SPECIAL ARTICLE

Trends in Opioid Analgesic Abuse and Mortality in the United States

Richard C. Dart, M.D., Ph.D., Hilary L. Surratt, Ph.D., Theodore J. Cicero, Ph.D., Mark W. Parrino, M.P.A., S. Geoff Severtson, Ph.D., Becki Bucher-Bartelson, Ph.D., and Jody L. Green, Ph.D.

ABSTRACT

BACKGROUND

The use of prescription opioid medications has increased greatly in the United States during the past two decades; in 2010, there were 16,651 opioid-related deaths. In response, hundreds of federal, state, and local interventions have been implemented. We describe trends in the diversion and abuse of prescription opioid analgesics using data through 2013.

METHODS

We used five programs from the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) System to describe trends between 2002 and 2013 in the diversion and abuse of all products and formulations of six prescription opioid analgesics: oxycodone, hydrocodone, hydromorphone, fentanyl, morphine, and tramadol. The programs gather data from drug-diversion investigators, poison centers, substance-abuse treatment centers, and college students.

RESULTS

Prescriptions for opioid analgesics increased substantially from 2002 through 2010 in the United States but then decreased slightly from 2011 through 2013. In general, RADARS System programs reported large increases in the rates of opioid diversion and abuse from 2002 to 2010, but then the rates flattened or decreased from 2011 through 2013. The rate of opioid-related deaths rose and fell in a similar pattern. Reported nonmedical use did not change significantly among college students.

CONCLUSIONS

Postmarketing surveillance indicates that the diversion and abuse of prescription opioid medications increased between 2002 and 2010 and plateaued or decreased between 2011 and 2013. These findings suggest that the United States may be making progress in controlling the abuse of opioid analgesics. (Funded by the Denver Health and Hospital Authority.)

From the Rocky Mountain Poison and Drug Center, Denver Health and Hospital Authority, Denver (R.C.D., S.G.S., B.B.-B., J.L.G.); the Center for Applied Research on Substance Use and Health Disparities, Nova Southeastern University, Ft. Lauderdale, FL (H.L.S.); the Department of Psychiatry, Washington University School of Medicine, St. Louis (T.J.C.); and the American Association for the Treatment of Opioid Dependence, New York (M.W.P.). Address reprint requests to Dr. Dart at the Rocky Mountain Poison and Drug Center, Denver Health and Hospital Authority, 777 Bannock St., Mailcode 0180, Denver, CO 80204, or at richard.dart@rmpdc.org.

N Engl J Med 2015;372:241-8.
DOI: 10.1056/NEJMsa1406143

Whatever the measure, the past two decades have been characterized by increasing abuse and diversion of prescription drugs, including opioid medications, in the United States. An estimated 25 million people initiated nonmedical use of pain relievers between 2002 and 2011.[1] The number of deaths per year attributed to prescription opioid medications reached 16,651 in 2010.[2] In response to the epidemic, hundreds of local, regional, state, and federal interventions have been implemented. For example, 49 states have enacted legislation to create prescription-drug monitoring programs.[3] The U.S. Office of National Drug Control Policy has responded to the epidemic with numerous recommendations, including the need to evaluate "current databases that measure the extent of prescription drug use, misuse, and toxicity."[4] In 2013, a Pew Research Center survey showed that only 16% of Americans believed that the United States was making progress in reducing prescription-drug abuse.[5]

The impressive response to the epidemic is heartening, but the effect of these programs is not yet known. Some local and state interventions have described a reduction in the abuse and diversion of prescription opioids after the enactment of state legislation.[6,7] We used the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) System to describe the diversion and abuse of prescription opioid analgesics, using data from January 2002 through December 2013. Because drug abuse is an illegal activity that is often concealed from authorities, the RADARS System uses a "mosaic" approach, measuring abuse and diversion from multiple perspectives, to describe this hidden phenomenon as comprehensively as possible.[8]

Methods

Data Sources and Oversight

We used data from five separate RADARS System programs (Table 1). The Poison Center Program records the substances involved in poison-center cases classified as intentional abuse. The Drug Diversion Program records the drugs involved in cases opened by law-enforcement agencies investigating prescription-drug diversion. The Opioid Treatment Program and the Survey of Key Informants' Patients (SKIP) Program query new patients entering substance-abuse treatment about medications that they have abused in the previous 30 days. The College Survey Program is a Web-based survey in which self-identified college students report their nonmedical use of prescription drugs during the previous 30 days. Further information on each program is provided in Table 1, the Supplementary Appendix (available with the full text of this article at NEJM.org), and previous publications.[9-13] Several analyses describe the relations among these programs and other information sources such as the Drug Abuse Warning Network and the National Vital Statistics System.[10,14]

To represent the trends with respect to prescription opioid analgesics, we grouped all marketed products and formulations (branded and generic) of six prescription analgesics: oxycodone, hydrocodone, hydromorphone, fentanyl, morphine, and tramadol. More recent market entrants with smaller market shares (e.g., oxymorphone and tapentadol) were excluded so that the trend analysis involved a consistent profile of analgesics. Sensitivity analyses showed that the results were not materially affected by the exclusion of these products. In addition, we retrieved data on reported heroin use in the past 30 days in the Opioid Treatment, SKIP, and College Survey Programs. (Not all programs include heroin because the RADARS System focuses on prescription opioids.) Because the RADARS Poison Center Program does not collect data on heroin, we obtained counts of heroin-related cases from the National Poison Data System (American Association of Poison Control Centers) and data on reported heroin use in the past 30 days (National Survey on Drug Use and Health).[15,16] Data on prescription volume were obtained from IMS Health.[17]

The RADARS System is independently owned and operated by the Denver Health and Hospital Authority, which operates the public hospital for the city and county of Denver. The system is supported by subscriptions from pharmaceutical companies that produce prescription opioids or stimulants, which use the data for risk management and postmarketing surveillance reporting to the Food and Drug Administration. Subscribers had no role in the conception, execution, or reporting of this analysis. Each program in the RADARS System is approved by the institutional review board of the principal investigator's institution (Tables S1 through S6 in the Supplementary Appendix).

STATISTICAL ANALYSIS

We plotted the quarterly event rate by dividing the total number of events for the prescription-opioid group for each program by the population of the jurisdiction or coverage area of the program. Population data were obtained from the 2000 and 2010 U.S. Census at the level of the three-digit ZIP Code. Interpolation and extrapolation at this level adjusted for population changes over time. Because the plots were suggestive of a second-degree polynomial fit, we used a Poisson regression model with linear and quadratic terms for time. Quadratic and cubic models were evaluated, and the quadratic model was chosen because it fit the largest number of programs. We computed the time of the maximum predicted value (vertex) of the curve, which indicates when the population rate changed from an increasing to a decreasing trajectory. A negative quadratic coefficient indicates that the quadratic curve is concave (with the apex at the top and the curve opening downward). The t-statistic was used to test whether the quadratic coefficient differed from zero. A significant result indicates that the quadratic term provided a better fit to the data than the linear term.

RESULTS

TRENDS IN OPIOID ANALGESIC USE

Prescription data from IMS Health indicate that at the beginning of 2006, there were 47 million prescriptions dispensed per quarter in the United States for the opioid analgesics included in this study. Prescription volume peaked in the fourth quarter of 2012 at 62 million prescriptions dispensed. Except for this one quarter, the number of prescriptions trended slightly downward from 2011 through 2013, ending at 60 million prescriptions per calendar quarter for study medications (Fig. 1A).

In the Drug Diversion Program, the calculated quarterly event rate for prescription opioids increased from approximately 1.5 per 100,000 population in 2002 to 2.9 in 2012 and then decreased to 2.5 by the end of 2013 (Fig. 1B). In the Poison Center Program, the quarterly abuse rate for opioid analgesics increased from 0.20 per 100,000 population in 2003 to 0.56 in 2010 and then decreased to 0.35 by the end of 2013 (Fig. 1C). In the Opioid Treatment Program, the rate of prescription opioid abuse increased from

Table 1. Description of Surveillance Programs in the RADARS System.*

Program	Definition of Event	Respondent	Program Coverage	Data Collection	No. of Events Involving Opioid Analgesic and Corresponding Drug Mentions
Drug Diversion	Written complaint or report	Law-enforcement agencies	260 drug-diversion respondents in 49 states, with jurisdictions covering 38.1% of U.S. population	Standardized report	145,090 cases involving 146,786 opioid analgesic mentions, 2002–2013
Poison Center	Person choosing to contact a poison center	Patient, acquaintance, or health care professional	49 regional U.S. poison centers in 46 states (91.5% of total U.S. population)	Electronic medical record	456,610 cases involving 491,874 opioid analgesic mentions, 2003–2013
Opioid Treatment	Reported use of drugs to get "high"	Patient entering substance-abuse treatment program	66 programs in 34 states	Standardized questionnaire on admission	41,031 cases involving 183,573 opioid analgesic mentions, 2005–2013
Survey of Key Informants' Patients	Reported use of drugs to get "high"	Patient entering substance-abuse treatment program	109 programs in 45 states	Standardized questionnaire on admission	10,214 cases involving 64,678 opioid analgesic mentions, 2008–2013
College Survey	Reported nonmedical use of prescription drugs	Self-identified college students	2000 students each term (spring, summer, and fall)	Web-based survey	3564 cases involving 11,871 opioid analgesic mentions, 2008–2013

* RADARS denotes Researched Abuse, Diversion, and Addiction-Related Surveillance.

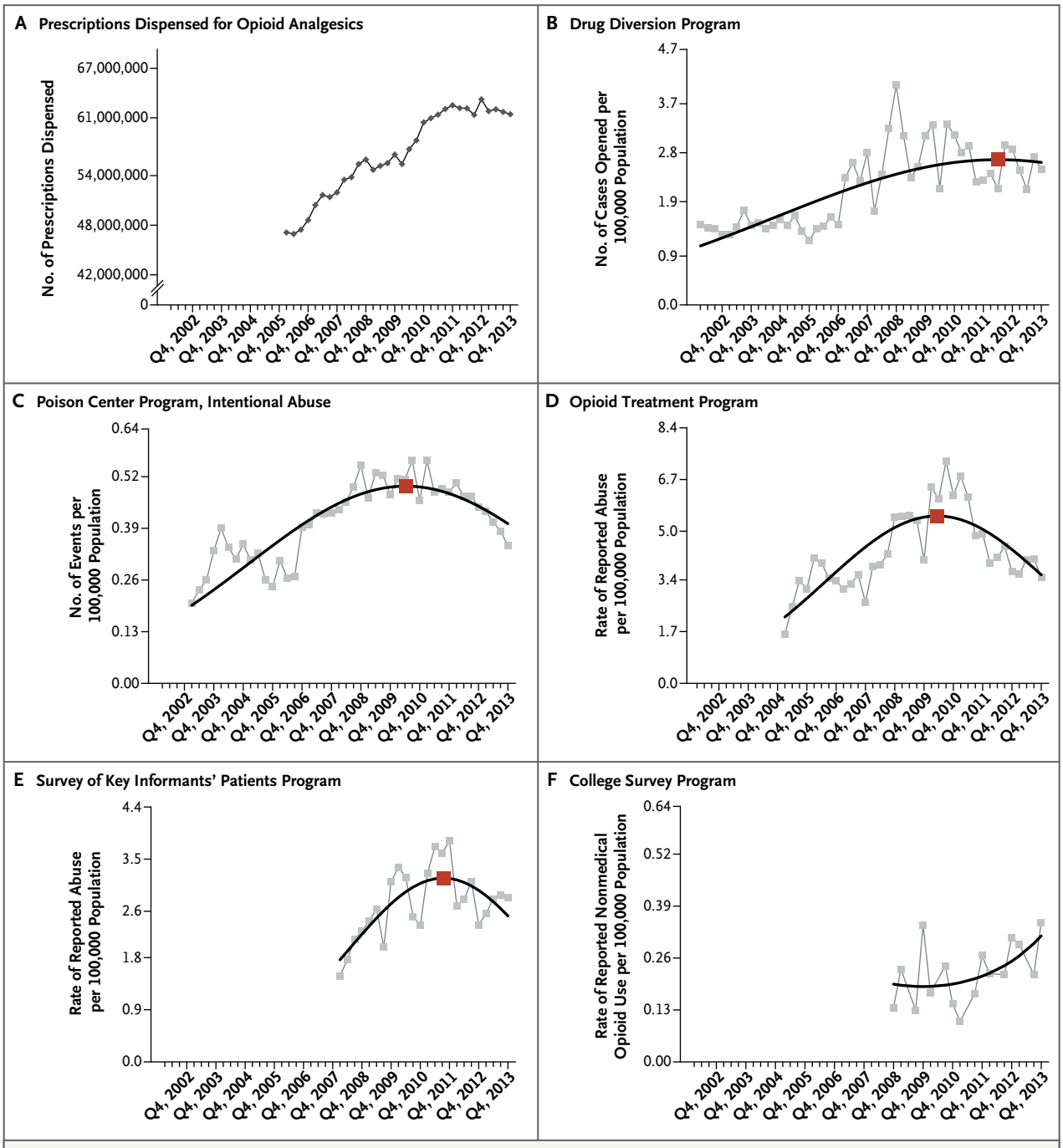

Figure 1. Prescriptions Dispensed for Opioid Analgesics and Rates of Abuse and Diversion, RADARS System, 2002–2013.

Data are displayed according to calendar quarter. Panel A shows the number of prescriptions dispensed for the opioid analgesics included in the analysis (IMS Health). Panel B shows the rate of drug-diversion cases opened. Panel C shows the rate of cases of intentional abuse reported to participating poison centers. Panel D shows the rate of reported abuse by persons entering methadone programs. Panel E shows the rate of reported abuse by patients entering other substance-abuse treatment programs. Panel F shows the rate of reported nonmedical opioid use by college students. The red boxes in Panels B through E indicate the vertex of the quadratic curve. (There is no red box in Panel F because the quadratic terms were not significant; Panel A is provided for context and was not part of the planned analysis.) Details of the data-collection procedure and case definition are provided in the Supplementary Appendix. RADARS denotes Researched Abuse, Diversion, and Addiction-Related Surveillance.

1.6 per 100,000 population in 2005 to 7.3 in 2010 and then decreased to 3.5 by the end of 2013 (Fig. 1D). In the SKIP Program, the rate of prescription opioid abuse increased from 1.5 per 100,000 population in 2008 to 3.8 in 2011 and then decreased to 2.8 by the end of 2013 (Fig. 1E). In the College Survey Program, the rate of nonmedical use increased from 0.14 per 100,000 population in 2008 to 0.35 by the end of 2013 (Fig. 1F). Using a Poisson regression model, we found that the quadratic coefficient was negative and significantly different from zero in the Poison Center Program ($P<0.001$), the Drug Diversion Program ($P=0.009$), the Opioid Treatment Program ($P<0.001$), and the SKIP Program ($P=0.001$). Before mid-2010, the rate of diversion or abuse was increasing in each program; however, the rate in each program trended downward by 2013. The only exception was the College Survey Program, in which the quadratic term was not significant ($P=0.41$).

Reported heroin use generally increased over time. In poison centers, as evidenced by data from the National Poison Data System, the rate of heroin-related cases started increasing in 2006 and appeared to accelerate in late 2010 (Fig. 2A). In conjunction with increasing heroin use, cases involving the extended-release formulation of oxycodone (OxyContin, Purdue Pharma) decreased substantially after the introduction of an abuse-deterrent formulation (Fig. 2A). In the Opioid Treatment Program, the rate of heroin use was flat for the period from 2005 through 2013, and the rate of abuse of reformulated extended-release oxycodone decreased after 2010 (Fig. 2B). In the SKIP Program, the rate of heroin use increased in 2011 and remained increased, whereas the rate of abuse of reformulated extended-release oxycodone decreased (Fig. 2C). In the College Survey Program, the rate of heroin use was volatile but generally flat, whereas the rate of abuse of reformulated extended-release oxycodone edged upward (Fig. 2D). Reported use of heroin increased after 2005 in the National Survey on Drug Use and Health (Fig. 2E).

OPIOID-RELATED DEATHS

The rate of death associated with heroin use (data from the National Poison Data System) was inversely related to the rate of death associated with the use of prescription opioid drugs. The rate of opioid-related death increased from 2002 to 2006, plateaued from 2006 through 2008, then decreased slightly from 2009 through 2013 (Fig. 3). In contrast, the rate of heroin-related death was flat from 2002 to 2010 but increased each subsequent year through 2013.

DISCUSSION

Our results show a parallel relationship between the availability of prescription opioid analgesics through legitimate pharmacy channels and the diversion and abuse of these drugs and associated adverse outcomes. Availability increased greatly in the 1990s and continued through 2010 but then plateaued from 2011 through 2013. In concert with these findings, four of five RADARS System surveillance programs reported large increases in diversion and abuse from 2002 to 2010. An inflection point was reached in each program, however, and the rates of diversion and abuse of prescription analgesics subsequently decreased.

For the period before 2011, our results are similar to those in other research reports, with increasing rates of opioid analgesic abuse. The Drug Abuse Warning Network reported an increase of 183% in medical emergencies related to opioid pharmaceuticals from 2004 to 2011, the last year for which data are available.[18] The National Survey on Drug Use and Health noted increasing dependence on and abuse of prescription pain relievers from 2002 through 2012, the last year for which data are available.[19] Similarly, admissions for the treatment of opioid dependence and addiction increased through 2011.[20] These increases in drug availability and abuse have been reflected in the numbers of deaths caused by prescription opioids, which increased for 11 consecutive years and reached 16,651 deaths nationally in 2010.[2]

Few data regarding national trends in prescription-drug abuse and diversion since 2010 have been published. However, emerging data suggest that abuse of prescription opioids may have lessened in some environments. For example, local and state efforts have resulted in a reduction after the enactment of state legislation.[6] Florida had a substantial decrease in the diversion of prescription analgesics, especially oxycodone, after several interventions were implemented in 2010 and 2011.[7] Reported prescription-drug abuse was also reduced in a study

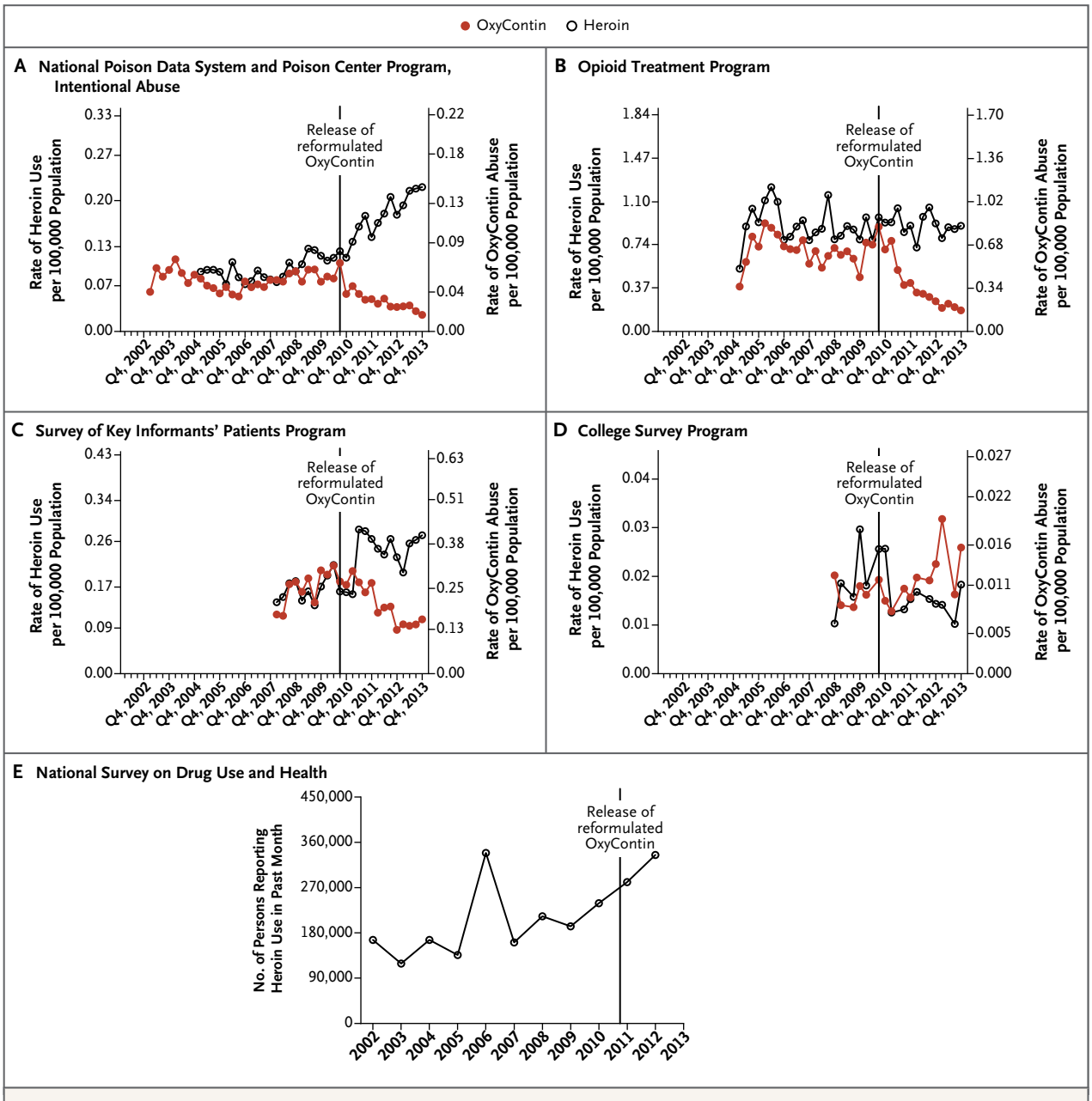

Figure 2. Rates of Heroin Use and OxyContin Abuse before and after OxyContin Reformulation.

Data are displayed according to calendar quarter and in relation to the release of reformulated OxyContin in August 2010 (vertical line in each panel). Panel A shows data for heroin use (National Poison Data System, American Association of Poison Control Centers) and intentional abuse of OxyContin (RADARS Poison Center Program). Panel B shows the rate of reported heroin use and OxyContin abuse by patients entering the RADARS Opioid Treatment Program. Panel C shows the rate of reported heroin use and OxyContin abuse by patients entering the RADARS Survey of Key Informants' Patients Program. Panel D shows the rate of reported heroin use and OxyContin abuse in the RADARS College Survey Program. Panel E shows the rate of reported heroin use in the National Survey on Drug Use and Health (Substance Abuse and Mental Health Services Administration).

involving college students.[21] In contrast, the prevalence of nonmedical use of prescription analgesics remained unchanged in the National Survey on Drug Use and Health through 2012.[19]

The observed trends in opioid analgesic abuse could be related to several factors. The flattening rate of prescription volume since 2011 may have limited the availability of prescription opi-

oids for abuse. This trend may be evidence of either a decreased supply, because prescribers have reduced the number of prescriptions that they write, or a decreased demand, because the number of patients requesting these drugs has decreased. Although it may be assumed that the prescribers control the supply of a drug, the supply is influenced by persons who feign a painful illness to acquire a prescription. A decrease in requests by these persons will result in a decrease in the number of prescriptions filled. For example, studies show that the introduction of a less desirable formulation of oxycodone can rapidly decrease demand for that formulation.[22]

Another explanation involves the hundreds of programs implemented by local, state, and federal governments to improve opioid prescribing, reduce doctor-shopping, limit questionable practices by pain clinics, and otherwise improve the use of opioid analgesics in the United States.[3] In addition, other organizations have implemented myriad programs such as guidelines for responsible opioid prescribing and educational initiatives designed to decrease experimentation. Prescription-monitoring programs now operate in most states, and early studies indicate their effectiveness.[23,24] New opioid analgesic formulations that resist tampering have been introduced. Finally, law enforcement has intervened successfully in some cases, such as closing so-called pill mills in Florida.[7] It seems plausible that these efforts have started to take effect.

The role of switching from the abuse of a prescription opioid to the use of high-purity, low-cost heroin must also be considered.[25] Our results support this explanation, as do results from the National Survey on Drug Use and Health, in which reported use of heroin in the previous month increased from 2006 to 2012 (Fig. 2E).[19] The introduction of abuse-deterrent OxyContin coincided with a flattening of the trajectory of opioid analgesic prescriptions but occurred after the increase in reported heroin use became apparent. Given that 79.5% of new heroin initiates in the National Survey on Drug Use and Health reported that their initial drug was a prescription opioid and that reported heroin use by patients in a substance-abuse program nearly doubled after the introduction of abuse-deterrent OxyContin, it seems likely that the reformulation of extended-release oxycodone in 2010 has contributed to the increase in reported heroin use.[26,27]

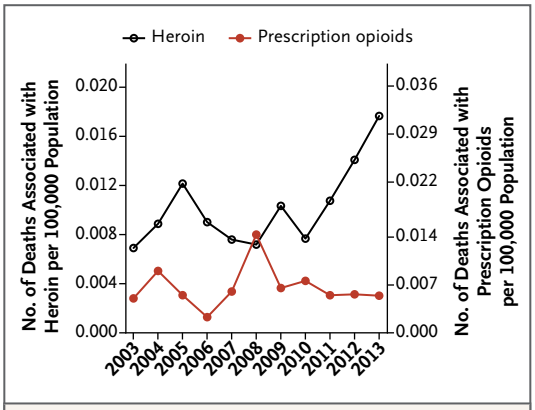

Figure 3. Rates of Death Associated with Heroin and Prescription Opioids, 2002–2013.

Shown is the rate of death associated with prescription opioid drugs (RADARS Poison Center Program) and with heroin (National Poison Data System, American Association of Poison Control Centers), with adjustment for population.

Whatever the precise cause, changes in rates of opioid analgesic abuse are associated with increasing heroin-related mortality. The similarities between data from the National Survey on Drug Use and Health and data from the National Poison Data System with respect to heroin use and adverse consequences are striking (Fig. 2A and 2E, and Fig. 3). A better understanding of the relation between prescription opioid abuse and heroin use is crucial for developing public health policy as well as guiding prevention and treatment initiatives.

The largest threat to the validity of our results is secular change in the study populations. Another concern is methodologic idiosyncrasy resulting in a systematic bias toward reduced diversion and abuse. We believe these explanations for our findings are unlikely because each RADARS program is operated independently by separate principal investigators and each addresses a different aspect of drug abuse. The data source, methods, and data management are different for each program. We cannot identify any programmatic changes that would have created an artifactual decrease in reported opioid use. Further limitations are described in the Supplementary Appendix.

Our results suggest that the United States is making progress in combating the abuse of prescription opioid analgesics. If our observa-

tion of decreased abuse is confirmed, changes in public health policy and strategy will be needed.

Supported by the Denver Health and Hospital Authority.
Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Results from the 2011 National Survey on Drug Use and Health: summary of national findings. (NSDUH series H-44, HHS publication no. (SMA) 12-4713.) Rockville, MD: Substance Abuse and Mental Health Services Administration, 2012.
2. National Vital Statistics System. Multiple cause of death file. Atlanta: Centers for Disease Control and Prevention, 2012 (http://www.cdc.gov/nchs/data/dvs/Record_Layout_2012.pdf).
3. Home and recreational safety: laws by state. Atlanta: Centers for Disease Control and Prevention (http://www.cdc.gov/HomeandRecreationalSafety/Poisoning/laws/state/index.html).
4. Epidemic: responding to America's prescription drug abuse crisis. Washington, DC: Office of National Drug Control Policy, 2011 (http://www.whitehouse.gov/sites/default/files/ondcp/issues-content/prescription-drugs/rx_abuse_plan_0.pdf).
5. Doherty C. Americans see U.S. losing ground against mental illness, prescription drug abuse. Washington, DC: Pew Research Center, November 13, 2013.
6. Franklin GM, Mai J, Turner J, Sullivan M, Wickizer T, Fulton-Kehoe D. Bending the prescription opioid dosing and mortality curves: impact of the Washington State opioid dosing guideline. Am J Ind Med 2012;55:325-31.
7. Surratt HL, O'Grady C, Kurtz SP, et al. Reductions in prescription opioid diversion following recent legislative interventions in Florida. Pharmacoepidemiol Drug Saf 2014;23:314-20.
8. Dart RC. Monitoring risk: post marketing surveillance and signal detection. Drug Alcohol Depend 2009;105:Suppl 1: S26-S32.
9. Inciardi JA, Surratt HL, Stivers Y, Cicero TJ. FDA approvals of generic drugs: impact on the diversion of opioid analgesics with a potential for abuse. J Opioid Manag 2009;5(2):81-7.
10. 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. Pharmacoepidemiol Drug Saf 2014;23:18-25.
11. Rosenblum A, Parrino M, Schnoll SH, et al. Prescription opioid abuse among enrollees into methadone maintenance treatment. Drug Alcohol Depend 2007;90:64-71.
12. Cicero TJ, Inciardi JA, Surratt H. Trends in the use and abuse of branded and generic extended release oxycodone and fentanyl products in the United States. Drug Alcohol Depend 2007;91:115-20.
13. Dart RC, Bartelson BB, Adams EH. Nonmedical use of tapentadol immediate release by college students. Clin J Pain 2014;30:685-92.
14. Dasgupta N, Davis J, Jonsson Funk M, Dart R. Using poison center exposure calls to predict methadone poisoning deaths. PLoS One 2012;7(7):e41181.
15. Mowry JB, Spyker DA, Cantilena LR Jr, Bailey JE, Ford M. 2012 Annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 30th annual report. Clin Toxicol (Phila) 2013;51:949-1229.
16. National Survey on Drug Use and Health. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2013 (https://nsduhweb.rti.org/respweb/homepage.cfm).
17. IMS Institute for Healthcare Informatics. HSRN data brief: Xponent. August 2011 (http://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/Health%20Services%20Research%20Network/Xponent_Data_Brief_Final.pdf).
18. Drug Abuse Warning Network, 2011: national estimates of drug-related emergency department visits. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2013 (http://www.samhsa.gov/data/sites/default/files/DAWN2k11ED/DAWN2k11ED/DAWN2k11ED.pdf).
19. Results from the 2012 National Survey on Drug Use and Health: summary of national findings. (NSDUH series H-46, HHS publication no. (SMA) 13-4795.) Rockville, MD: Substance Abuse and Mental Health Services Administration, 2013.
20. Treatment Episode Data Set (TEDS): 2001–2011 — state admissions to substance abuse treatment services. (BHSIS series S-68, HHS publication no. (SMA) 14-4832.) Rockville, MD: Substance Abuse and Mental Health Services Administration, 2013.
21. McCabe SE, West BT, Teter CJ, Boyd CJ. Trends in medical use, diversion, and nonmedical use of prescription medications among college students from 2003 to 2013: connecting the dots. Addict Behav 2014;39:1176-82.
22. Severtson SG, Bucher Bartelson B, Davis JM, et al. Reduced abuse, diversion, and therapeutic errors following reformulation of extended-release oxycodone in 2010. J Pain 2013;14:1122-30.
23. Prescription drugs: state monitoring programs provide useful tool to reduce diversion. Washington, DC: General Accounting Office, May 2002 (http://www.gao.gov/new.items/d02634.pdf).
24. Reifler LM, Droz D, Bailey JE, et al. Do prescription monitoring programs impact state trends in opioid abuse/misuse? Pain Med 2012;13:434-42.
25. Unick GJ, Rosenblum D, Mars S, Ciccarone D. Intertwined epidemics: national demographic trends in hospitalizations for heroin- and opioid-related overdoses, 1993-2009. PLoS One 2013;8(2):e54496.
26. Muhuri PK, Gfroerer JC, Christine Davies M. Associations of nonmedical pain reliever use and initiation of heroin use in the United States. CBHSQ [Center for Behavioral Health Statistics and Quality] Data Review. August 2013 (http://www.samhsa.gov/data/2k13/DataReview/DR006/nonmedical-pain-reliever-use-2013.htm).
27. Cicero TJ, Ellis MS, Surratt HL. Effect of abuse-deterrent formulation of OxyContin. N Engl J Med 2012;367:187-9.