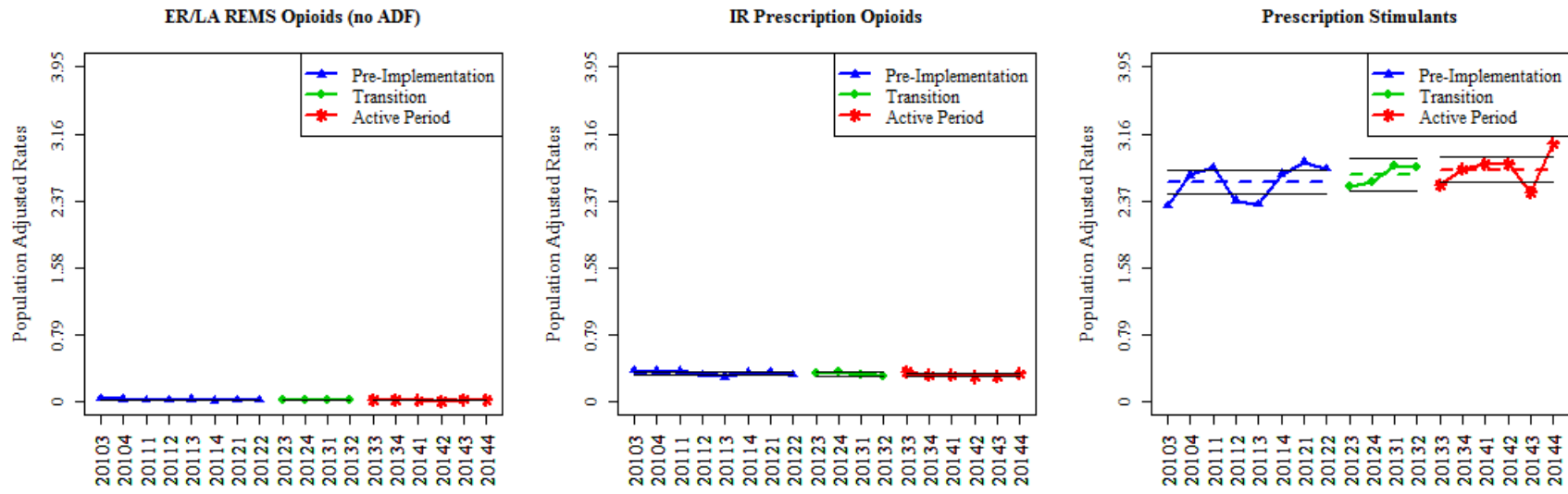


Figure 6.3.3.2

The RADARS System Poison Center Program

Child and Adolescent Unintentional Exposure Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

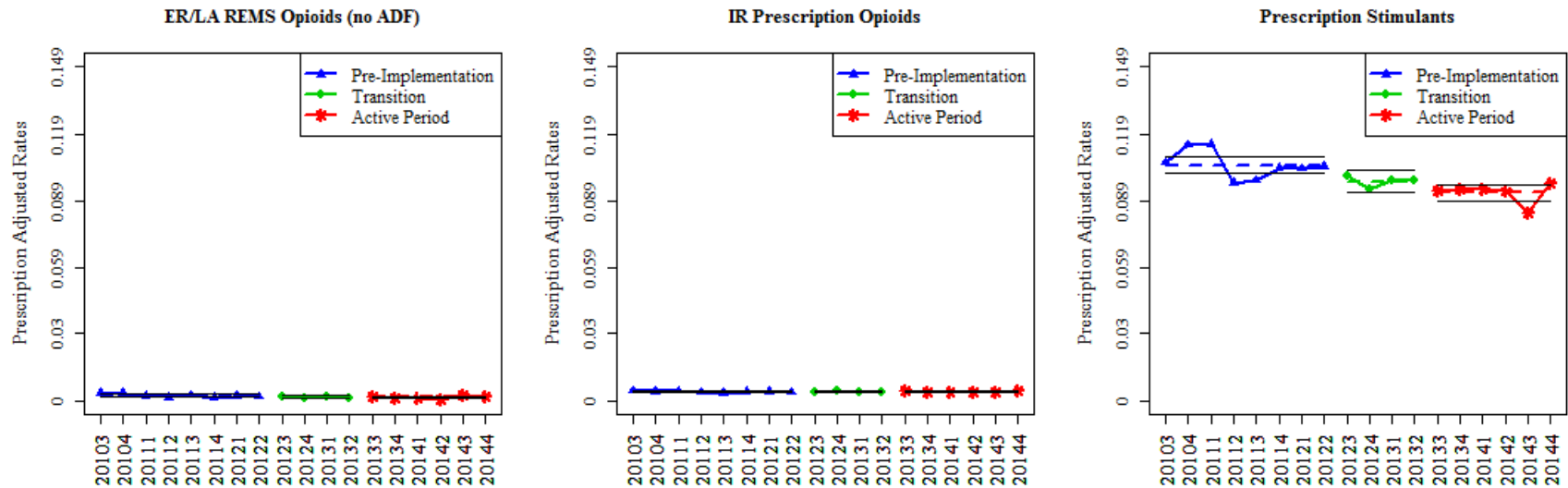


Table 6.3.3.1

The RADARS System Poison Center Program
**Child and Adolescent Unintentional Exposure Rates per 100,000 Population and per 1,000
Prescriptions Dispensed**
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Pre-Implementation Mean Exposure	Transition Mean Exposure	Active Period Mean Exposure	Active Period to Pre-Implementation % change (95% CI)	p-value for % change	p-value for interaction
Population Adjusted Rates/100,000						
ER/LA REMS Opioids (no ADF)	0.017	0.012	0.012	-25.69%(-52.04%,15.16%)	0.184	.
IR Prescription Opioids	0.334	0.323	0.309	-7.39%(-14.28%,0.04%)	0.051	0.332
Prescription Stimulants	2.590	2.674	2.735	5.60%(-2.28%,14.11%)	0.168	0.122
Prescription Adjusted Rates/1,000						
ER/LA REMS Opioids (no ADF)	0.002	0.002	0.002	-31.44%(-55.03%,4.53%)	0.079	.
IR Prescription Opioids	0.004	0.004	0.004	-1.31%(-9.20%,7.26%)	0.757	0.097
Prescription Stimulants	0.105	0.098	0.093	-11.75%(-16.35%,-6.89%)	<.001	0.244

The mean ER/LA REMS opioids child and adolescent unintentional exposure population rate decreased 25.69% between the Pre-Implementation and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids child and adolescent unintentional exposure population rate decreased 7.39% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the child and adolescent unintentional exposure population rate is not statistically significant, indicating that the mean difference in child and adolescent unintentional exposure population rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for IR prescription opioids (p=0.332).

The mean stimulants child and adolescent unintentional exposure population rate increased 5.60% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the child and adolescent unintentional exposure population rate is not statistically significant, indicating that the mean difference in child and adolescent unintentional exposure population rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for stimulants (p=0.122).

The mean ER/LA REMS opioids child and adolescent unintentional exposure prescriptions dispensed rate decreased 31.44% between the Pre-Implementation and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids child and adolescent unintentional exposure prescriptions dispensed rate decreased 1.31% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the child and adolescent unintentional exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in child and adolescent unintentional exposure prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for IR prescription opioids ($p=0.097$).

The mean stimulants child and adolescent unintentional exposure prescriptions dispensed rate decreased 11.75% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the child and adolescent unintentional exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in child and adolescent unintentional exposure prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for stimulants ($p=0.244$).

6.3.4. Pediatric Unintentional Exposures from the RADARS System Poison Center Program

Figure 6.3.4.1 through Figure 6.3.4.2 show the observed and predicted population, prescription dispensed, and dosing unit mean pediatric unintentional exposure rates and 95% confidence intervals for ER/LA REMS opioids excluding ADFs and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 6.3.4.1

The RADARS System Poison Center Program
Pediatric Unintentional Exposure Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

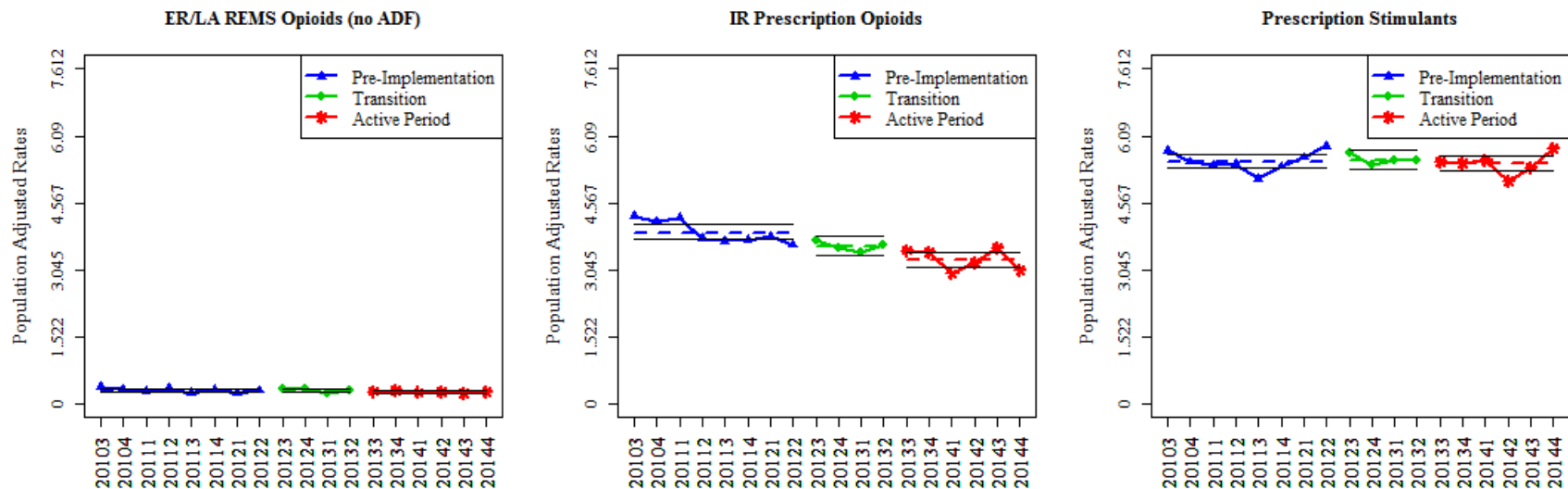


Figure 6.3.4.2

The RADARS System Poison Center Program
Pediatric Unintentional Exposure Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

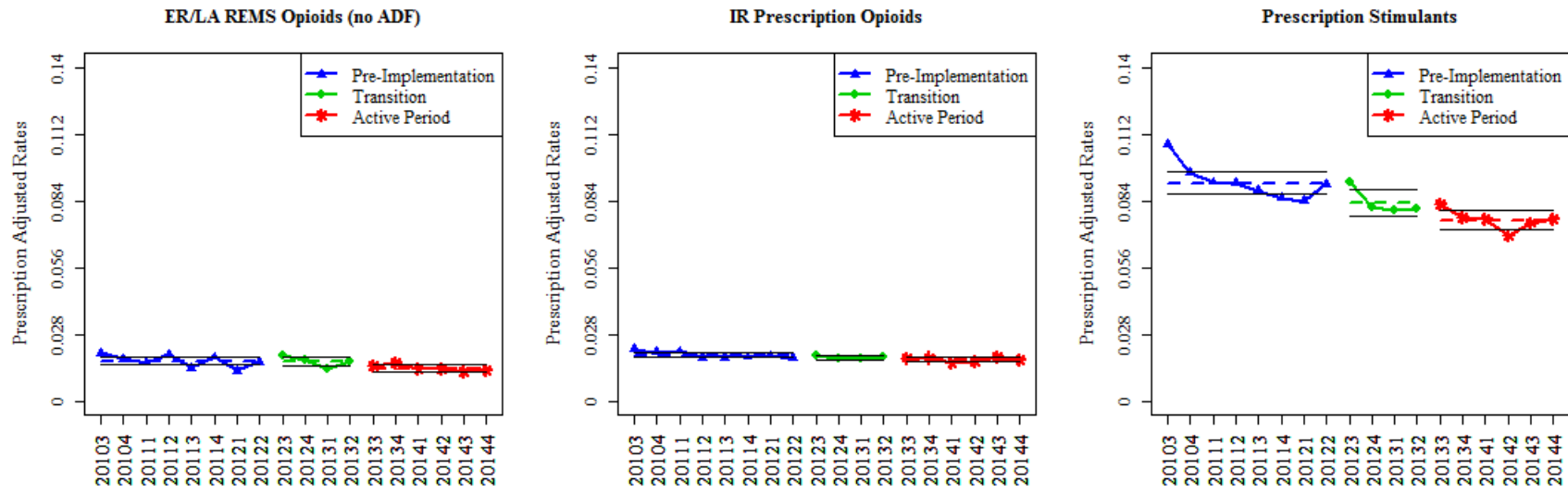


Table 6.3.4.1

The RADARS System Poison Center Program
**Pediatric Unintentional Exposure Rates per 100,000 Population and per 1,000
Prescriptions Dispensed**
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Pre-Implementation Mean Exposure	Transition Mean Exposure	Active Period Mean Exposure	Active Period to Pre-Implementation % change (95% CI)	p-value for % change	p-value for interaction
Population Adjusted Rates/100,000						
ER/LA REMS Opioids (no ADF)	0.301	0.306	0.266	-11.72%(-24.03%,2.59%)	0.104	.
IR Prescription Opioids	3.895	3.578	3.277	-15.89%(-21.52%,-9.84%)	<.001	0.567
Prescription Stimulants	5.511	5.543	5.453	-1.05%(-5.09%,3.16%)	0.619	0.151
Prescription Adjusted Rates/1,000						
ER/LA REMS Opioids (no ADF)	0.017	0.017	0.014	-18.20%(-29.33%,-5.31%)	0.007	.
IR Prescription Opioids	0.019	0.018	0.018	-9.96%(-15.78%,-3.74%)	0.002	0.242
Prescription Stimulants	0.092	0.083	0.076	-16.94%(-22.79%,-10.65%)	<.001	0.855

The mean ER/LA REMS opioids pediatric unintentional exposure population rate decreased 11.72% between the Pre-Implementation and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional exposure population rate decreased 15.89% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional exposure population rate is not statistically significant, indicating that the mean difference in pediatric unintentional exposure population rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for IR prescription opioids (p=0.567).

The mean stimulants pediatric unintentional exposure population rate decreased 1.05% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional exposure population rate is not statistically significant, indicating that the mean difference in pediatric unintentional exposure population rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for stimulants (p=0.151).

The mean ER/LA REMS opioids pediatric unintentional exposure prescriptions dispensed rate decreased 18.20% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids pediatric unintentional exposure prescriptions dispensed rate decreased 9.96% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional exposure prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for IR prescription opioids ($p=0.242$).

The mean stimulants pediatric unintentional exposure prescriptions dispensed rate decreased 16.94% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional exposure prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for stimulants ($p=0.855$).

6.3.5. Pediatric Unintentional General Exposures from the RADARS System Poison Center Program

[Figure 6.3.5.1](#) through [Figure 6.3.5.2](#) show the observed and predicted population, prescription dispensed, and dosing unit mean pediatric unintentional general exposure rates and 95% confidence intervals for ER/LA REMS opioids excluding ADFs and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 6.3.5.1

The RADARS System Poison Center Program
Pediatric Unintentional General Exposure Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

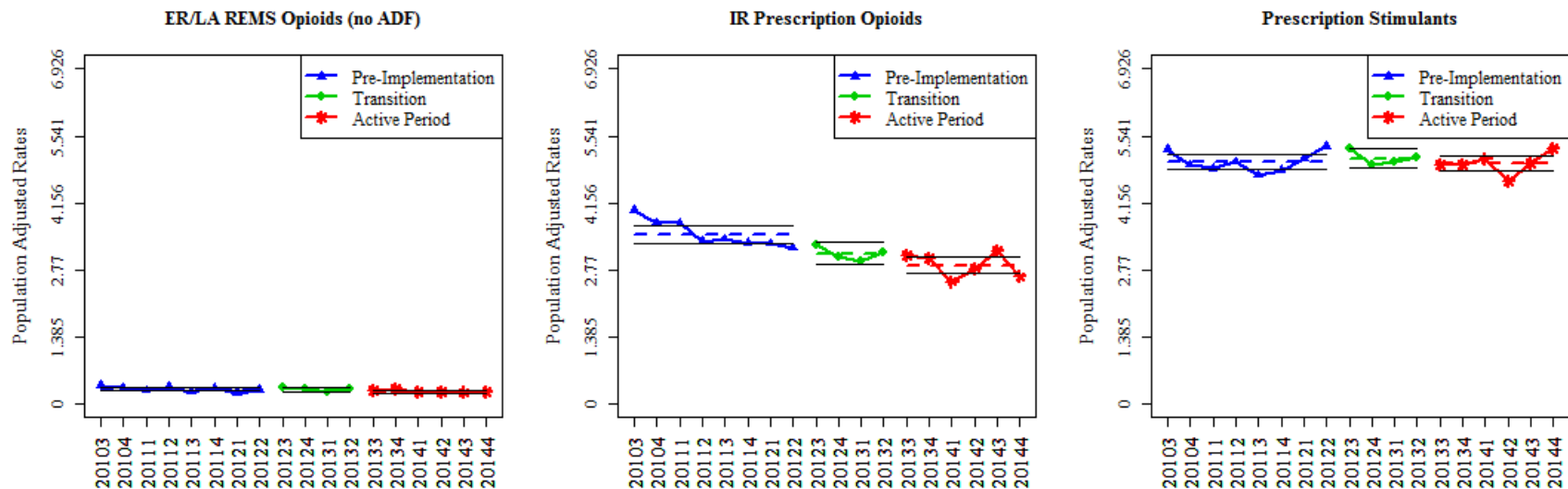


Figure 6.3.5.2

The RADARS System Poison Center Program

Pediatric Unintentional General Exposure Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

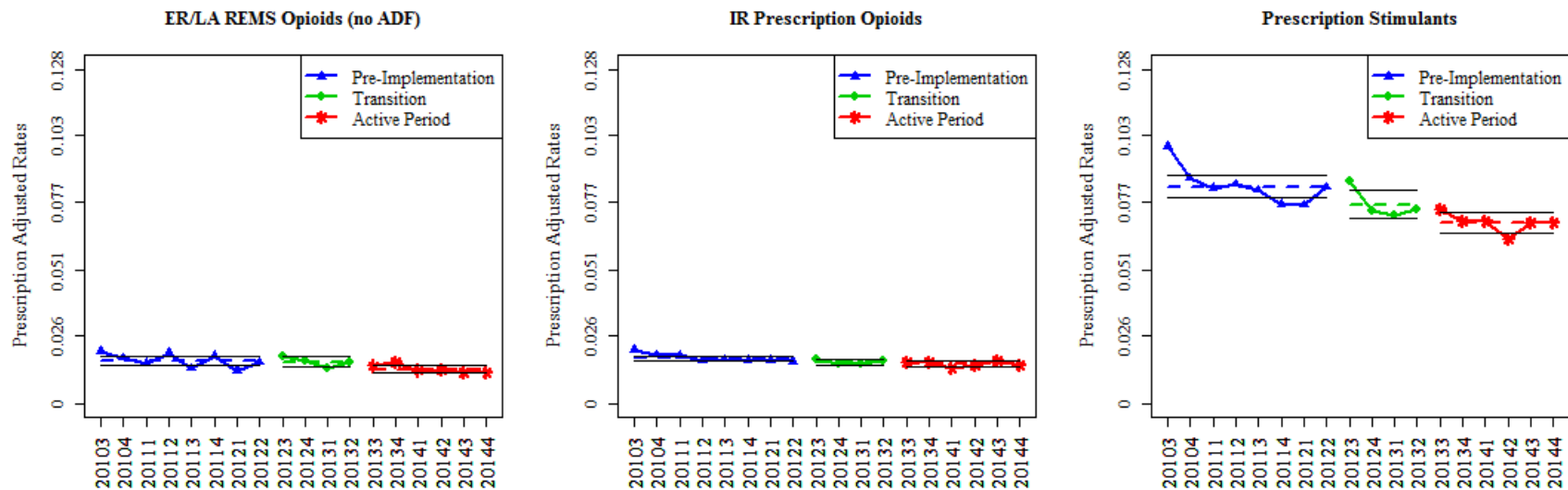


Table 6.3.5.1

The RADARS System Poison Center Program
**Pediatric Unintentional General Exposure Rates per 100,000 Population and per 1,000
Prescriptions Dispensed**
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Pre-Implementation Mean Exposure	Transition Mean Exposure	Active Period Mean Exposure	Active Period to Pre-Implementation % change (95% CI)	p-value for % change	p-value for interaction
Population Adjusted Rates/100,000						
ER/LA REMS Opioids (no ADF)	0.293	0.293	0.255	-13.16%(-25.82%,1.66%)	0.079	.
IR Prescription Opioids	3.504	3.102	2.864	-18.27%(-24.71%,-11.28%)	<.001	0.504
Prescription Stimulants	5.001	5.075	4.967	-0.69%(-4.86%,3.67%)	0.753	0.107
Prescription Adjusted Rates/1,000						
ER/LA REMS Opioids (no ADF)	0.017	0.016	0.013	-19.53%(-31.02%,-6.14%)	0.006	.
IR Prescription Opioids	0.018	0.016	0.015	-12.51%(-19.25%,-5.22%)	0.001	0.345
Prescription Stimulants	0.083	0.076	0.069	-16.63%(-22.76%,-10.02%)	<.001	0.686

The mean ER/LA REMS opioids pediatric unintentional general exposure population rate decreased 13.16% between the Pre-Implementation and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure population rate decreased 18.27% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure population rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure population rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for IR prescription opioids (p=0.504).

The mean stimulants pediatric unintentional general exposure population rate decreased 0.69% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure population rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure population rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for stimulants (p=0.107).

The mean ER/LA REMS opioids pediatric unintentional general exposure prescriptions dispensed rate decreased 19.53% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure prescriptions dispensed rate decreased 12.51% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for IR prescription opioids ($p=0.345$).

The mean stimulants pediatric unintentional general exposure prescriptions dispensed rate decreased 16.63% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for stimulants ($p=0.686$).

6.3.6. Pediatric Unintentional General Exposures Resulting in a Major Medical Outcome, Hospitalization or Death from the RADARS System Poison Center Program

Figure 6.3.6.1 through Figure 6.3.6.2 show the observed and predicted population, prescription dispensed, and dosing unit mean pediatric unintentional general exposures resulting in a major medical outcome, hospitalization, or death rates and 95% confidence intervals for ER/LA REMS opioids excluding ADFs and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 6.3.6.1

The RADARS System Poison Center Program
Pediatric Unintentional General Exposures Resulting in a Major Medical Outcome, Hospitalization or Death
Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

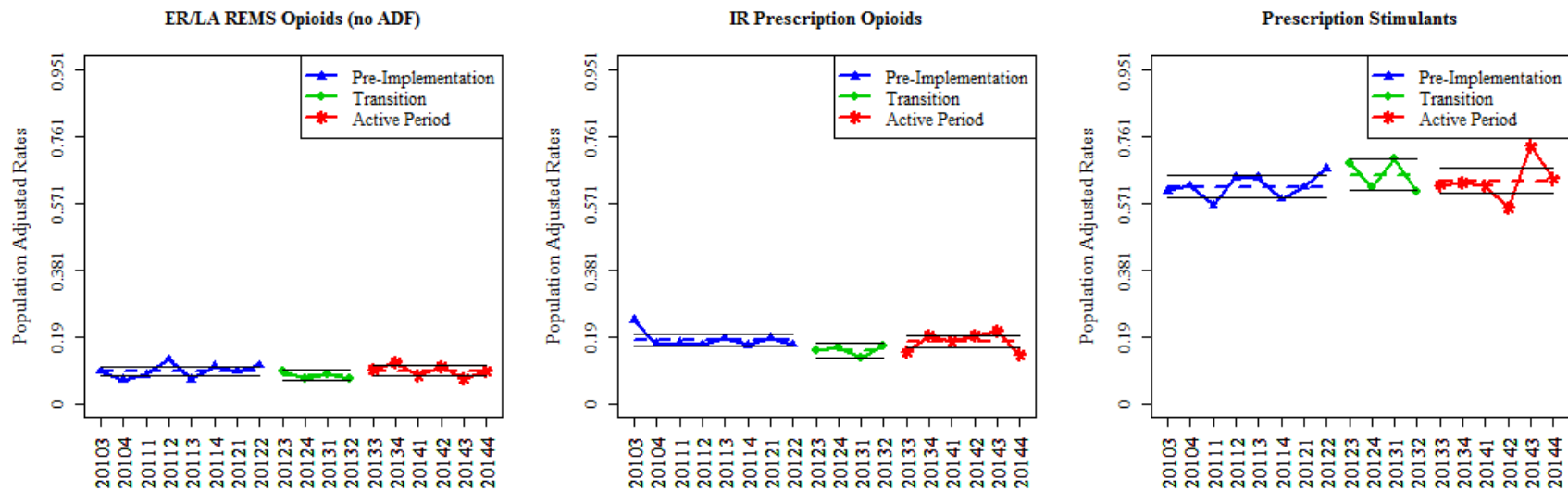


Figure 6.3.6.2

The RADARS System Poison Center Program
Pediatric Unintentional General Exposures Resulting in a Major Medical Outcome, Hospitalization or Death
Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

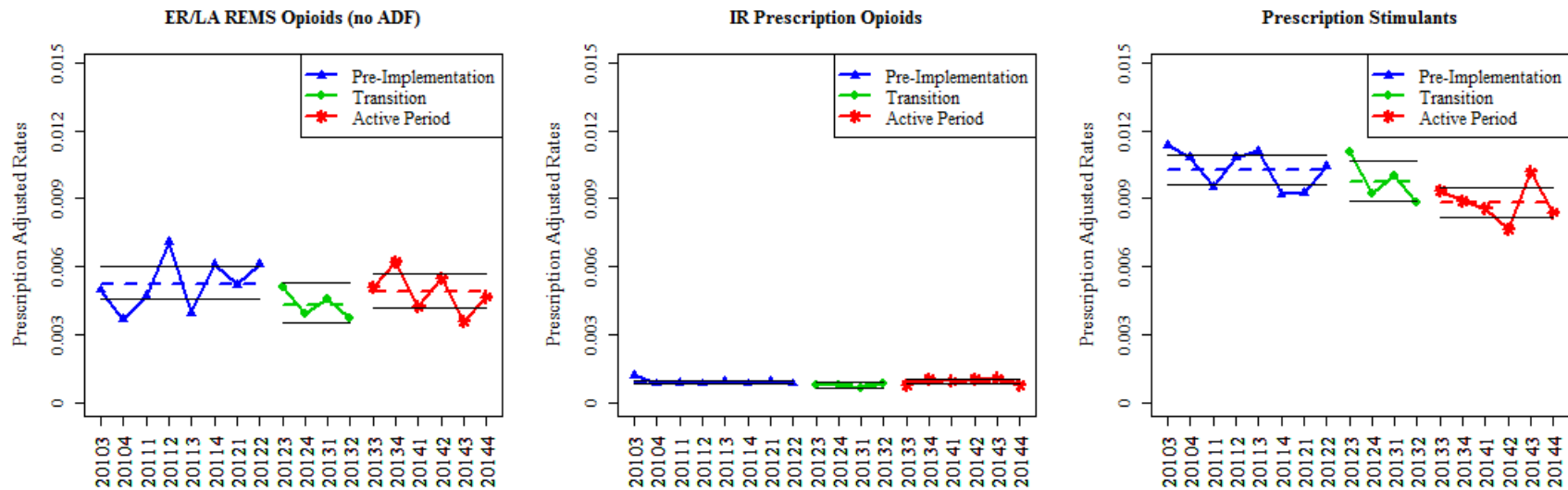


Table 6.3.6.1

The RADARS System Poison Center Program
**Pediatric Unintentional General Exposures Resulting in a Major Medical Outcome,
Hospitalization or Death**
Rates per 100,000 Population and per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Pre-Implementation Mean Exposure	Transition Mean Exposure	Active Period Mean Exposure	Active Period to Pre-Implementation % change (95% CI)	p-value for % change	p-value for interaction
Population Adjusted Rates/100,000						
ER/LA REMS Opioids (no ADF)	0.093	0.080	0.094	0.87%(-17.27%,23.00%)	0.931	.
IR Prescription Opioids	0.182	0.150	0.176	-3.29%(-16.01%,11.36%)	0.642	0.734
Prescription Stimulants	0.618	0.649	0.633	2.48%(-5.02%,10.57%)	0.527	0.884
Prescription Adjusted Rates/1,000						
ER/LA REMS Opioids (no ADF)	0.005	0.004	0.005	-6.53%(-23.88%,14.79%)	0.520	.
IR Prescription Opioids	<.001	<.001	<.001	3.52%(-10.05%,19.14%)	0.629	0.421
Prescription Stimulants	0.010	0.010	0.009	-13.97%(-21.99%,-5.14%)	0.003	0.474

The mean ER/LA REMS opioids pediatric unintentional general exposures resulting in a major medical outcome, hospitalization, or death population rate increased 0.87% between the Pre-Implementation and Active Period time periods. This increase is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposures resulting in a major medical outcome, hospitalization, or death population rate decreased 3.29% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposures resulting in a major medical outcome, hospitalization, or death population rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposures resulting in a major medical outcome, hospitalization, or death population rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for IR prescription opioids (p=0.734).

The mean stimulants pediatric unintentional general exposures resulting in a major medical outcome, hospitalization, or death population rate increased 2.48% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposures resulting in a major medical outcome, hospitalization, or death population rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposures resulting in a major medical outcome, hospitalization,

or death population rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for stimulants ($p=0.884$).

The mean ER/LA REMS opioids pediatric unintentional general exposures resulting in a major medical outcome, hospitalization, or death prescriptions dispensed rate decreased 6.53% between the Pre-Implementation and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposures resulting in a major medical outcome, hospitalization, or death prescriptions dispensed rate increased 3.52% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposures resulting in a major medical outcome, hospitalization, or death prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposures resulting in a major medical outcome, hospitalization, or death prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for IR prescription opioids ($p=0.421$).

The mean stimulants pediatric unintentional general exposures resulting in a major medical outcome, hospitalization, or death prescriptions dispensed rate decreased 13.97% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposures resulting in a major medical outcome, hospitalization, or death prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposures resulting in a major medical outcome, hospitalization, or death prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for stimulants ($p=0.474$).

6.3.7. Pediatric Unintentional General Exposures Treated/Evaluated and Released from the RADARS System Poison Center Program

Figure 6.3.7.1 through Figure 6.3.7.2 show the observed and predicted population, prescription dispensed, and dosing unit mean pediatric unintentional general exposure treated/evaluated and released rates and 95% confidence intervals for ER/LA REMS opioids excluding ADFs and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 6.3.7.1

The RADARS System Poison Center Program
Pediatric Unintentional General Exposure Treated/Evaluated and Released
Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

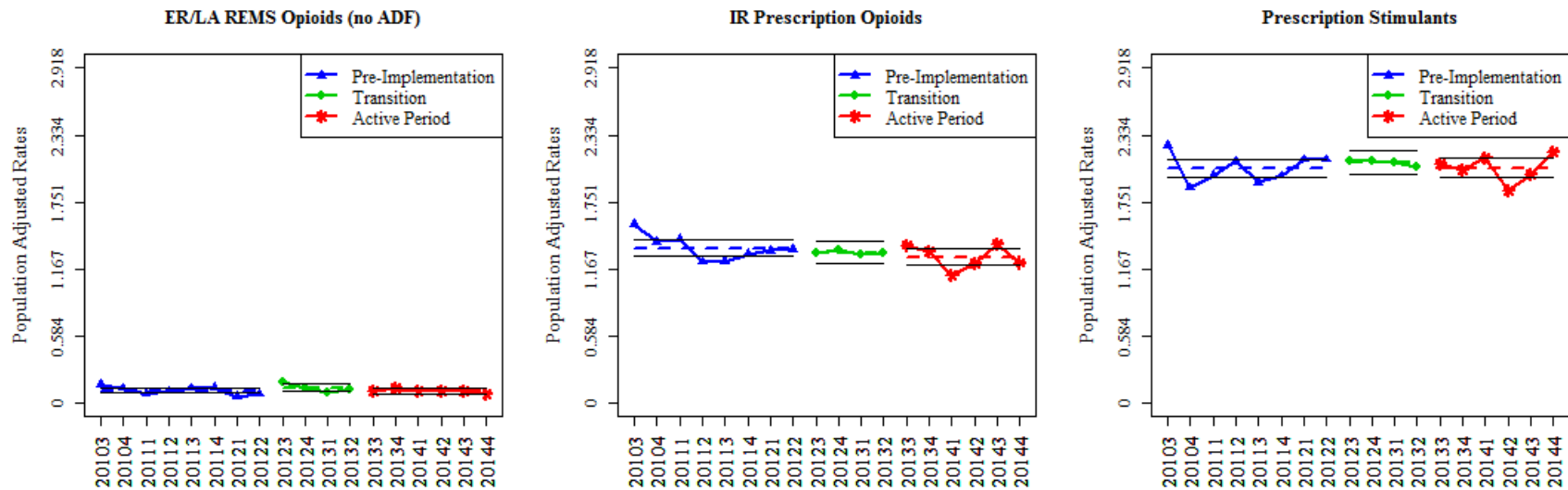


Figure 6.3.7.2

The RADARS System Poison Center Program

**Pediatric Unintentional General Exposure Treated/Evaluated and Released
Rates per 1,000 Prescriptions Dispensed**

From Third Quarter 2010 to Fourth Quarter 2014

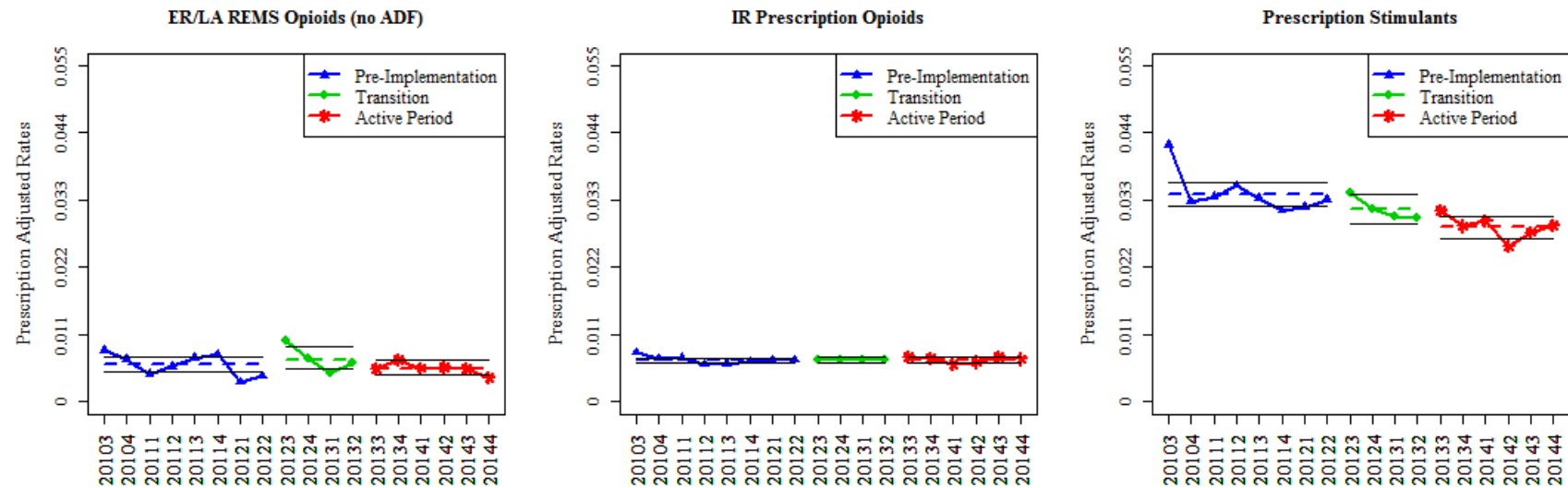


Table 6.3.7.1

The RADARS System Poison Center Program
Pediatric Unintentional General Exposure Treated/Evaluated and Released
Rates per 100,000 Population and per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Pre-Implementation Mean Exposure	Transition Mean Exposure	Active Period Mean Exposure	Active Period to Pre-Implementation % change (95% CI)	p-value for % change	p-value for interaction
Population Adjusted Rates/100,000						
ER/LA REMS Opioids (no ADF)	0.105	0.127	0.103	-2.61%(-28.13%,31.97%)	0.864	.
IR Prescription Opioids	1.349	1.307	1.271	-5.77%(-12.81%,1.83%)	0.133	0.837
Prescription Stimulants	2.043	2.092	2.046	0.15%(-5.32%,5.94%)	0.958	0.859
Prescription Adjusted Rates/1,000						
ER/LA REMS Opioids (no ADF)	0.006	0.007	0.005	-9.76%(-33.42%,22.32%)	0.508	.
IR Prescription Opioids	0.007	0.007	0.007	0.86%(-6.81%,9.18%)	0.831	0.488
Prescription Stimulants	0.034	0.031	0.029	-15.93%(-22.79%,-8.46%)	<.001	0.660

The mean ER/LA REMS opioids pediatric unintentional general exposure treated/evaluated and released population rate decreased 2.61% between the Pre-Implementation and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure treated/evaluated and released population rate decreased 5.77% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure treated/evaluated and released population rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure treated/evaluated and released population rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for IR prescription opioids (p=0.837).

The mean stimulants pediatric unintentional general exposure treated/evaluated and released population rate increased 0.15% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure treated/evaluated and released population rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure treated/evaluated and released population rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for stimulants (p=0.859).

The mean ER/LA REMS opioids pediatric unintentional general exposure treated/evaluated and released prescriptions dispensed rate decreased 9.76% between the Pre-Implementation and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids pediatric unintentional general exposure treated/evaluated and released prescriptions dispensed rate increased 0.86% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure treated/evaluated and released prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure treated/evaluated and released prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for IR prescription opioids ($p=0.488$).

The mean stimulants pediatric unintentional general exposure treated/evaluated and released prescriptions dispensed rate decreased 15.93% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the pediatric unintentional general exposure treated/evaluated and released prescriptions dispensed rate is not statistically significant, indicating that the mean difference in pediatric unintentional general exposure treated/evaluated and released prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for stimulants ($p=0.660$).

6.3.8. Unintentional Therapeutic Errors from the RADARS System Poison Center Program

Figure 6.3.8.1 through Figure 6.3.8.2 show the observed and predicted population, prescription dispensed, and dosing unit mean unintentional therapeutic error rates and 95% confidence intervals for ER/LA REMS opioids excluding ADFs and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 6.3.8.1

The RADARS System Poison Center Program
Unintentional Therapeutic Error Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

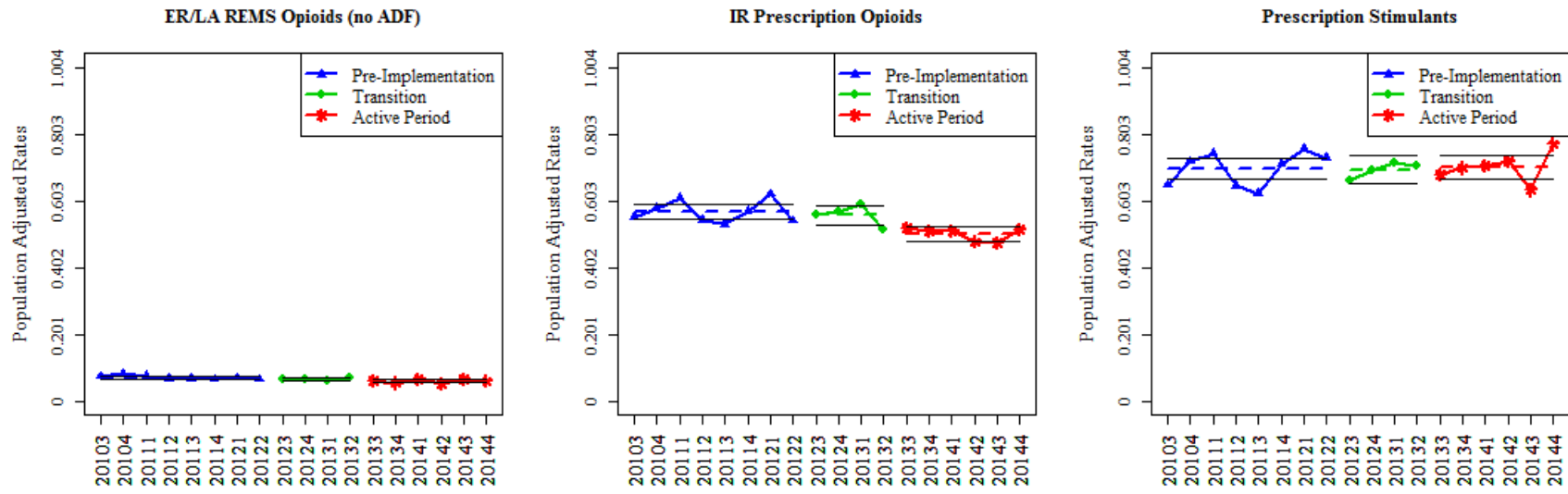


Figure 6.3.8.2

The RADARS System Poison Center Program

Unintentional Therapeutic Error Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

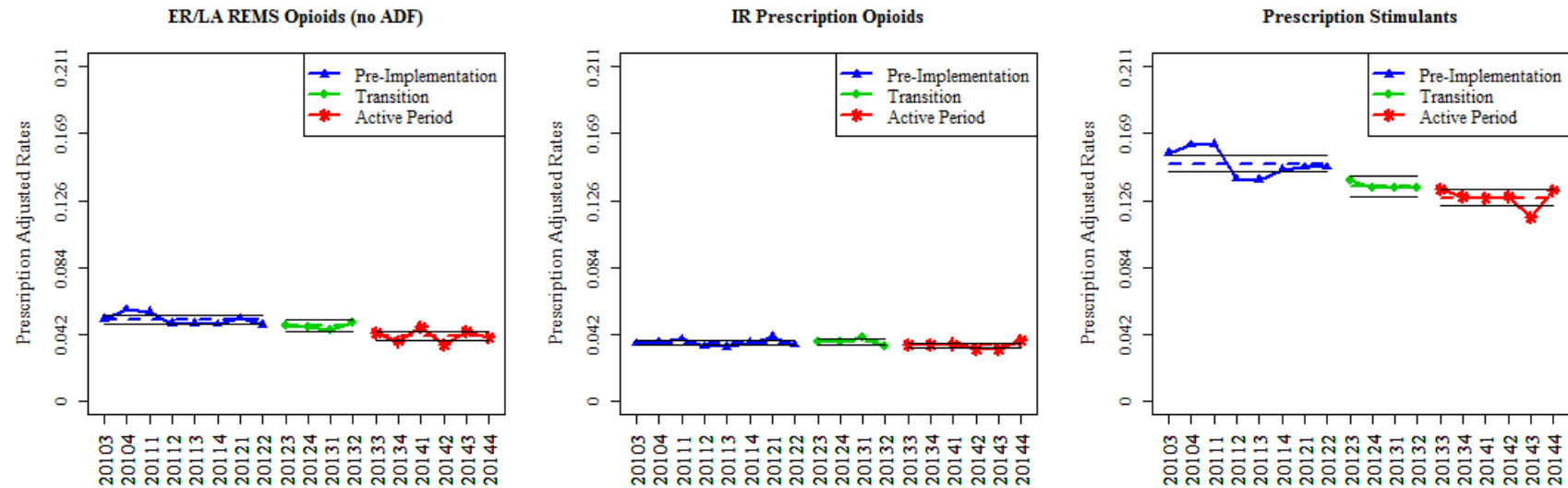


Table 6.3.8.1

The RADARS System Poison Center Program
**Unintentional therapeutic error Rates per 100,000 Population and per 1,000 Prescriptions
Dispensed**
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Pre-Implementation Mean Exposure	Transition Mean Exposure	Active Period Mean Exposure	Active Period to Pre-Implementation % change (95% CI)	p-value for % change	p-value for interaction
Population Adjusted Rates/100,000						
ER/LA REMS Opioids (no ADF)	0.071	0.067	0.060	-15.11%(-22.40%,-7.13%)	<.001	.
IR Prescription Opioids	0.570	0.559	0.503	-11.83%(-16.67%,-6.70%)	<.001	0.484
Prescription Stimulants	0.700	0.695	0.703	0.51%(-6.02%,7.49%)	0.883	0.003
Prescription Adjusted Rates/1,000						
ER/LA REMS Opioids (no ADF)	0.051	0.047	0.041	-20.23%(-26.60%,-13.32%)	<.001	.
IR Prescription Opioids	0.037	0.037	0.035	-4.30%(-10.05%,1.82%)	0.165	<.001
Prescription Stimulants	0.150	0.136	0.128	-14.45%(-18.85%,-9.81%)	<.001	0.164

The mean ER/LA REMS opioids unintentional therapeutic error population rate decreased 15.11% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids unintentional therapeutic error population rate decreased 11.83% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the unintentional therapeutic error population rate is not statistically significant, indicating that the mean difference in unintentional therapeutic error population rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for IR prescription opioids (p=0.484).

The mean stimulants unintentional therapeutic error population rate increased 0.51% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the unintentional therapeutic error population rate is statistically significant, indicating that the mean difference in unintentional therapeutic error population rates for ER/LA REMS opioids excluding ADFs is significantly different than the mean difference observed for stimulants (p=0.003).

The mean ER/LA REMS opioids unintentional therapeutic error prescriptions dispensed rate decreased 20.23% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids unintentional therapeutic error prescriptions dispensed rate decreased 4.03% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the unintentional therapeutic error prescriptions dispensed rate is statistically significant, indicating that the mean difference in unintentional therapeutic error prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is significantly different than the mean difference observed for IR prescription opioids ($p < 0.001$).

The mean stimulants unintentional therapeutic error prescriptions dispensed rate decreased 14.45% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the unintentional therapeutic error prescriptions dispensed rate is not statistically significant, indicating that the mean difference in unintentional therapeutic error prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for stimulants ($p = 0.164$).

6.4. Deaths from the RADARS System Poison Center Program

6.4.1. Exposures Resulting in a Major Medical Outcome, Hospitalization or Death from the RADARS System Poison Center Program

Figure 6.4.1.1 through Figure.6.4.1.2 show the observed and predicted population, prescription dispensed, and dosing unit mean exposures resulting in a major medical outcome, hospitalization, or death rates and 95% confidence intervals for ER/LA REMS opioids excluding ADFs and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 6.4.1.1
The RADARS System Poison Center Program
Exposures Resulting in a Major Medical Outcome, Hospitalization or Death
Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

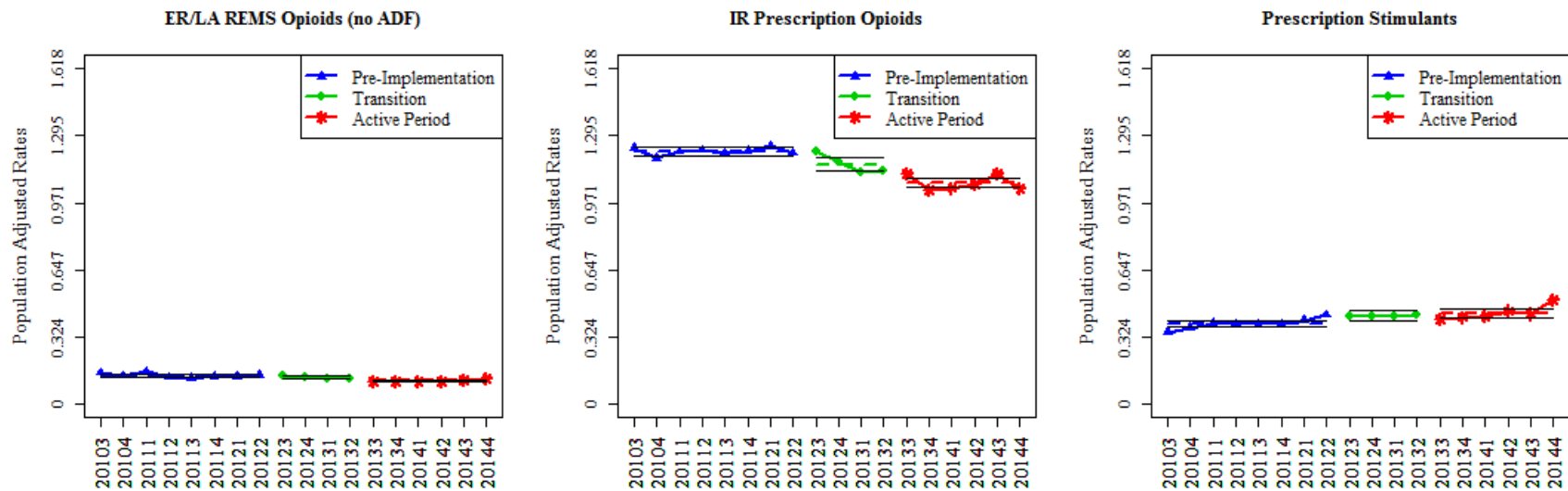


Figure.6.4.1.2

The RADARS System Poison Center Program
Exposures Resulting in a Major Medical Outcome, Hospitalization or Death
Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

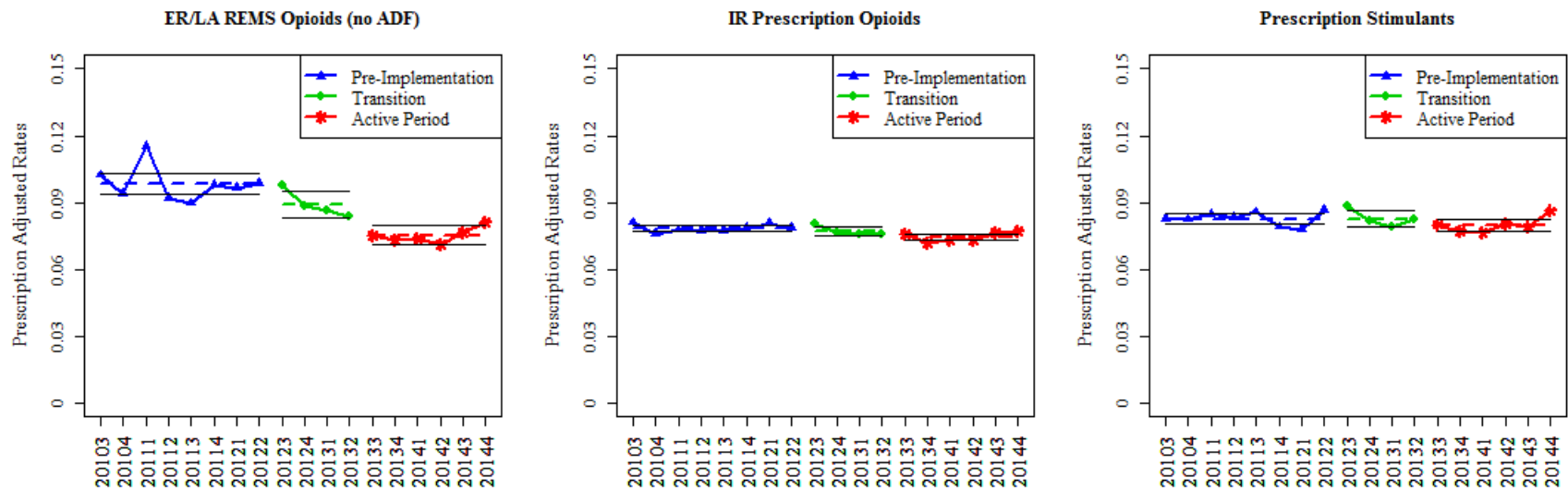


Table 6.4.1.1

The RADARS System Poison Center Program
Exposures Resulting in a Major Medical Outcome, Hospitalization or Death
Rates per 100,000 Population and per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Pre-Implementation Mean Exposure	Transition Mean Exposure	Active Period Mean Exposure	Active Period to Pre-Implementation % change (95% CI)	p-value for % change	p-value for interaction
Population Adjusted Rates/100,000						
ER/LA REMS Opioids (no ADF)	0.136	0.126	0.111	-18.46% (-24.34%, -12.14%)	<.001	.
IR Prescription Opioids	1.220	1.158	1.068	-12.47% (-15.02%, -9.85%)	<.001	0.084
Prescription Stimulants	0.387	0.424	0.438	13.39% (6.19%, 21.09%)	<.001	<.001
Prescription Adjusted Rates/1,000						
ER/LA REMS Opioids (no ADF)	0.098	0.089	0.075	-23.39% (-28.84%, -17.52%)	<.001	.
IR Prescription Opioids	0.078	0.077	0.075	-5.00% (-7.64%, -2.28%)	<.001	<.001
Prescription Stimulants	0.083	0.083	0.080	-3.48% (-7.72%, 0.95%)	0.122	<.001

The mean ER/LA REMS opioids exposures resulting in a major medical outcome, hospitalization, or death population rate decreased 18.46% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids exposures resulting in a major medical outcome, hospitalization, or death population rate decreased 12.47% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the exposures resulting in a major medical outcome, hospitalization, or death population rate is not statistically significant, indicating that the mean difference in exposures resulting in a major medical outcome, hospitalization, or death population rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for IR prescription opioids (p=0.084).

The mean stimulants exposures resulting in a major medical outcome, hospitalization, or death population rate increased 13.39% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the exposures resulting in a major medical outcome, hospitalization, or death population rate is statistically significant, indicating that the mean difference in exposures resulting in a major medical outcome, hospitalization, or death population rates for ER/LA REMS opioids excluding ADFs is significantly different than the mean difference observed for stimulants (p<0.001).

The mean ER/LA REMS opioids exposures resulting in a major medical outcome, hospitalization, or death prescriptions dispensed rate decreased 23.39% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids exposures resulting in a major medical outcome, hospitalization, or death prescriptions dispensed rate decreased 5.00% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the exposures resulting in a major medical outcome, hospitalization, or death prescriptions dispensed rate is statistically significant, indicating that the mean difference in exposures resulting in a major medical outcome, hospitalization, or death prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is significantly different than the mean difference observed for IR prescription opioids ($p < 0.001$).

The mean stimulants exposures resulting in a major medical outcome, hospitalization, or death prescriptions dispensed rate decreased 3.48% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the exposures resulting in a major medical outcome, hospitalization, or death prescriptions dispensed rate is statistically significant, indicating that the mean difference in exposures resulting in a major medical outcome, hospitalization, or death prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is significantly different than the mean difference observed for stimulants ($p < 0.001$).

6.4.2. Exposures Resulting in a Death from the RADARS System Poison Center Program

Figure 6.4.2.1 through Figure 6.4.2.2 show the observed and predicted population, prescription dispensed, and dosing unit mean exposures resulting in death rates and 95% confidence intervals for ER/LA REMS opioids excluding ADFs and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 6.4.2.1
The RADARS System Poison Center Program
Exposures Resulting in Death
Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

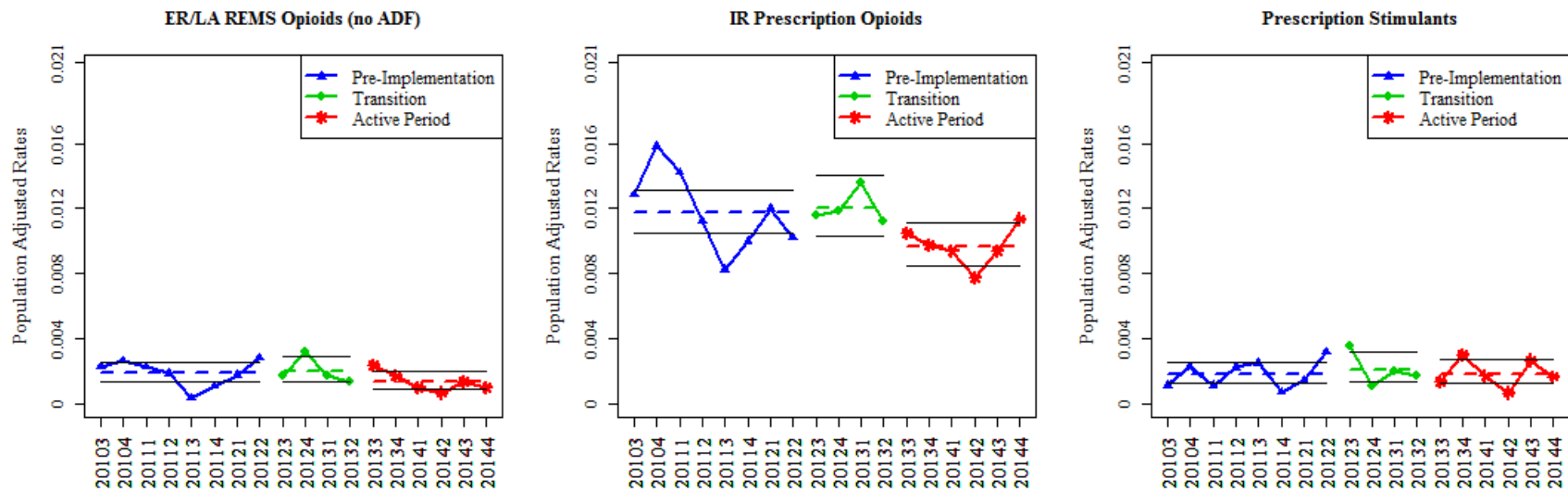


Figure 6.4.2.2
The RADARS System Poison Center Program
Exposures Resulting in Death
Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

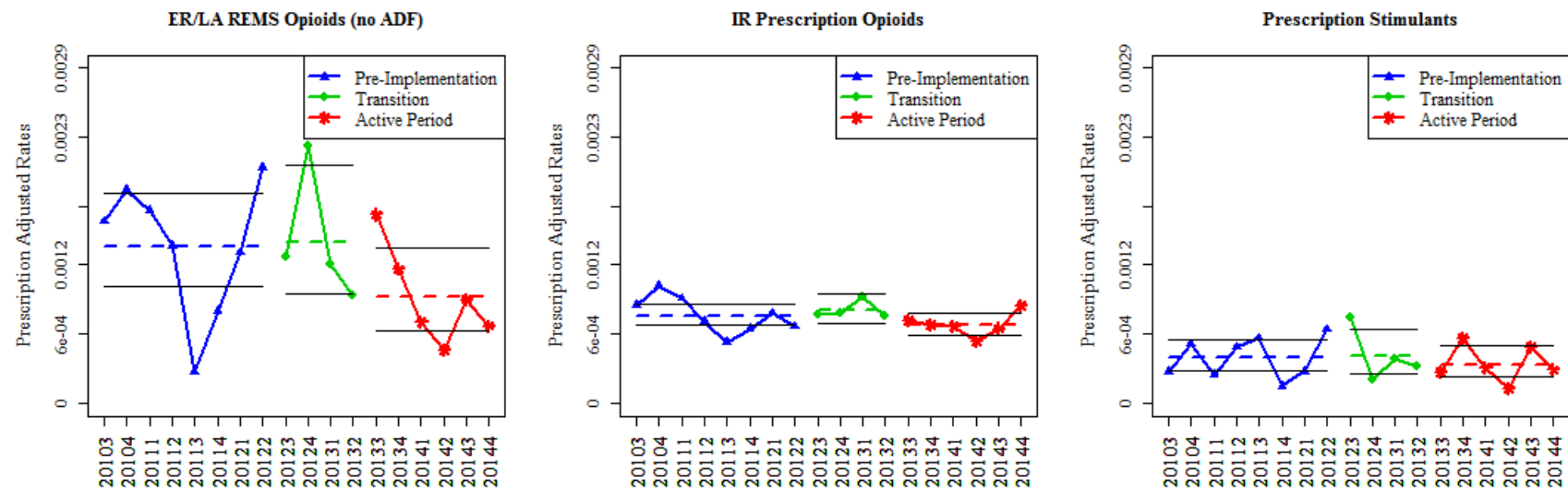


Table 6.4.2.1

The RADARS System Poison Center Program
Exposures Resulting in Death
Rates per 100,000 Population and per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Pre-Implementation Mean Exposure	Transition Mean Exposure	Post-Implementation Mean Exposure	Post-Implementation to Pre-Implementation % change (95% CI)	p-value for % change	p-value for interaction
Population Adjusted Rates/100,000						
ER/LA REMS Opioids (no ADF)	0.002	0.002	0.001	-28.12%(-55.67%,16.56%)	0.181	.
IR Prescription Opioids	0.012	0.012	0.010	-17.66%(-31.11%,-1.57%)	0.033	0.605
Prescription Stimulants	0.002	0.002	0.002	1.31%(-39.02%,68.31%)	0.960	0.337
Prescription Adjusted Rates/1,000						
ER/LA REMS Opioids (no ADF)	0.001	0.001	<.001	-32.46%(-58.17%,9.05%)	0.108	.
IR Prescription Opioids	<.001	<.001	<.001	-10.63%(-25.63%,7.41%)	0.231	0.285
Prescription Stimulants	<.001	<.001	<.001	-13.77%(-48.75%,45.10%)	0.577	0.498

The mean ER/LA REMS opioids exposures resulting in death population rate decreased 28.12% between the Pre-Implementation and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids exposures resulting in death population rate decreased 17.66% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the exposures resulting in death population rate is not statistically significant, indicating that the mean difference in exposures resulting in death population rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for IR prescription opioids (p=0.605).

The mean stimulants exposures resulting in death population rate increased 1.31% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the exposures resulting in death population rate is not statistically significant, indicating that the mean difference in exposures resulting in death population rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for stimulants (p=0.337).

The mean ER/LA REMS opioids exposures resulting in death prescriptions dispensed rate decreased 32.46% between the Pre-Implementation and Active Period time periods. This decrease is not statistically significant.

The mean IR prescription opioids exposures resulting in death prescriptions dispensed rate decreased 10.63% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the exposures resulting in death prescriptions dispensed rate is not statistically significant, indicating that the mean difference in exposures resulting in death prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for IR prescription opioids ($p=0.285$).

The mean stimulants exposures resulting in death prescriptions dispensed rate decreased 13.77% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the exposures resulting in death prescriptions dispensed rate is not statistically significant, indicating that the mean difference in exposures resulting in death prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for stimulants ($p=0.498$).

6.5. Abuse from the RADARS System Treatment Center Programs Combined

6.5.1. Abuse from the RADARS System Treatment Center Programs Combined

Figure 6.5.1.1 through Figure 6.5.1.2 show the observed and predicted population, prescription dispensed, and dosing unit mean past 30 day use to get high (abuse) mention rates and 95% confidence intervals for ER/LA REMS opioids excluding ADFs and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 6.5.1.1

The RADARS System Treatment Center Programs Combined
Past 30 Day Mention Rates per 100,000 Population
 From Third Quarter 2010 to Fourth Quarter 2014

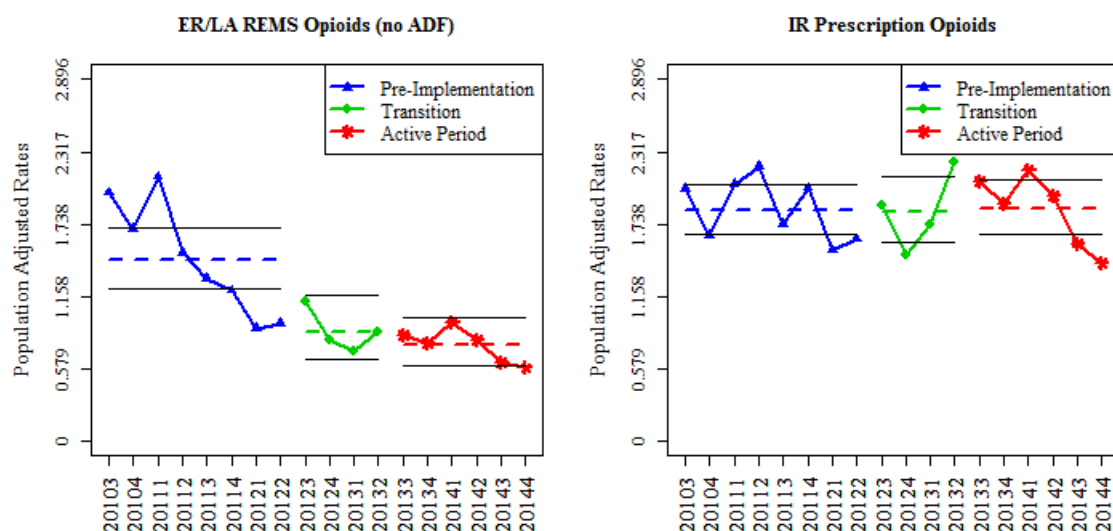


Figure 6.5.1.2

The RADARS System Treatment Center Programs Combined
Past 30 Day Mention Rates per 1,000 Prescriptions Dispensed
 From Third Quarter 2010 to Fourth Quarter 2014

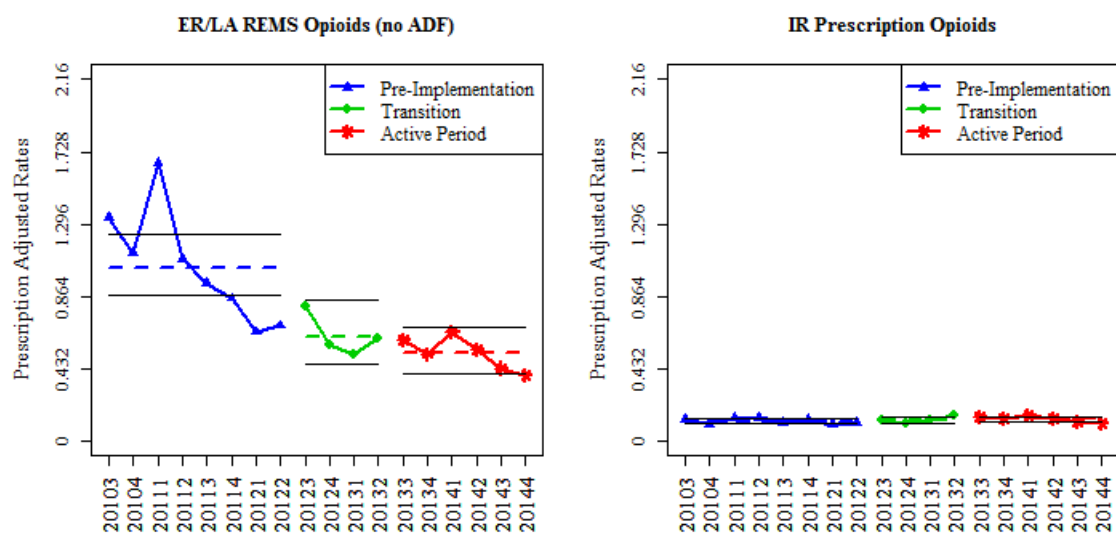


Table 6.5.1.1

**The RADARS System Treatment Center Programs Combined
Past 30 Day Mention Rates per 100,000 Population and per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014**

Drug Group	Pre-Implementation Mean Exposure	Transition Mean Exposure	Active Period Mean Exposure	Active Period to Pre-Implementation % change (95% CI)	p-value for % change	p-value for interaction
Population Adjusted Rates/100,000						
ER/LA REMS Opioids (no ADF)	1.447	0.874	0.769	-46.87% (-60.69%, -28.19%)	<.001	.
IR Prescription Opioids	1.847	1.837	1.858	0.60% (-14.26%, 18.05%)	0.941	<.001
Prescription Adjusted Rates/1,000						
ER/LA REMS Opioids (no ADF)	1.035	0.624	0.524	-49.35% (-62.90%, -30.85%)	<.001	.
IR Prescription Opioids	0.117	0.125	0.131	11.83% (-4.22%, 30.58%)	0.157	<.001

The mean ER/LA REMS opioids past 30 day use to get high (abuse) mention population rate decreased 46.87% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids past 30 day use to get high (abuse) mention population rate increased 0.60% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the past 30 day use to get high (abuse) mention population rate is statistically significant, indicating that the mean difference in past 30 day use to get high (abuse) mention population rates for ER/LA REMS opioids excluding ADFs is significantly different than the mean difference observed for IR prescription opioids ($p < 0.001$).

The mean ER/LA REMS opioids past 30 day use to get high (abuse) mention prescriptions dispensed rate decreased 49.35% between the Pre-Implementation and Active Period time periods. This decrease is statistically significant.

The mean IR prescription opioids past 30 day use to get high (abuse) mention prescriptions dispensed rate increased 11.83% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the past 30 day use to get high (abuse) mention prescriptions dispensed rate is statistically significant, indicating that the mean difference in past 30 day use to get high (abuse) mention prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is significantly different than the mean difference observed for IR prescription opioids ($p < 0.001$).

6.6. Abuse from the RADARS System College Survey Program

6.6.1. Abuse from the RADARS System College Survey Program

Figure 6.6.1.1 through Figure.6.6.1.2 show the observed and predicted population, prescription dispensed, and dosing unit mean past 90 day non-medical use (abuse) mention rates and 95% confidence intervals for ER/LA REMS opioids excluding ADFs and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

Figure 6.6.1.1

The RADARS System College Survey Program
Mean Past 90 Day Abuse Mention Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

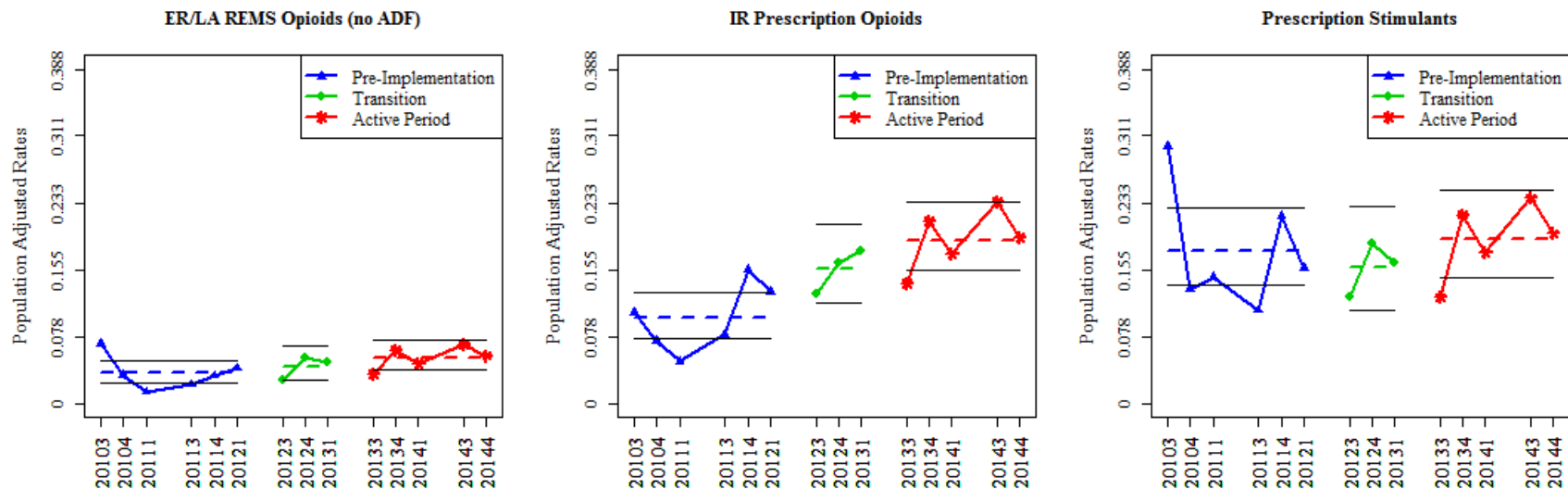


Figure.6.6.1.2

The RADARS System College Survey Program
Mean Past 90 Day Abuse Mention Rates per 1,000 Prescriptions Dispensed
From Third Quarter 2010 to Fourth Quarter 2014

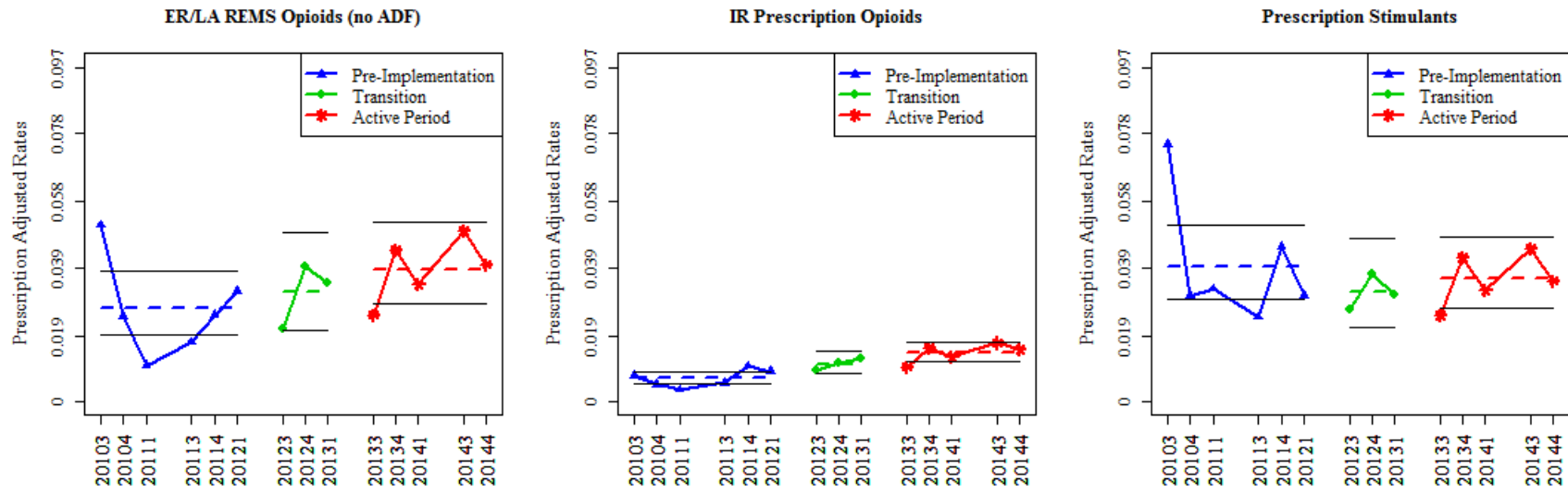


Table 6.6.1.1

The RADARS System College Survey Program
Mean Past 90 Day Abuse Mention Rates per 100,000 Population
From Third Quarter 2010 to Fourth Quarter 2014

Drug Group	Pre-Implementation Mean Exposure	Transition Mean Exposure	Active Period Mean Exposure	Active Period to Pre-Implementation % change (95% CI)	p-value for % change	p-value for interaction
Population Adjusted Rates/100,000						
ER/LA REMS Opioids (no ADF)	0.035	0.043	0.053	51.67%(-5.65%,143.79%)	0.085	.
IR Prescription Opioids	0.099	0.156	0.190	91.83%(37.71%,167.23%)	<.001	0.426
Prescription Stimulants	0.177	0.158	0.191	7.72%(-25.25%,55.23%)	0.690	0.263
Prescription Adjusted Rates/1,000						
ER/LA REMS Opioids (no ADF)	0.027	0.032	0.039	42.60%(-9.20%,123.95%)	0.123	.
IR Prescription Opioids	0.007	0.011	0.014	109.83%(50.95%,191.68%)	<.001	0.175
Prescription Stimulants	0.039	0.032	0.036	-8.24%(-38.05%,35.90%)	0.668	0.149

The mean ER/LA REMS opioids past 90 day mention population rate increased 51.67% between the Pre-Implementation and Active Period time periods. This increase is not statistically significant.

The mean IR prescription opioids past 90 day mention population rate increased 91.83% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the past 90 day mention population rate is not statistically significant, indicating that the mean difference in past 90 day mention population rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for IR prescription opioids (p=0.426).

The mean stimulants past 90 day mention population rate increased 7.72% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the past 90 day mention population rate is not statistically significant, indicating that the mean difference in past 90 day mention population rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for stimulants (p=0.263).

The mean ER/LA REMS opioids past 90 day mention prescriptions dispensed rate increased 42.60% between the Pre-Implementation and Active Period time periods. This increase is not statistically significant.

The mean IR prescription opioids past 90 day mention prescriptions dispensed rate increased 109.83% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the past 90 day mention prescriptions dispensed rate is not statistically significant, indicating that the mean difference in past 90 day mention prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for IR prescription opioids ($p=0.175$).

The mean stimulants past 90 day mention prescriptions dispensed rate decreased 8.24% between the Pre-Implementation and Active Period time periods. The interaction of drug by time period for the past 90 day mention prescriptions dispensed rate is not statistically significant, indicating that the mean difference in past 90 day mention prescriptions dispensed rates for ER/LA REMS opioids excluding ADFs is not significantly different than the mean difference observed for stimulants ($p=0.149$).

7. LIMITATIONS

More cautious prescribing in the ER/LA REMS may carry over to the IR opioid class, resulting in no difference between the ER/LA REMS opioid group and the IR opioid comparator group. Also, total reports of exposures to US Poison Centers varies annually; thus, a change in ER/LA REMS opioids without a corresponding difference in at least one control group may not be conclusive. Further, each of the programs is based on self-reported information which increases the likelihood of ambiguous answers and incomplete data.

8. STRENGTHS

The RADARS System data are drug- and formulation-specific allowing us to identify IR versus ER/LA product groups. The data will be available for analysis within 12 weeks of each calendar quarter conclusion, permitting identification of trends in near real-time. An additional strength is the large catchment area covered. Cases can arise from large metropolitan areas as well as rural populations and thus provide results that are more broadly applicable than those from a smaller geographic region. The joint use of RADARS System multiple detection programs allows for the assessment of trends by various populations and in different settings to enhance the generalizability of the data. Comprehensive results from independent programs provide better understanding of the trends of interest and allows for evaluations using the totality of evidence.

9. CONCLUSIONS

Pre-Implementation to Active Period mean decreases for both population and prescription rates were consistent for most outcome variables from the Poison Center Program and Treatment Center Programs Combined for the ER/LA REMS group. However, mean decreases were also seen for many of the Poison Center Program outcomes for IR prescription opioids. The mean decrease in the ER/LA REMS group significantly exceeded the mean decreases with the population denominator for Poison Center Program abuse; major medical outcome or death; treated/evaluated and released; adolescent abuse; and for the Treatment Center Programs Combined abuse outcome. For the prescription denominator, mean decreases for the ER/LA REMS group exceeded decreases for the IR prescription opioid group for Poison Center Program abuse; misuse; major medical outcome or death; treated/evaluated and released; unintentional therapeutic errors; and adolescent abuse. Increases were seen in the College Survey Program for both drug groups. This may represent a particularly vulnerable population. Attributability of decreases to the REMS are confounded by other interventions such as the increase in states with active prescription monitoring plans and the continued effect of abuse deterrent formulation on abuse, misuse and diversion rates.

10. REFERENCES

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