Evaluation of the Extended Release and Long-Acting (ER/LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Programs: Comments for Docket No. FDA-2016-N-0820

04 June 2016

RADARS® System
Richard C. Dart, MD, PhD, Executive Director
Jody L. Green, PhD, CCRP, Director of Research

Comments for Docket No. FDA-2016-N-0820: Evaluation of the Extended Release and Long-Acting (ER/LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Programs

KEY POINTS

1) Programs from the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS®) System were used to evaluate the impact of the extended release and long-acting (ER/LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS), utilizing a mosaic approach with convergent validity. The point of convergent validity is to see if results can be triangulated, thus reassuring interpretation of the results.

2) The RADARS System Programs have limitations as outlined in the RADARS System and United States Food and Drug Administration (FDA) Briefing Books submitted for the May 2016 ER/LA Opioid Analgesics REMS advisory committee meeting. All post-market surveillance systems have limitations, as do randomized controlled trials and other human subject research, but limitations do not invalidate the findings.

3) Sensitivity analyses were conducted to evaluate the potential impact of bias and control for confounders. The results of these analyses indicate both sensitivity and specificity within the RADARS System Programs. External validation is demonstrated by the high correlation between RADARS System Programs and other data sources such as the Drug Abuse Warning Network (DAWN), the Treatment Episode Dataset (TEDS), and the National Survey of Drug Use and Health (NSDUH).

4) While most of the concerns are methodologically sound, convergence of multiple programs as well as the results from sensitivity analyses and external validation suggest these programs are not only informative but essential in studying prescription drug misuse and abuse.

BACKGROUND

On 03 and 04 May 2016, the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee convened to provide advice and recommendations to the FDA regarding the evaluation of the ER/LA Opioid Analgesics REMS program and proposed modifications. Within the briefing materials and during the course of the meeting, concerns pertaining to the utilization of postmarketing surveillance to evaluate the ER/LA Opioid Analgesics REMS were advanced by the committee and FDA representatives. While most of the concerns are methodologically sound, the convergence of trends from multiple systems as well as the results from sensitivity analyses and external validation suggest these programs are not only informative but essential in studying prescription drug abuse and misuse.

ABOUT THE RADARS® SYSTEM

The RADARS System was initiated in 2002 and since 2006 has been independently owned and operated by Rocky Mountain Poison & Drug Center, a department of Denver Health and Hospital Authority, a not-for-profit safety net hospital. The RADARS System provides continuous product- and geographic-specific surveillance of the abuse, misuse, and diversion of prescription and illicit drugs throughout the United States (www.RADARS.org). The RADARS

System is composed of several core programs, each run independently by their respective principal investigator:

1. Poison Center Program, PI: Richard C. Dart, MD, PhD
2. Opioid Treatment Program, PI: Mark Parrino
3. Survey of Key Informants' Patients Program, PI: Theodore Cicero, PhD
4. Drug Diversion Program, PI: Steve Kurtz, PhD
5. College Survey Program, PI: Richard C. Dart, MD, PhD
6. StreetRx Program, PI: Nabarun Dasgupta, PhD
7. Web Monitoring Program, PI: Jody L. Green, PhD

These programs represent geographically diverse data-collection systems, developed to capture information on individuals along various stages of the drug dependence pathway, and provide surveillance on prescription drug abuse and misuse trends [1].

Drugs affecting the central nervous system form a unique group of products for surveillance because they are often abused, misused, and diverted. These medications include opioid analgesics, stimulants, sedative-hypnotics, muscle relaxants, and anticonvulsants, among others. Abuse, misuse, 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 abuse, misuse, and diversion at all phases of the spectrum of abuse and ultimate addiction. Data from the core programs are interpreted together to provide a more complete picture of a drug's abuse, misuse, and diversion as well as to provide convergent validity.

EXECUTIVE SUMMARY

Below is a summary table of the identified limitations and a brief response. Each limitation is addressed in more detail in the following section.

Table 1. Summary of Data Collection Limitations and RADARS System Response

Limitation	RADARS System Response
DATA COLLECTION LIMITATIONS	
RADARS System Poison Center Program • Change in the utilization of poison centers in the United States during the study period	The decline in utilization affected age groups that are not involved is abuse of prescription opioid analgesics. The <u>total</u> volume of exposure cases reported to poison centers in the US decreased during the study period. However, the decline is primarily limited to children <6 years of age. During the period of analysis, exposure case volume increased and decreased consistent with random variation. Therefore, we conclude that a secular trend in poison center utilization is unlikely to have accounted for the observed decrease in abuse of ER/LA opioid analgesics.
RADARS System Poison Center Program • Utilization of poison centers is influenced by media and other social factors	Intense media coverage can increase the number of people contacting a poison center. In the case of opioids, media coverage has progressively increased in recent years. In theory, this could increase contacts to poison centers. Opioid abuse cases are decreasing rather than increasing with increased media coverage. The diverging trends strengthen the likelihood that the decreases observed are real.

RADARS System Poison Center Program • Participating poison centers varied during the study period	The number of participating poison centers ranged from 47 to 49 during the study period. Sensitivity analyses confirmed that the results are unchanged when restricting only to centers who participated in both the pre- and post-REMS evaluation periods. For the sensitivity analysis, there were 44 centers from 4 states covering 82% of the US population that participated in both the pre- and post-REMS study periods.
RADARS System Poison Center Program • Unknown how well trends and patterns in poison center calls reflect trends and patterns in actual misuse and abuse of prescription opioids nationally	The correlation of RADARS System Poison Center trends in the Intentional Abuse category and DAWN emergency department cases are very strong (R=0.97). Trends for individual active pharmaceutical ingredients are also very strong for the most commonly prescribed opioid analgesics (oxycodone R=0.97; hydrocodone R=0.95) and was strong for other less commonly prescribed opioid analgesics (hydromorphone R=0.99; fentanyl R=0.92; morphine R=0.84). These strong correlations support the use of the RADARS System Poison Center Program as a valid indicator of abuse and misuse in the US.
RADARS System Poison Center Program • Unclear how accurately the poison centers are able to classify 1) specific products, especially when there are various formulations and generics and 2) exposure categories (reason)	In a published study, accuracy of poison center data recording was assessed for acetaminophen-related events, recognizing the complexity of that market, which includes many different products with similar labeling. Accuracy of recording was good for each component with an overall accuracy score of 94% (95% CI 93.7,94.4). These data are supportive of acceptable poison center classification and categorization.
RADARS System Poison Center Program • Poison centers do not capture severe overdoses that result in death before a call to a poison center can be made. The fraction of overdose death cases captured in this data system may vary across products and over time, depending on likelihood of lethal overdose. This may not be an appropriate data source for incidence of death across drug products, classes or time periods.	The correlation between National Vital Statistics System (NVSS) natural and semi-synthetic opioid deaths and RADARS System Poison Center Program opioid deaths was good (R=0.67). The correlation between National Poison Data System (NPDS) and NVSS for heroin was even stronger (R=0.90). These correlations indicate that while poison centers do not capture all deaths they can be used to assess trends and more importantly study product-specificity which is not available in the NVSS.
RADARS System Treatment Center Programs • Participating treatment centers varied during the study period	Sensitivity analyses limited to only centers that reported during the pre- and post-REMS periods actually strengthened the results. The result was a greater reduction in abuse as reported in treatment centers for ER/LA opioid analgesics than immediate release (IR) opioid analgesics. The difference between the ER/LA and the IR opioid analgesic groups was statistically significant.
RADARS System Treatment Center Programs • Trends in surveyed centers may not represent national trends	Treatment Center Programs trends are highly correlated with the Treatment Episode Dataset (TEDS; R=0.94), thus suggesting that the program is representative of national trends.
RADARS System Treatment Center Programs • The survey instrument is amended periodically, abuse prevalence	Survey instruments must be amended periodically to include new products that come on the market. Otherwise, these important data would be lost. The only changes to the questionnaire during the study period were to add new

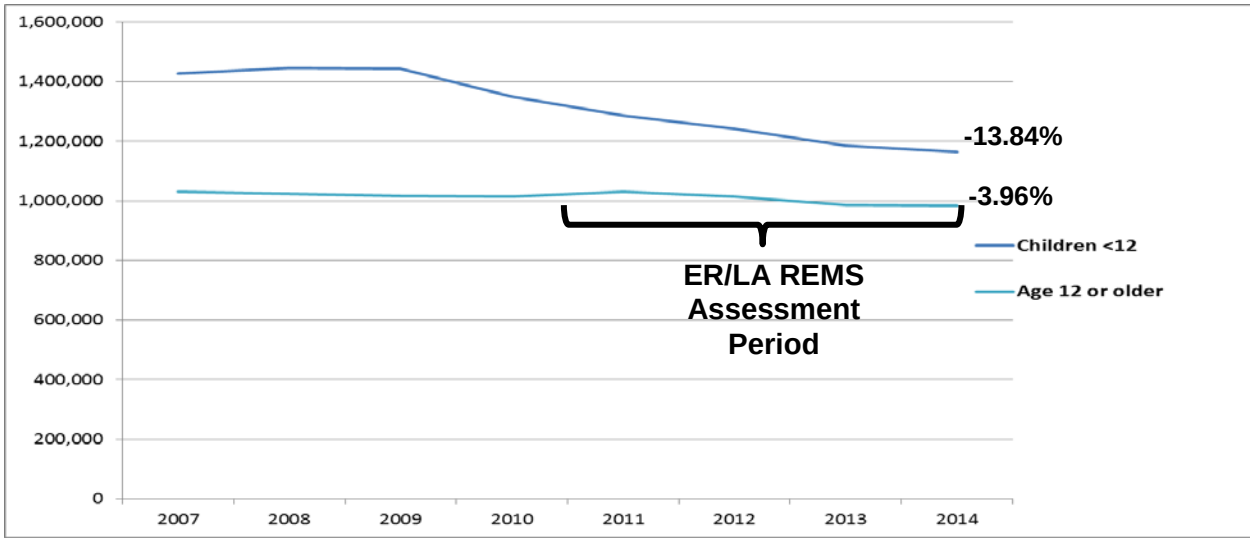
estimates can change over time due to these adjustments in the survey instrument	marketed drug products (no products were removed). Patients are instructed to endorse <u>all</u> drugs used to get high hence any bias would likely be toward more endorsements rather than fewer. Despite this potential bias, endorsements declined.
RADARS System College Survey Program • It is uncertain how well this program represents college students in the US or how the study sample might have changed over time • Trends in College Survey Program are different than other programs	Demographics are similar to that of the US college study population in the NSDUH, however it is unclear if there is a bias in those who would volunteer for an online survey. The demographics of the study participants did not change significantly during the study periods. It was not expected that College Survey would necessarily show the same trends. College students have very low rates of non-medical use of prescription opioids and are typically younger than those most commonly affected. This is a small independent cohort therefore would not necessarily be expected to follow trends of the entire population.

SUMMARY OF FINDINGS

Comment: RADARS System Poison Center Program – Change in the utilization of poison centers in the United States during the study period

The incidence of prescription drug abuse begins in adolescence and peaks in the ages of 18 to 35 years. Therefore, trends in total exposures from the NPDS were examined to assess whether any changes in case volume were observed. Figure 1 shows that exposures among persons age 12 years or greater, the number of exposure both increased and decreased consistent with random variation. In contrast, exposures in children under the age of 12 years decreased 13.84. Therefore, we conclude that a secular trend in poison center utilization is unlikely to have accounted for the observed decrease in abuse of ER/LA opioid analgesics.

Figure 1. National Poison Data System (NPDS) Exposures 2007 through 2014



Comment: RADARS System Poison Center Program – Utilization of poison centers is influenced by media and other social factors.

Utilization of poison centers can be affected in some cases by media and other factors. In the case of opioids, the most intense media coverage has occurred in the past few years. This attention would be expected to increase utilization of poison centers. However, we have instead seen a decrease in abuse of all prescription opioids and the ER/LA opioid analgesics specifically. One would expect the volume of exposures to increase if that were the case but exposures are actually trending down. Opioid abuse cases are decreasing rather than increasing with increased media coverage. The diverging trends strengthen the likelihood that the decreases observed are real. Also, it is possible that media and other factors effect emergency department visits as well as captured in DAWN (Substance Abuse and Mental Health Services Administration [SAMHSA]). Exposures reported to poison centers correlate well with emergency department visits reported by DAWN (data shown starting on page 7).

Comment: RADARS System Poison Center Program – Participating poison centers varied during the study period

The number of participating poison centers ranged from 47 to 49 during the study period. The table below shows the percentage of the US population, the number of centers, and the number of states covered. Two poison centers closed during the study period however the coverage area was then assigned to another poison center. Hence, the coverage throughout the study period has little variability. Sensitivity analyses for each of the primary outcomes were performed, restricting the analysis to only poison centers who participated in both the pre- and post-REMS evaluation periods. There were 44 centers from 4 states covering 82% of the US population that participated in both the pre- and post-REMS study periods. The results are unchanged as shown in Appendix A.

Table 2. RADARS System Poison Center Program Participation and Coverage 2010 through 2014

	2010	**2011**	**2012**	**2013**	**2014**
% of US population covered	85.4%	89.3%	90.2%	92.6%	92.6%
Number of centers	48	47	49	49	48
Number of states	44	44	45	46	46

Comment: RADARS System Poison Center Program – Unknown how well trends and patterns in poison center calls reflect trends and patterns in actual misuse and abuse of prescription opioids nationally

We have shown previously that RADARS System Poison Center Program trends correlate very well with DAWN data; however, this published analysis was performed before the unfortunate end of the DAWN program [2]. DAWN is regarded as a nationally representative program. A DAWN case is any emergency department visit where the patient was treated in the emergency department for a condition that was induced by or related to recent drug use [3]. The drug use must be implicated in the visit but it does not need to be the direct cause. A poison center intentional exposure is an exposure resulting from a purposeful action (exposure defined as an actual or suspect contact with any substance which has been ingested, inhaled, absorbed, applied to, or injected into the body, regardless of toxicity or clinical manifestation) [4]. The

figures below illustrate the high correlation between poison center intentional exposures and DAWN emergency department cases for all opioids combined as well as for specific opioid active pharmaceutical ingredients. These strong correlations support the use of the RADARS System Poison Center Program as a valid indicator of abuse and misuse in the US.

Figure 2. All Opioids - RADARS System Poison Center Program Intentional Exposures Correlated with DAWN Emergency Department Cases 2003 through 2011

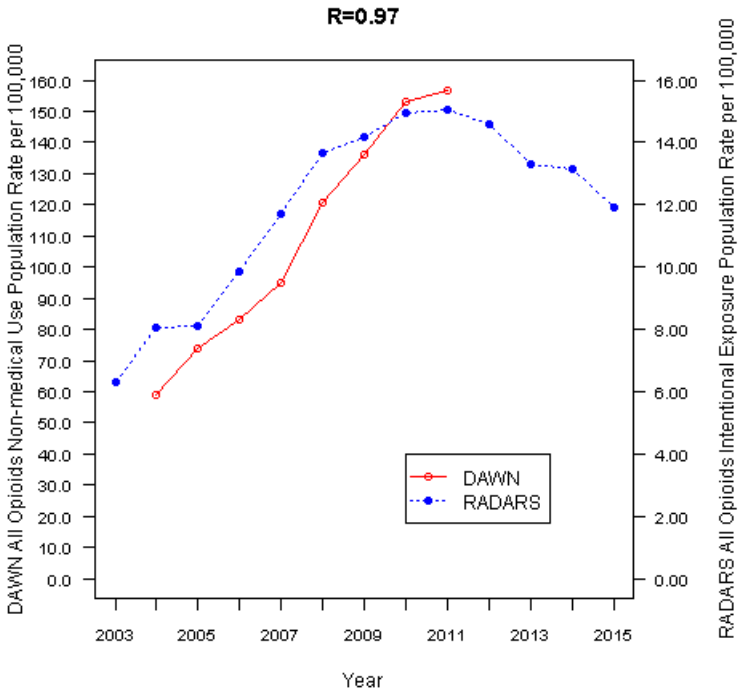


Figure 3. Oxycodone - RADARS System Poison Center Program Intentional Exposures Correlated with DAWN Emergency Department Cases 2003 through 2011

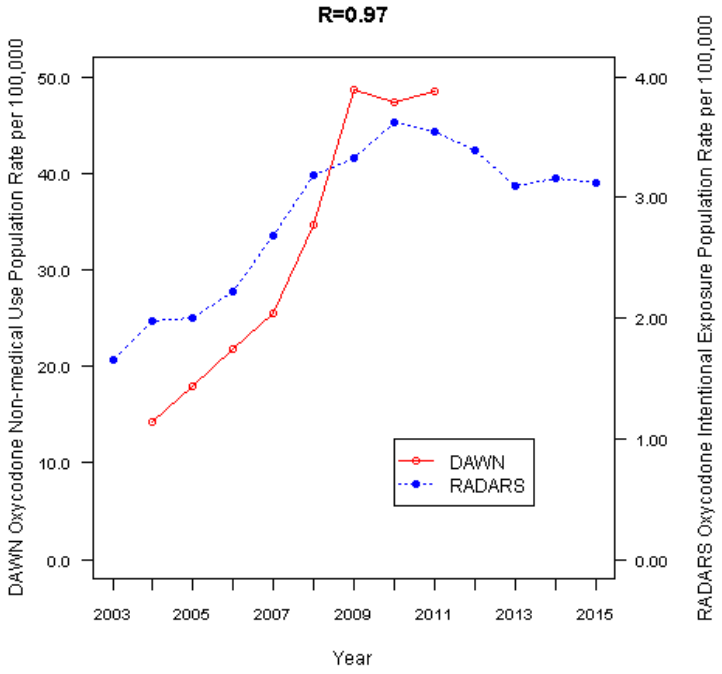


Figure 4. Hydrocodone - RADARS System Poison Center Program Intentional Exposures Correlated with DAWN Emergency Department Cases 2003 through 2011

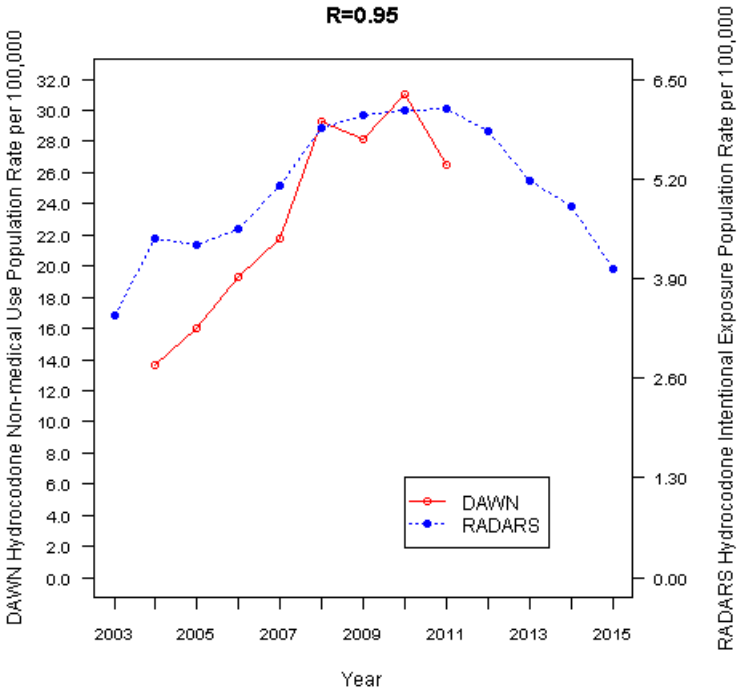


Figure 5. Hydromorphone - RADARS System Poison Center Program Intentional Exposures Correlated with DAWN Emergency Department Cases 2003 through 2011

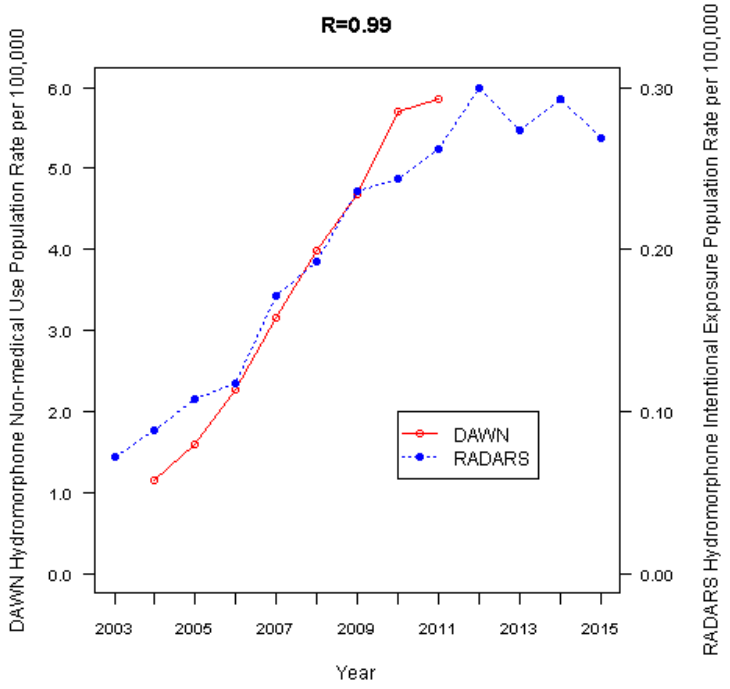


Figure 6. Fentanyl - RADARS System Poison Center Program Intentional Exposures Correlated with DAWN Emergency Department Cases 2003 through 2011

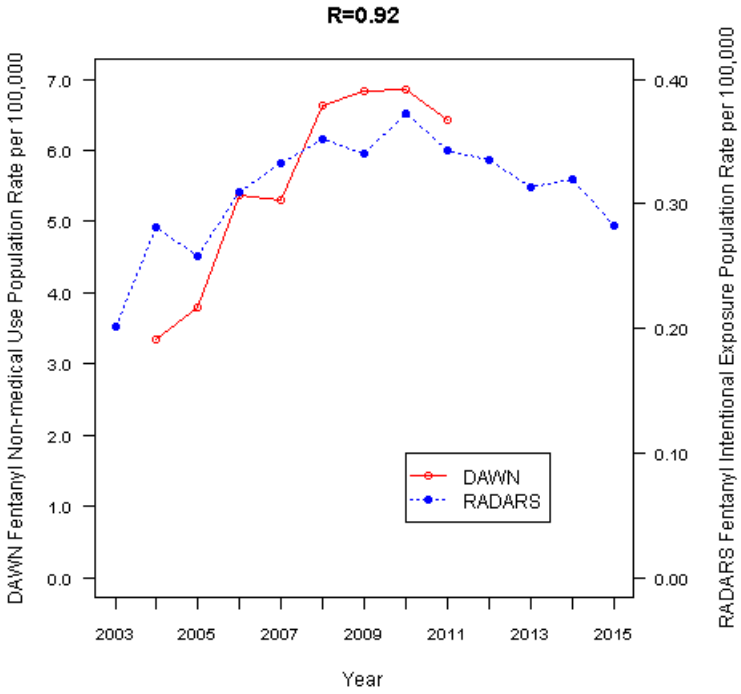
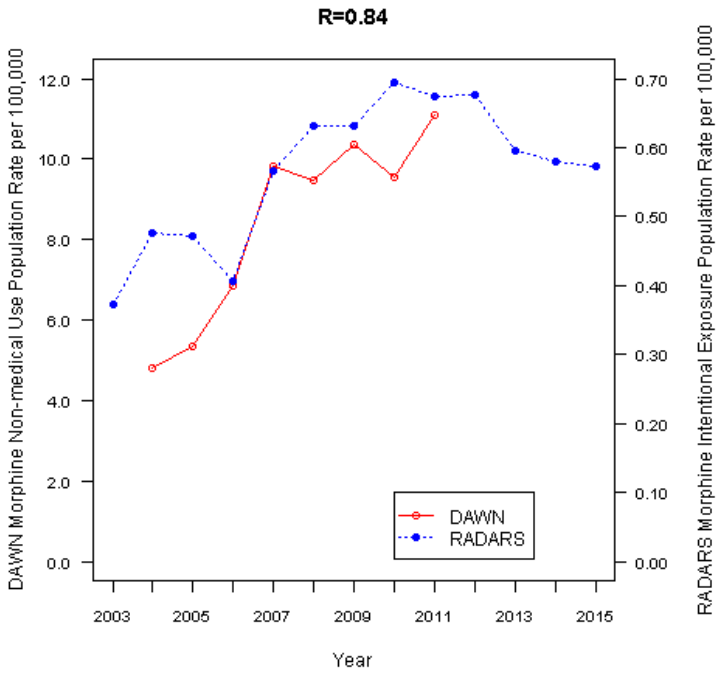


Figure 7. Morphine - RADARS System Poison Center Program Intentional Exposures Correlated with DAWN Emergency Department Cases 2003 through 2011



Comment: RADARS System Poison Center Program – Unclear how accurately the poison centers are able to classify 1) specific products, especially when there are various formulations and generics and 2) exposure categories (reason)

We have previously assessed and published on the topic of poison center accuracy in classifying specific products and generics as well as reason for the exposure. Accuracy of poison center data recording was assessed for exposures that involved acetaminophen-containing products, recognizing the complexity of that market, which includes many different over-the-counter and prescription, single-entity and combination products with similar labeling. While the published study involved an education intervention, the pre-training accuracy scores were very good for each component. While these data are supportive and reassuring, we recognize this is specific to acetaminophen-containing products (some of which include opioids) but that recognition of prescription opioids may be different. It also does not address the limitation of self-report which is an inherent bias in all spontaneous reporting programs. Nonetheless, it does support an acceptable level of product coding and exposure reason accuracy.

Excerpt from *Krenzelok EP, Reynolds KM, Dart RC, Green JL. A model to improve the accuracy of US Poison Center data collection. Clinical Toxicology 2014; 52:889-896.*

Excerpted Table 3. Mean Quality Component and Total Scores*, Pre- and Post-Training

Component	Pre-Training Score (95% CI)	Post-Training Score (95% CI)	p-value
Demographic Fields	96.6 (96.09,97.08)	97.0 (96.54,97.53)	0.204
Exposure Characteristic Fields	95.3 (94.80,95.82)	95.6 (95.07,96.09)	0.462
Outcome Fields	97.3 (96.78,97.76)	97.0 (96.56,97.54)	0.520
Substance Fields	88.9 (88.20,89.67)	93.0 (92.24,93.71)	<0.001
Total Score	94.0 (93.69,94.35)	95.3 (95.01,95.66)	<0.001

*Percentage of data correct for all expected data fields

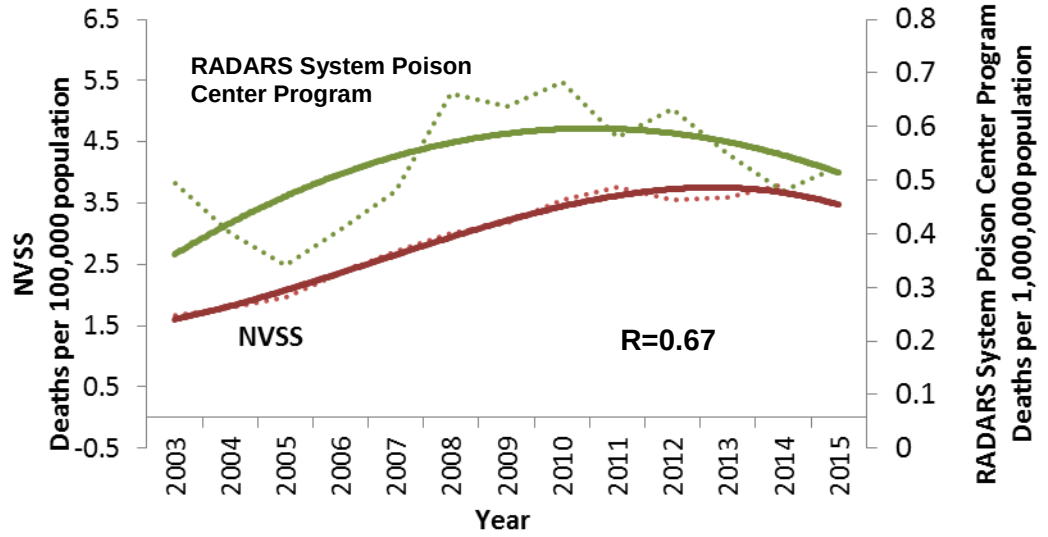
Comment: RADARS System Poison Center – Poison centers do not capture severe overdoses that result in death before a call to a poison center can be made. The fraction of overdose death cases captured in this data system may vary across products and over time, depending on likelihood of lethal overdose. This may not be an appropriate data source for incidence of death across drug products, classes or time periods.

Poison centers rely on spontaneous reports which results in underreporting, particularly of exposures that result in death prior to contact to a poison center. Deaths captured by poison centers represent about 8-10% of deaths as captured in the NVSS. In reviewing the trends over time we are able to correlate the two data sources. For deaths associated with natural and semisynthetic opioids the correlation between NVSS and the RADARS System Poison Center Program was good (R=0.67). When comparing NVSS and NPDS data for heroin, the correlation was even more impressive with R=0.90. These correlations indicate that while poison centers do not capture all deaths they can be used to assess trends and more importantly study product-specificity which is not available in the NVSS system.

Table 3. The National Vital Statistics System (NVSS) uses the following drug classifications:

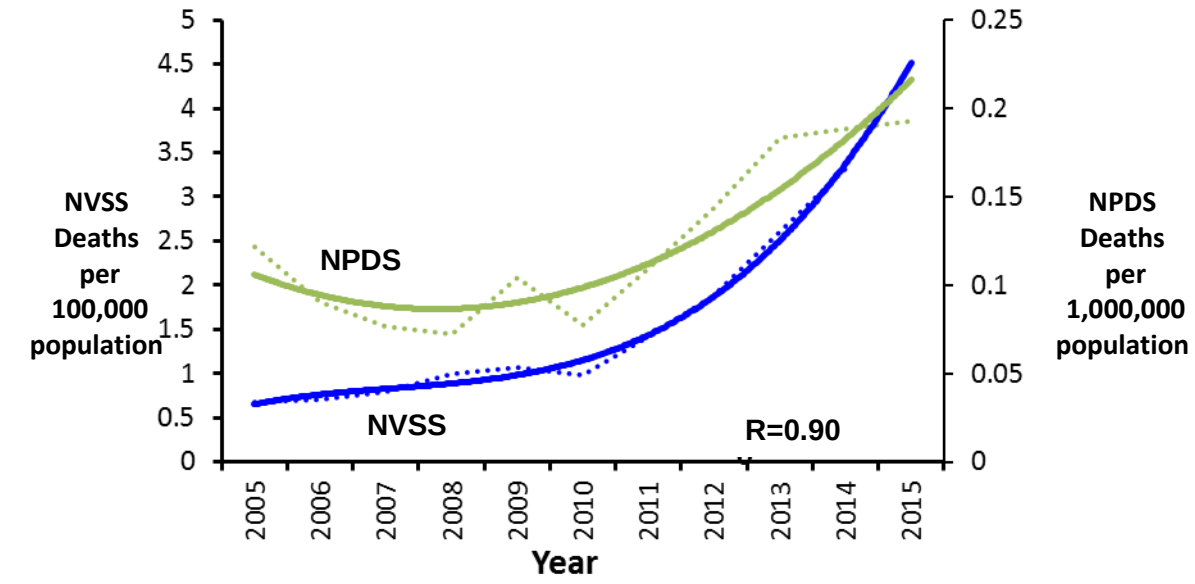
T40.1	Heroin	• Heroin
T40.2	Natural & Semisynthetic Opioids	• Hydrocodone • Hydromorphone • Morphine • Oxycodone • Oxymorphone • Plus ~57 other opioids
T40.3	Methadone	• Methadone
T40.4	Synthetic Opioids	• Buprenorphine • Fentanyl • Tramadol • Sufentanil • Tapentadol • Plus ~24 other opioids

Figure 8. Correlation of Mortality Reports of Natural and Semisynthetic Opioids in the National Vital Statistics System (NVSS)* and the RADARS System Poison Center Program** from 2003 through 2015



*T40.2 Natural and semisynthetic opioids: oxycodone, morphine, hydromorphone, oxymorphone, others.
**RADARS System opioids: oxycodone, hydrocodone, morphine, hydromorphone, and oxymorphone.
Deaths include cases followed to a known medical outcome whose death was related to the reported exposure.

Figure 9. Correlation of Mortality Reports of Heroin in the National Vital Statistics System (NVSS)* and the National Poison Data System (NPDS)** from 2005 through 2015



*T40.1 (heroin) was the multiple cause-of-death code that was used.

Comment: RADARS System Treatment Center Programs –Participating treatment centers varied during the study period

The table below shows the percentage of the US population, the number of centers, and the number of states covered during the study period. The program actually expanded during this time. Sensitivity analyses for each of the primary outcomes were performed, restricting the analysis to only treatment centers who participated in both the pre- and post-REMS evaluation periods (33.8% of US population in 46 states). The magnitude of the difference between the ER/LA opioid analgesics and the comparator group (IR opioid analgesics) increased, thus strengthening the result that indicated a greater reduction in abuse as reported in treatment centers for ER/LA opioid analgesics than for IR opioid analgesics. This analysis illustrates the sensitivity and specificity of this program.

Table 4. RADARS System Treatment Center Programs Participation and Coverage 2010 through 2014

	2010	**2011**	**2012**	**2013**	**2014**
% of US population covered	67.9%	68.9%	76.3%	75.3%	73.8%
Number of centers	174	197	208	232	207
Number of states	50	50	49	49	49

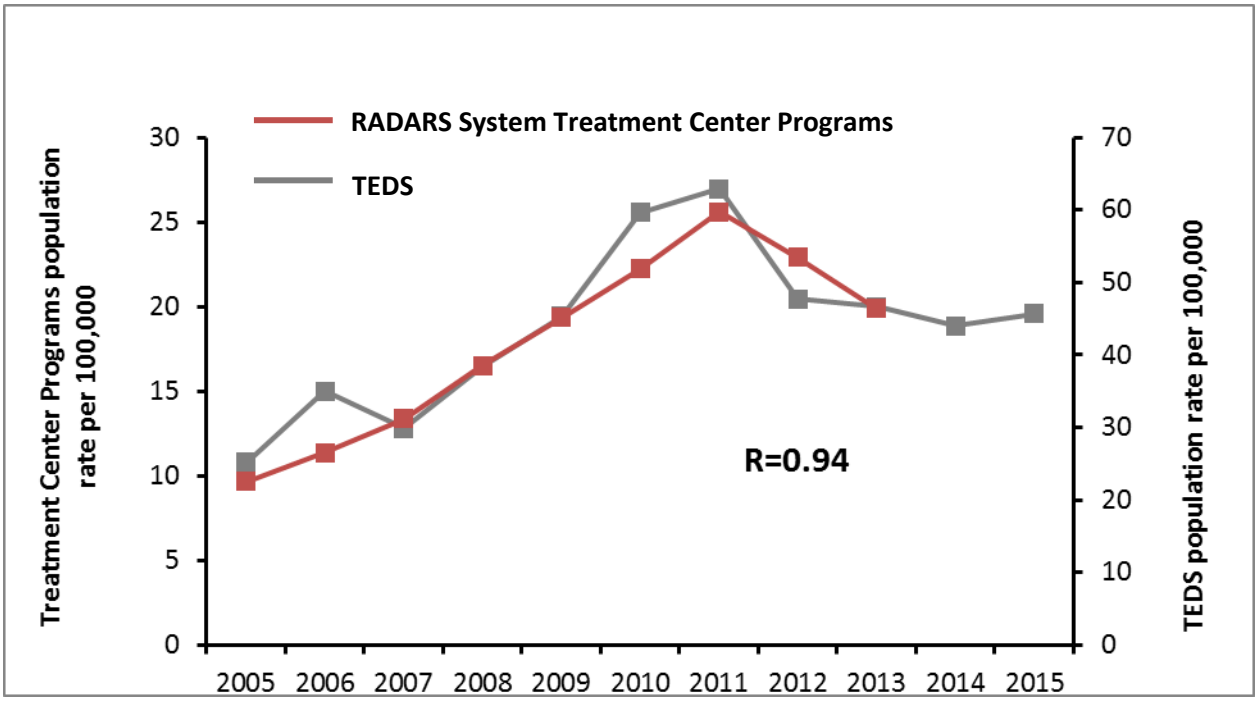
Table 5. RADARS System Treatment Center Program Sensitivity Analysis to Evaluate Potential Bias of Participating Centers

		All Data	**Centers Participating in all Quarters**
ER/LA Opioid Analgesics	Population	-47.02(-60.00,-29.81)	-48.93 (-61.44, -32.36)
	Prescription	-46.31(-59.60, -28.64)	-48.80(-61.50, -31.91)
	Dosing Units	-39.24(-53.27, -20.98)	-41.47(-54.82, -24.17)
IR Prescription Opioids	Population	-12.09(-27.31, 6.32)	-11.15(-24.71, 4.86)
	Prescription	-2.27 (-18.78, 17.6)	-3.61(-17.61, 12.16)
	Dosing Units	-1.74(-19.2, 19.48)	-2.46 (-16.95, 14.55)

Comment: RADARS System Treatment Center Programs – Trends in surveyed centers may not represent national trends

Another commonly referenced data source in studying the substance abuse treatment center population is the TEDS which is maintained by the Center for Behavioral Health Statistics and Quality at SAMHSA. There is high correlation between population based rates of opioid abuse in the RADARS System Treatment Center Programs and TEDS (R=0.94).

Figure 10. Correlation of Treatment Center Population Rates of Opioids in the RADARS System Treatment Center Programs and the Treatment Episode Dataset (TEDS) from 2005 through 2013



Comment: RADARS System Treatment Center Programs – The survey instrument is amended periodically, abuse prevalence estimates can change over time due to these adjustments in the survey instrument

The core questions of the questionnaire did not change during the study period. The questionnaire is updated quarterly to reflect any changes to the prescription opioid market. Otherwise, these important data would be lost. Products were added during the study period however no products were removed. Patients are encouraged to endorse all drugs used to get high hence any bias would likely be toward more endorsements rather than fewer. Despite this potential bias, endorsements declined.

Comment: RADARS System College Survey Program – It is uncertain how well this program represents college students in the US or how the study sample might have changed over time – Trends in College Survey Program are different than other programs

While the demographics of the College Survey Program participants are comparable to the NSDUH College Student sample, it is unclear if there is a bias in a population that would volunteer for an online survey. The demographics of the study participants did not change significantly during the study periods.

It was not expected that College Survey would necessarily show the same trends as other larger programs. College students have very low rates of non-medical use of prescription opioids and are typically younger than those most commonly affected. This is a small

independent cohort therefore would not necessarily be expected to follow trends of the entire population.

Table 6. Demographics of Participants in the RADARS System College Survey Program and the National Survey of Drug Use and Health (NSDUH)

	College Survey 18-22 Years n=16,078	**NSDUH College Students 18-22 Years n=32,245**
Gender		
Female	59.8%	52.5%
Male	40.2%	47.5%
Ethnicity/Race		
Non-Hispanic White	57.8%	59.3%
Non-Hispanic Black/African American	10.5%	12.8%
Non-Hispanic Asian	9.5%	7.2%
Non-Hispanic American Indian or Alaska Native	0.6%	0.4%
Non-Hispanic More than One Race	NA	2.2%
Non-Hispanic Native Hawaiian or Other Pacific Islander	0.5%	0.4%
Non-Hispanic Other Race	1.3%	NA
Hispanic	17.1%	17.7%
I do not wish to provide this information	2.6%	NA

CONCLUSION

We present this data to inform the discussion about the value and interpretation of postmarketing surveillance data. We can say that convergent validity is evident in that a wide range of sources indicate that prescription drug abuse overall is decreasing and that deaths did not increase from 2011 to 2014. The role of ER/LA Opioid Analgesic REMS in these trends cannot currently be proven due to the many other interventions and market changes that have occurred during the study period although it is possible it may have been one of several factors that contributed to the decline.

DISCLOSURE

No direct funding has been received for the preparation and submission of this document. The RADARS System is supported by subscriptions from pharmaceutical manufacturers for surveillance, research and reporting services. RADARS System is the property of Denver Health and Hospital Authority, a political subdivision of the State of Colorado. Denver Health retains exclusive ownership of all data, databases and systems. Subscribers do not participate in data collection or analysis, nor do they have access to the raw data.

REFERENCES

1. Dart RC, Surratt HL, Cicero TJ, Parrino MW, Severtson SG, Bucher Bartelson B, Green JL. Trends in opioid analgesic abuse and mortality in the United States. *N Engl J Med* 2015;372(3):241-8.

2. Davis JM, Severtson SG, Bucher-Bartelson B, Dart RC. Using poison center exposure calls to predict prescription opioid abuse and misuse-related emergency department visits. 2013. *Pharmacoepidemiology and Drug Safety*. 2014; 23(1):18-25.
3. Center for Behavioral Health Statistics and Quality (2013). *Drug Abuse Warning Network Methodology Report, 2011 Update*. Rockville, MD: Substance Abuse and Mental Health Services Administration.
4. Mowry JB, Spyker DA, Brooks DE, McMillan N, Schauben JL. 2014 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 32nd Annual Report. *Clin Toxicol.* 2015; 53(10):962–1146.)

APPENDIX A. RADARS System Poison Center Program Sensitivity Analysis to Control for Variation in Participating Centers

Figure A1.
The RADARS® System Poison Center Program
Treated/Evaluated and Released
Percent Change from Pre-Implementation to Active Period Average Population-Adjusted Rates for All Centers and Those Reporting Throughout the Study Period
From Third Quarter 2010 Through Fourth Quarter 2014

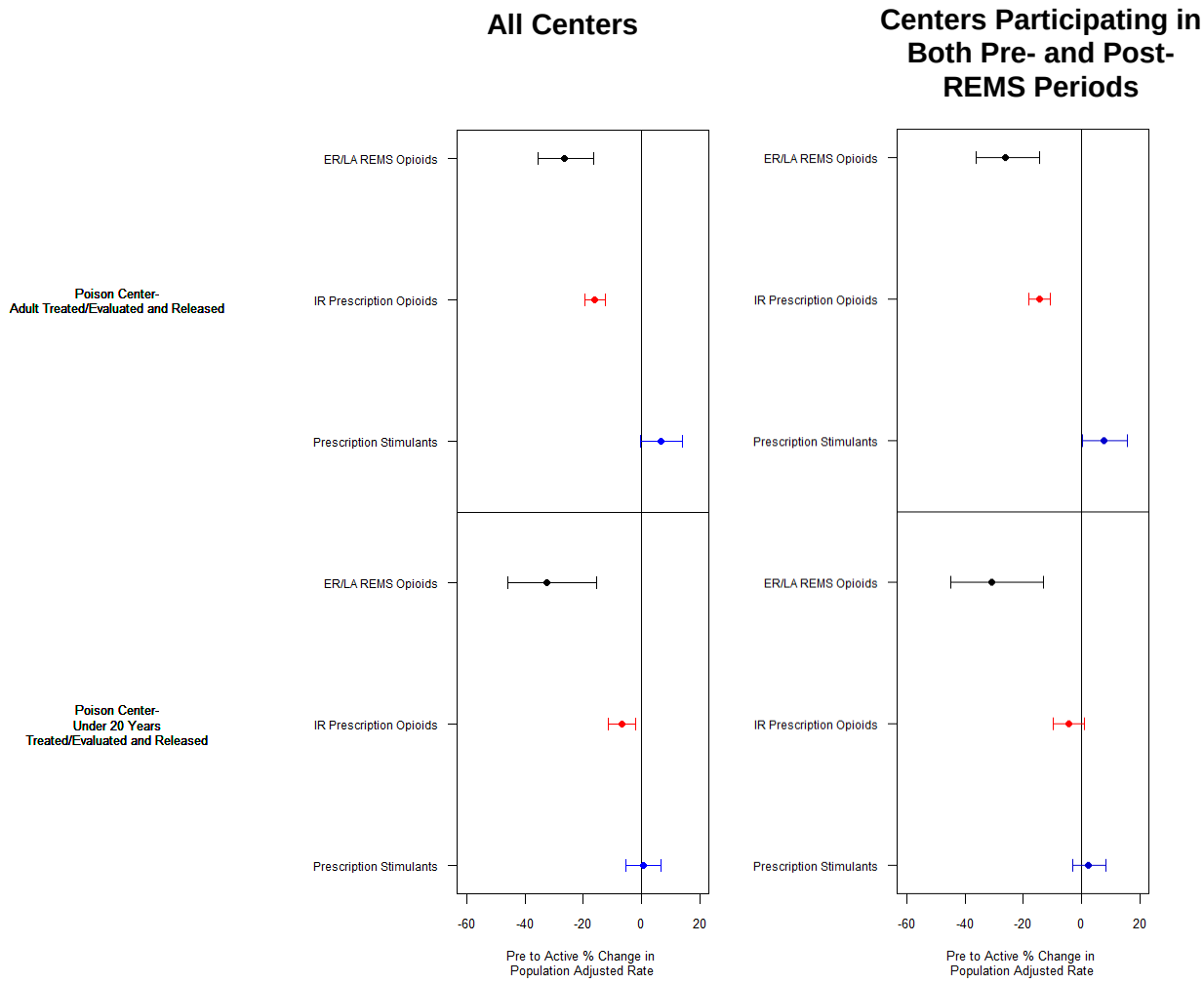


Figure A2.
The RADARS® System Poison Center Program
Treated/Evaluated and Released
Percent Change from Pre-Implementation to Active Period Average Prescription-Adjusted Rates for All Centers and Those Reporting Throughout the Study Period
From Third Quarter 2010 Through Fourth Quarter 2014

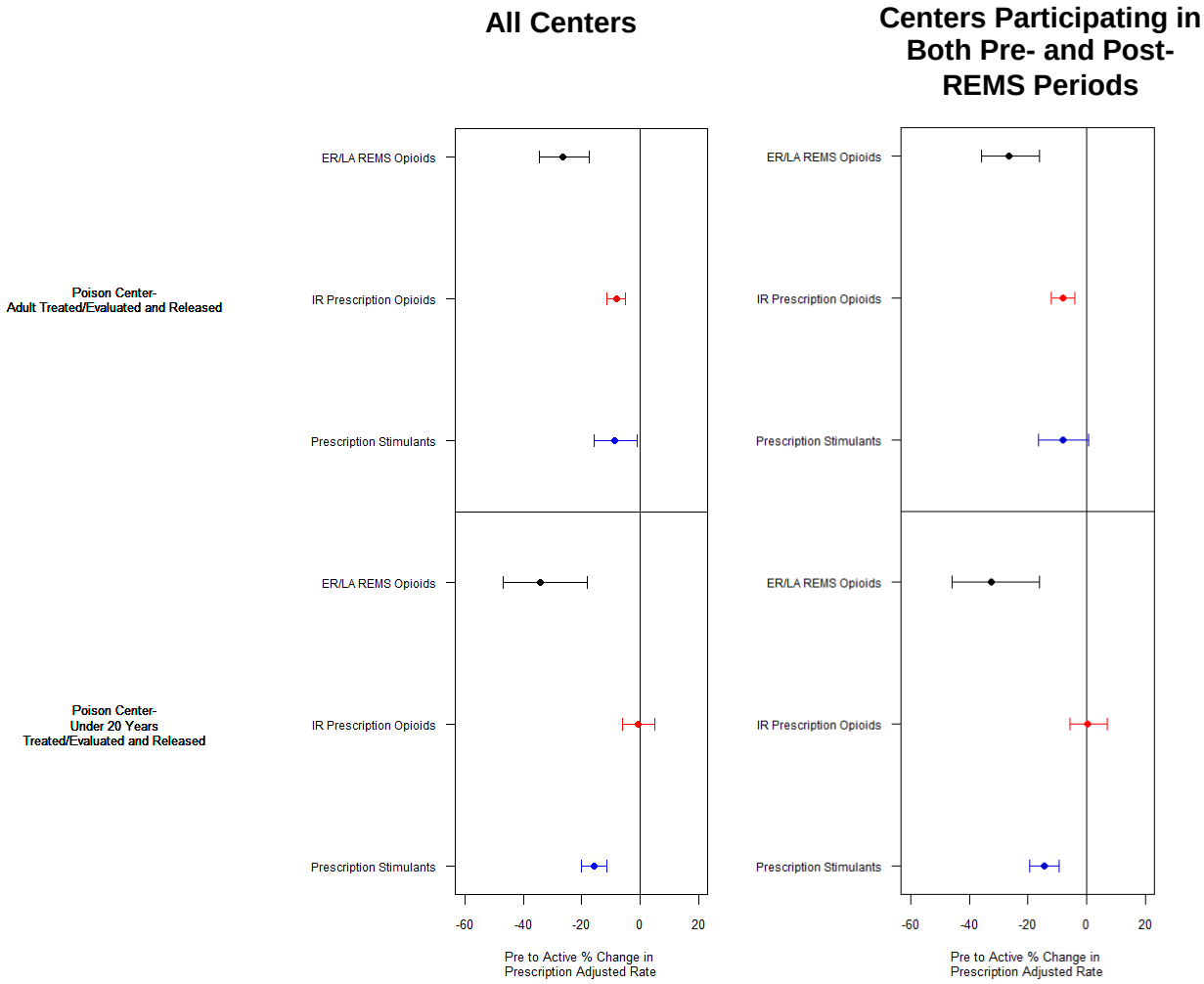


Figure A3.
The RADARS® System Poison Center Program
Intentional Abuse
Percent Change from Pre-Implementation to Active Period Average Population-Adjusted Rates for All Centers and Those Reporting Throughout the Study Period
From Third Quarter 2010 Through Fourth Quarter 2014

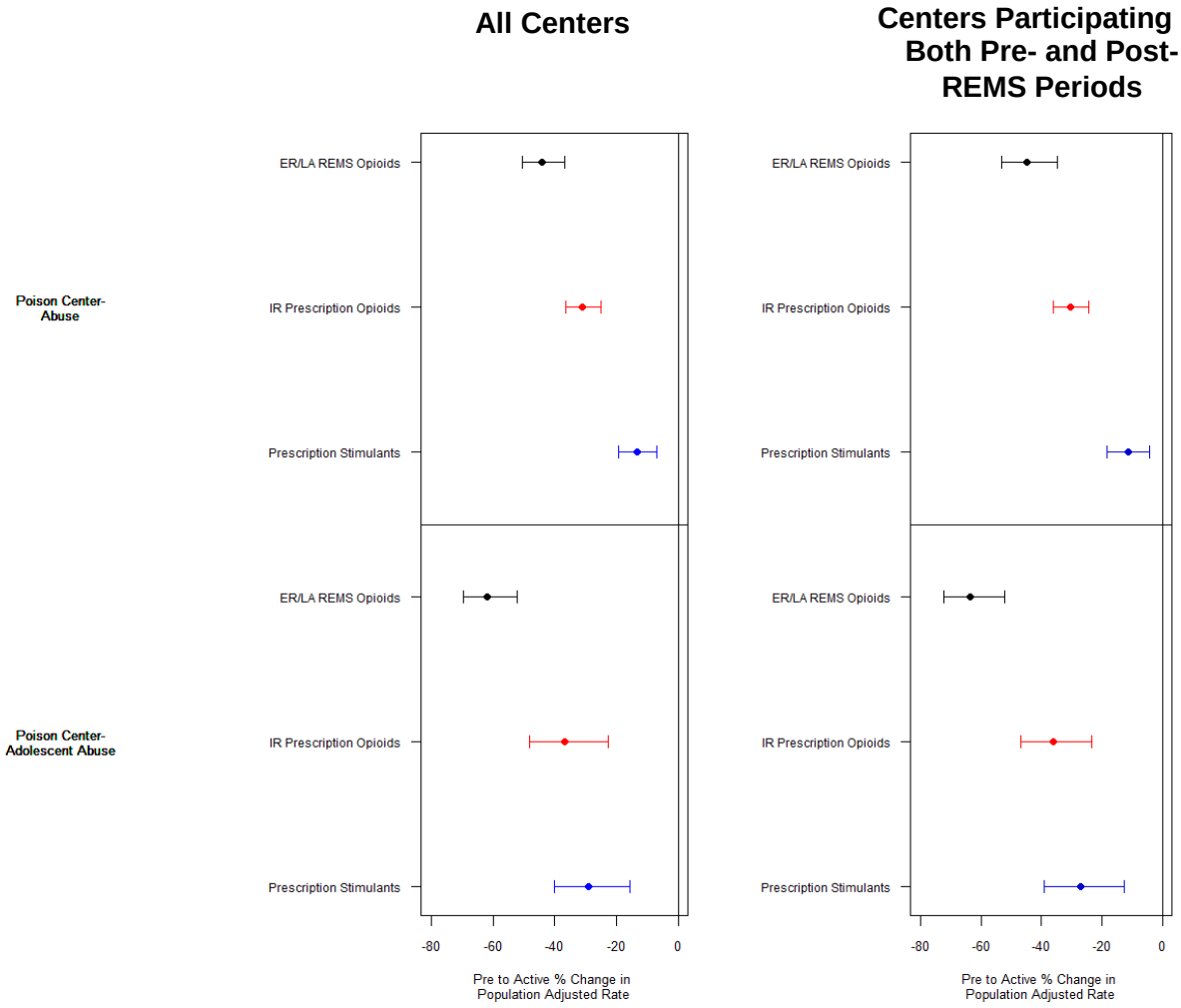


Figure A4.
The RADARS® System Poison Center Program
Intentional Abuse
Percent Change from Pre-Implementation to Active Period Average Prescription-Adjusted Rates for All Centers and Those Reporting Throughout the Study Period
From Third Quarter 2010 Through Fourth Quarter 2014

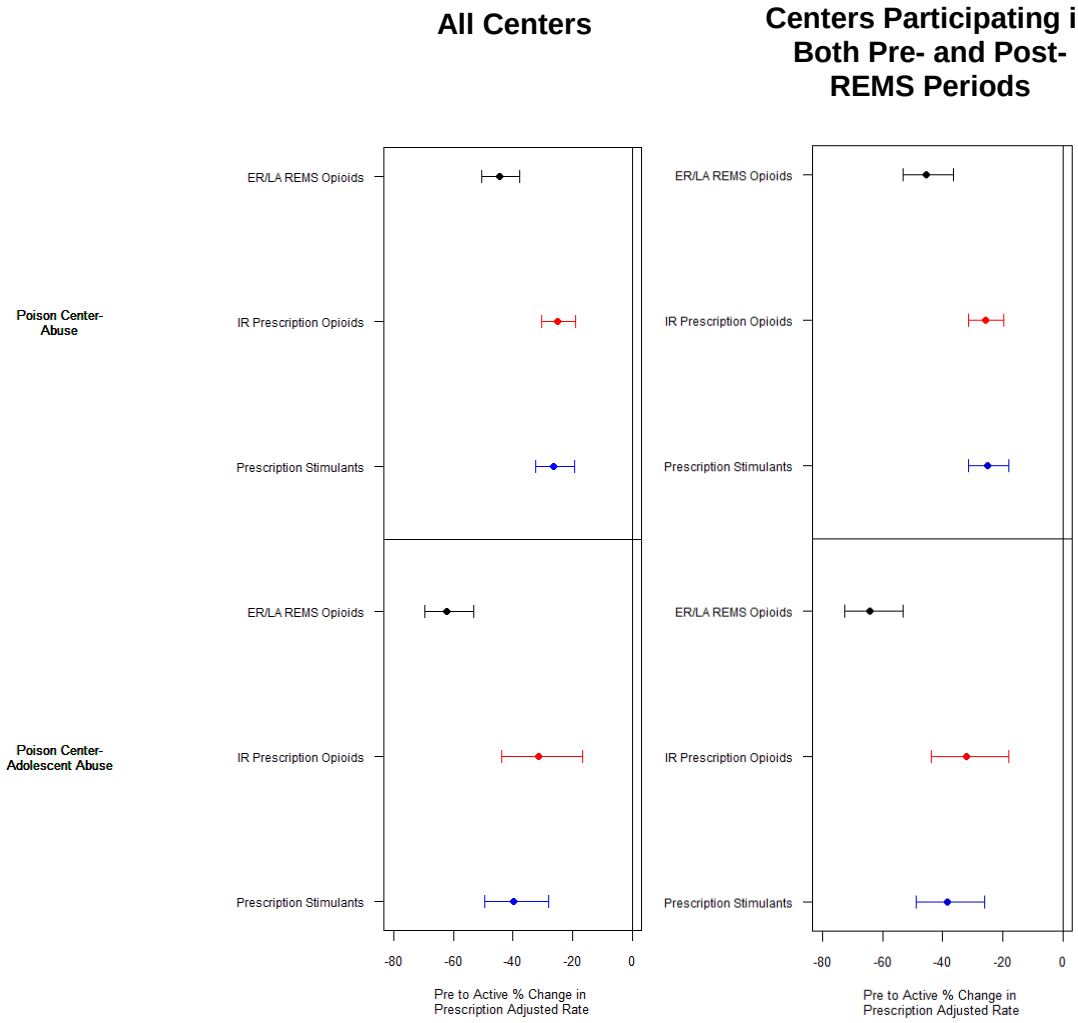


Figure A5.
The RADARS® System Poison Center Program
Misuse
Percent Change from Pre-Implementation to Active Period Average Population-Adjusted Rates for All Centers and Those Reporting Throughout the Study Period
From Third Quarter 2010 Through Fourth Quarter 2014

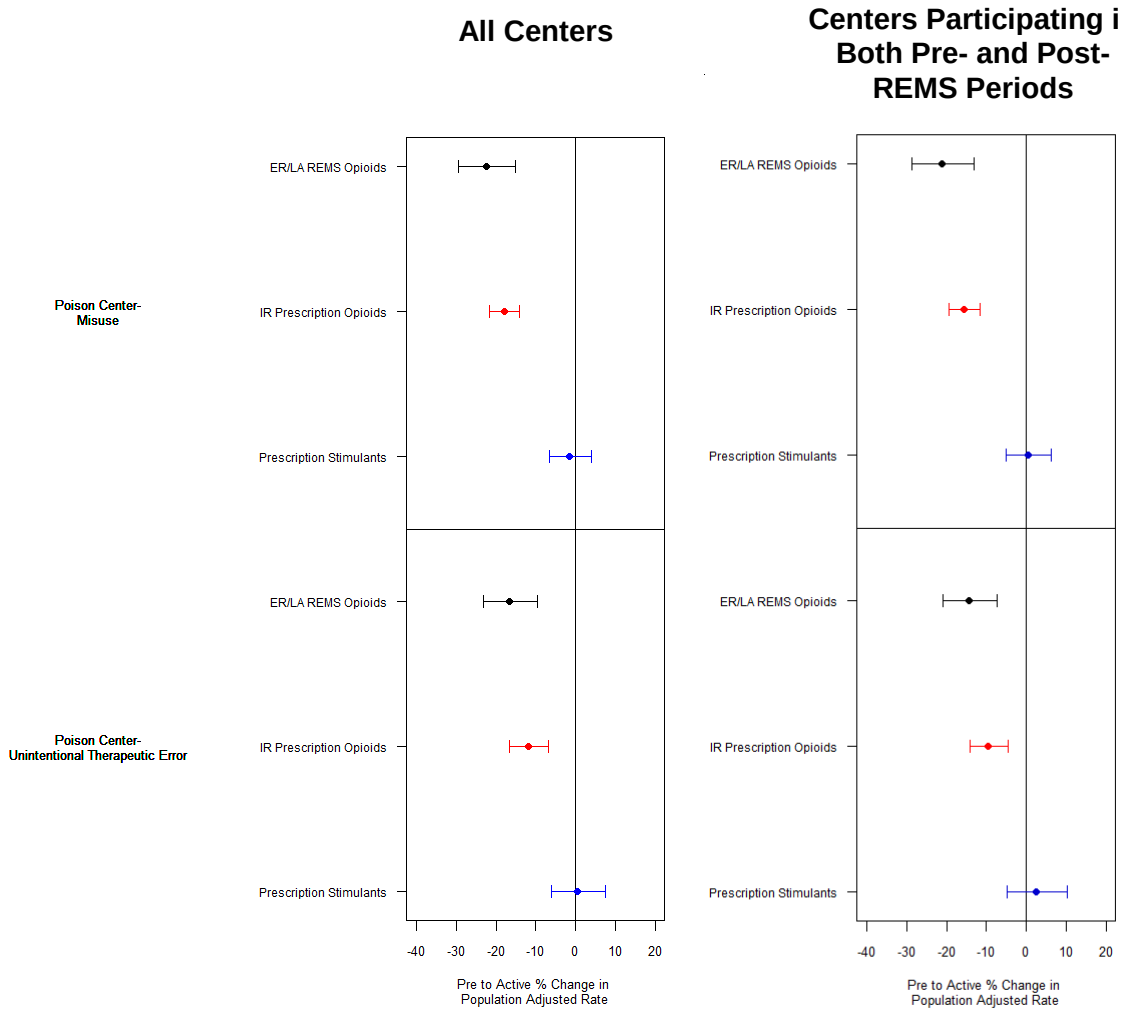


Figure A6.
The RADARS® System Poison Center Program
Misuse
Percent Change from Pre-Implementation to Active Period Average Prescription-Adjusted Rates for All Centers and Those Reporting Throughout the Study Period
From Third Quarter 2010 Through Fourth Quarter 2014

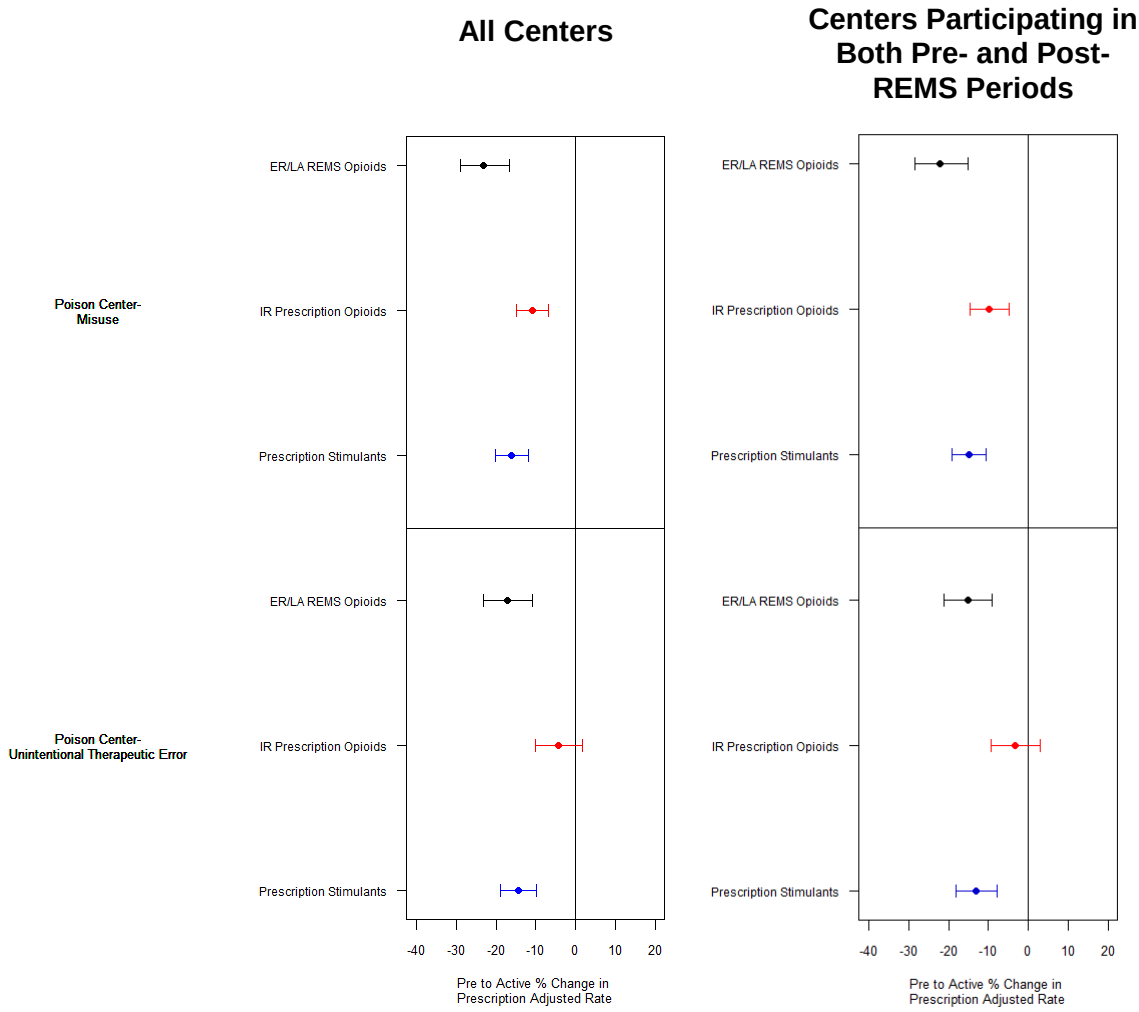


Figure A7.
The RADARS® System Poison Center Program
Unintentional Exposures
Percent Change from Pre-Implementation to Active Period Average Population-Adjusted Rates for All Centers and Those Reporting Throughout the Study Period
From Third Quarter 2010 Through Fourth Quarter 2014

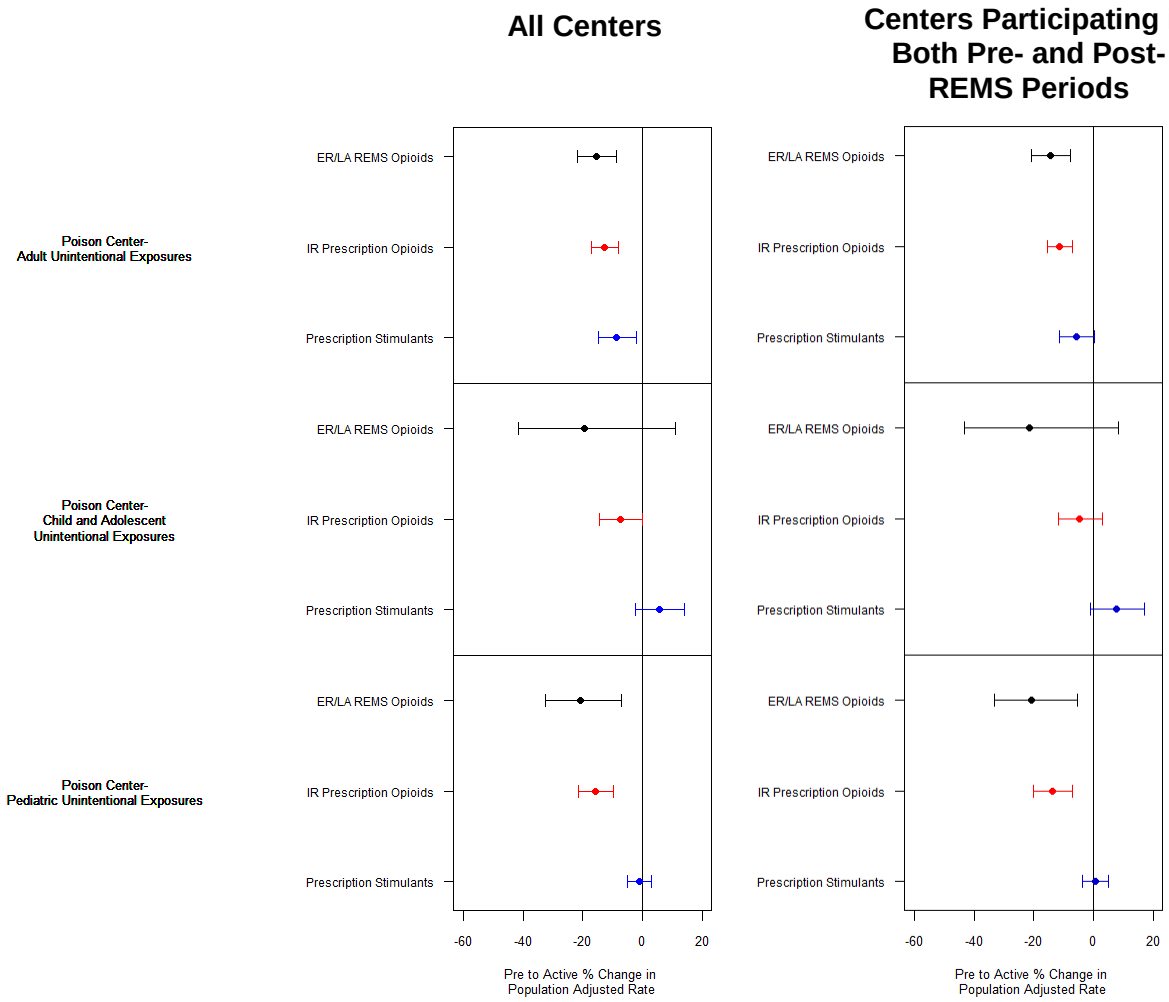


Figure A8.
The RADARS® System Poison Center Program
Unintentional Exposures
Percent Change from Pre-Implementation to Active Period Average Prescription-Adjusted Rates for All Centers and Those Reporting Throughout the Study Period
From Third Quarter 2010 Through Fourth Quarter 2014

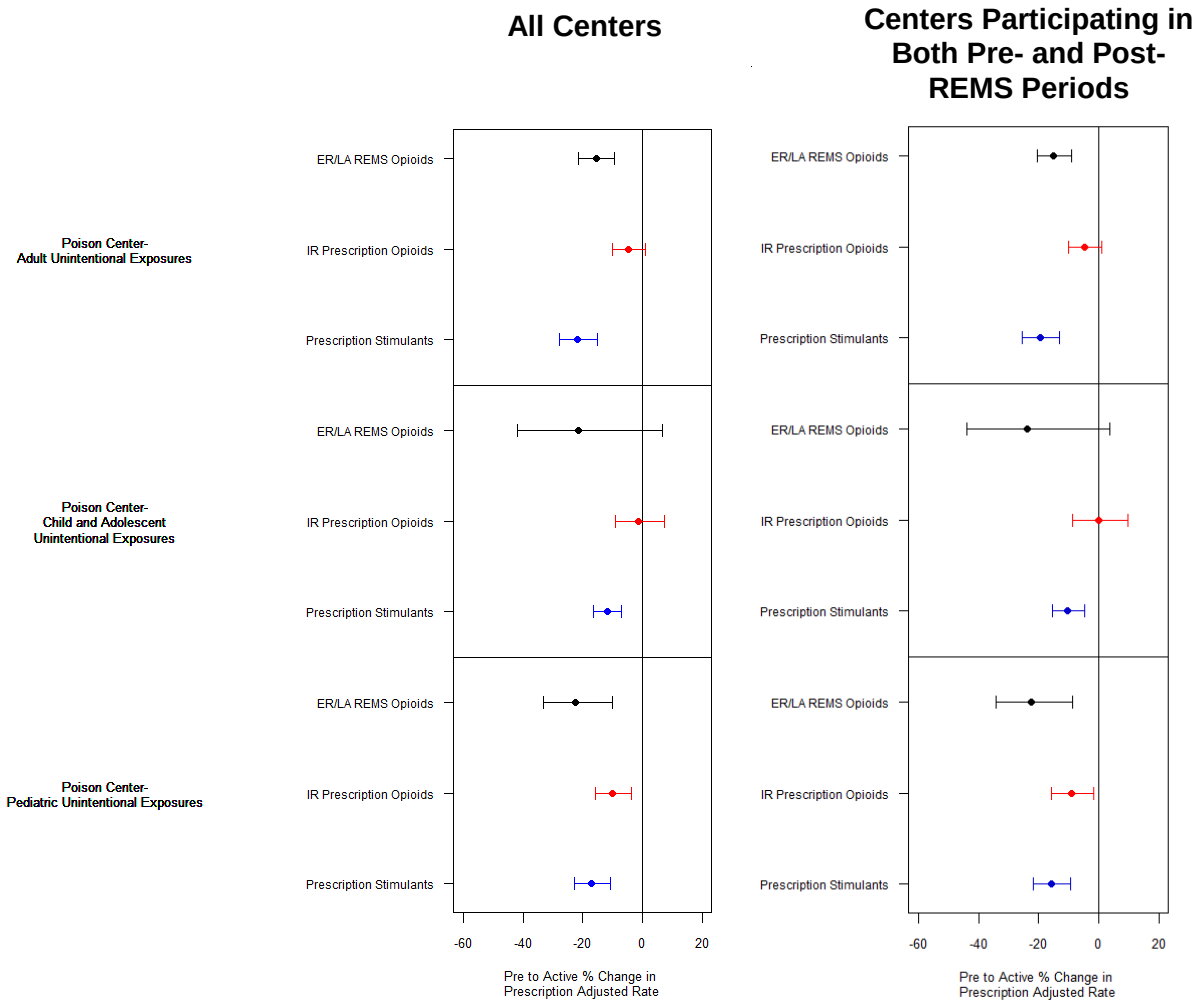


Figure A9.
The RADARS® System Poison Center Program
Pediatric Unintentional General Exposures
Percent Change from Pre-Implementation to Active Period Average Population-Adjusted Rates for All Centers and Those Reporting Throughout the Study Period
From Third Quarter 2010 Through Fourth Quarter 2014

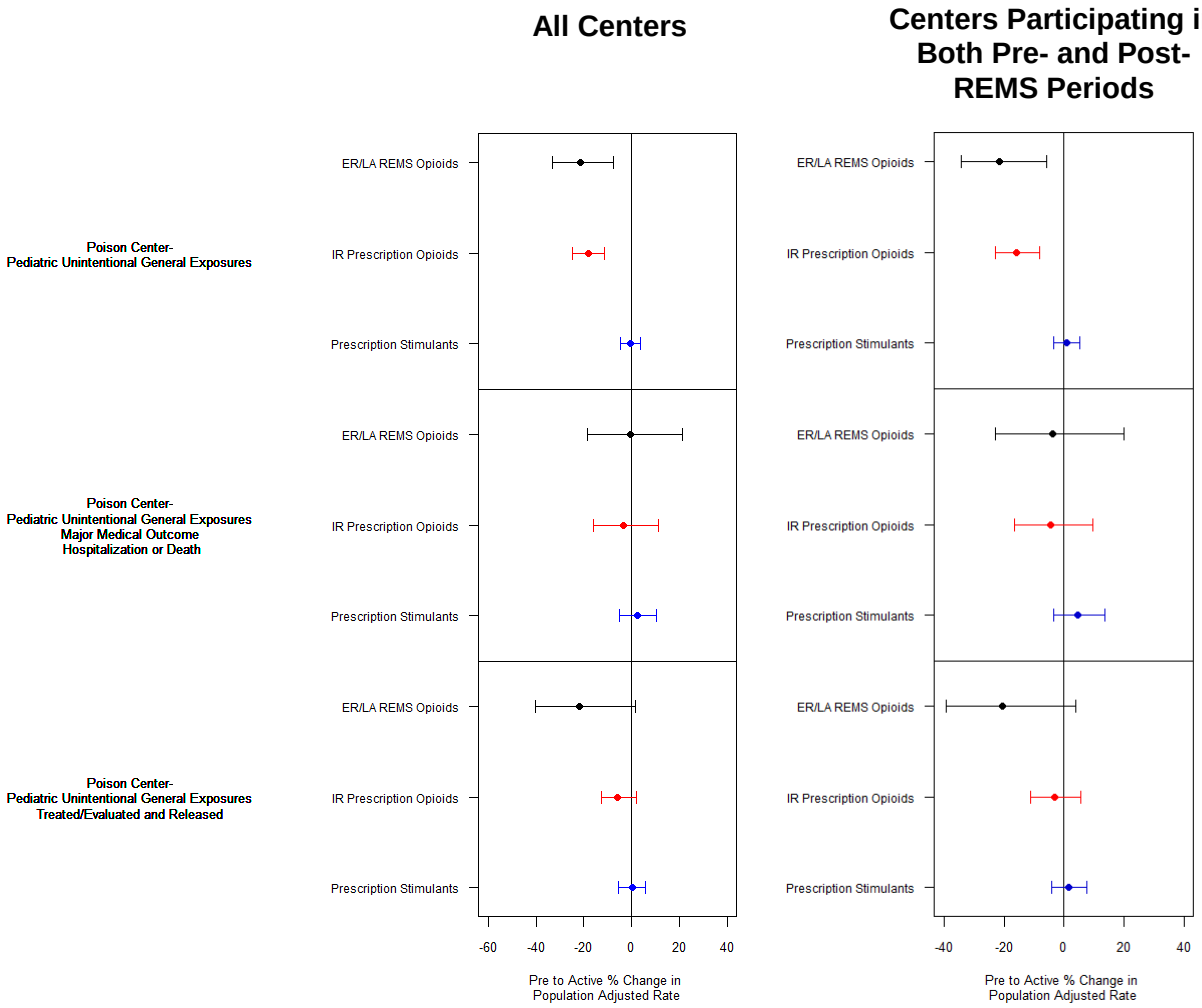


Figure A10.
The RADARS® System Poison Center Program
Pediatric Unintentional General Exposures
Percent Change from Pre-Implementation to Active Period Average Prescription-Adjusted Rates for All Centers and Those Reporting Throughout the Study Period
From Third Quarter 2010 Through Fourth Quarter 2014