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OPIOID OVERDOSES IN INDIANA: A CLOSER LOOK AT OPIOID TYPE

Summary

» The misuse of prescription and illicit opioids remains at epidemic proportions throughout the nation, costing the United States billions of dollars annually.
» Overdose deaths in both the U.S. and Indiana have seen a dramatic rise over the past ten years. Until recently, prescription opioids were responsible for the greatest number of overdose deaths across the country, but now have been surpassed by those from heroin and illicitly manufactured narcotics, primarily fentanyl.
» Persons at greatest risk for a fatal overdose include:
  ○ those who use opioids jointly with alcohol or benzodiazepines,
  ○ those who have chronic health conditions,
  ○ those who have a history of nonfatal overdoses, and
  ○ those who have recently been released from substance abuse treatment or incarceration.
» A number of approaches are available to help prevent fatal overdoses, including:
  ○ Strengthening guidelines for the prescribing of opioids and enacting pain clinic laws to help prevent long-term use of these drugs and limit the risk of diversion;
  ○ Encouraging healthcare professionals who prescribe and/or dispense opioids to use prescription drug monitoring programs in order to monitor opioid use by their patients;
  ○ Increasing the availability of medication-assisted treatment in order to help those addicted to opioids to stop using them; and
  ○ Enhancing availability of and access to naloxone to users of opioids, their families, and persons in the community.

INTRODUCTION

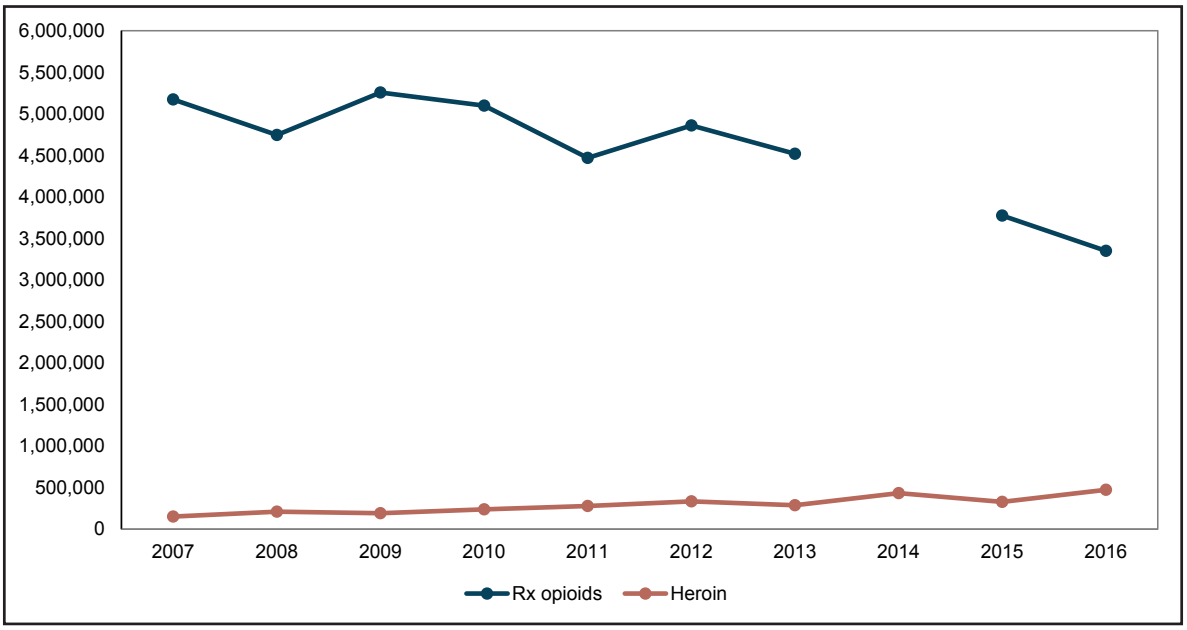
The United States' ongoing opioid epidemic remains a serious public health threat for the nation. The most commonly abused opioids by U.S. citizens are prescription pain medication and heroin, although recently, the use of illegally manufactured fentanyl has risen significantly [1-3]. The opioid epidemic cost the nation $504 billion in 2015 due to lost productivity, substance use treatment, healthcare, criminal justice, social service expenditures, and loss of life [4]. Loss of life due to overdose is the most tragic consequence of the opioid epidemic, a consequence that has been dramatically increasing in frequency for at least the last decade [1, 5]. The purpose of this brief report is to give a summary of the prevalence of opioid use, highlight the rates of fatal overdoses attributable to opioids, describe the risk factors for fatal overdoses, and suggest policies that could potentially help decrease the rate of such overdoses in Indiana.

THE OPIOID EPIDEMIC AND RATES OF OPIOID USE

The start of the opioid epidemic can be traced back to the late 1990s and the campaign by the American Pain Society (APS) to acknowledge pain as the fifth vital sign while simultaneously promoting opioid analgesics as a safe form of treatment. The APS campaign led to a dramatic increase in both production and prescribing of opioid-based pain medications as well as the diversion of these drugs for nonmedical use. As a consequence, the nation experienced a steady rise in both medical and nonmedical opioid use and a concomitant rise in the number of individuals developing opioid use disorders and addiction. In an attempt to curb illicit use, pharmaceutical companies released abuse-deterrent formulations of their drugs while states established prescription monitoring programs and implemented stricter prescribing guidelines as methods for decreasing overall prescribing of these drugs [6, 7]. Consequently, many users of prescription opioids transitioned to heroin use as a cheaper, more accessible, more powerful alternative, while new users of opioids often began their use with heroin rather than prescription pain medication [7-9]. More recently, the powerful synthetic opioid fentanyl, which is often illicitly produced, and its derivatives (e.g., carfentanil) have seen increased popularity as drugs of abuse either on their own or in combination with heroin [2, 3, 10].

Nationally, abuse of prescription opioids peaked in 2009, when the National Survey of Drug Use and Health (NSDUH) estimated that 5,257,000 US citizens ages 12 and older were using opioids. By 2016, the number of current users had dropped by approximately 36% to 3,350,000. As prescription drug misuse declined, heroin use began to rise. The NSDUH reported that in 2016, there were 475,000 current heroin users 12 years of age and

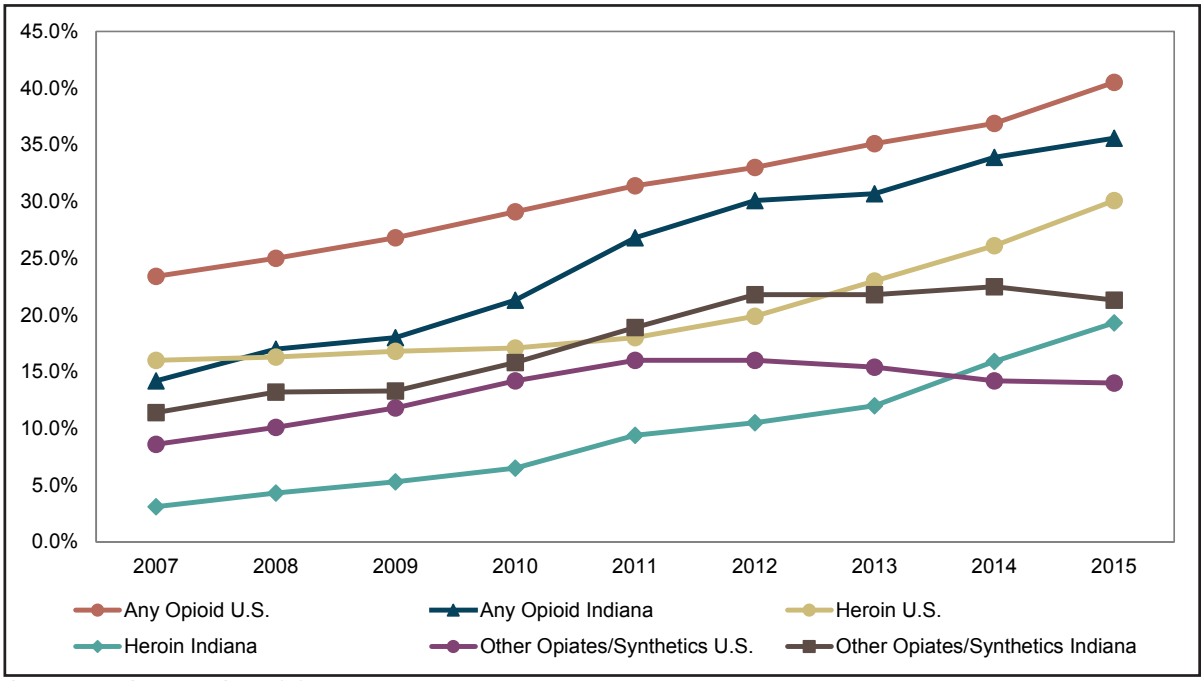
Figure 1. Number of current (past-month) users of prescription opioids and heroin in the United States*



**Note: In 2014, the NSDUH revised its methodology for collection information on use of opioid analgesics, hence data are not available for 2014. Due to this change, data from 2015 and 2016 are not directly comparable to data from previous years.*

older, more than in any previous year. This represented a 210% increase from 2007 (see Figure 1). Although data on current use of heroin or opioid analgesics are not available for Indiana, the NSDUH estimated that in 2016, approximately 24,000 Hoosiers (or 0.4%) ages 12 and older used heroin and 270,000 (or 4.9%) misused opioid analgesics in the past year [11].

Figure 2. Percentage of treatment admissions with reported opioid misuse (TEDS 2007-2015)



Source: SAMHSA, 2015

Evidence of the overall increase in the use of opioids also comes from the Treatment Episode Data Set (TEDS) which collects information on individuals entering substance use treatment. Nationally, persons entering treatment who reported the use of any opioid (i.e., heroin, nonprescription methadone, or opiates/synthetics[1]) increased from 23.4% of admissions in 2007 to 40.5% of admissions in 2015. Similarly, heroin was reported by 30.1% of admissions in 2015, an 88% increase from 2007. Admissions who reported using other opiates/synthetics increased from 8.6% in 2007 peaking at 16.0% in 2011 and 2012 and having dropped slightly to 14.0% in 2015. Indiana has experienced similar trends; however, the percentage of admissions to treatment in Indiana reporting prescription opioids has consistently been higher than that seen in the rest of the country (see Figure 2) [12].

PREVALENCE OF NON-FATAL AND FATAL OPIOID OVERDOSES

Nonfatal Overdoses

An individual can experience an overdose when she or he consumes a larger quantity or a stronger dose of an opioid than the body is capable of metabolizing. The symptoms of an opioid overdose typically include sleepiness, problems breathing, low blood pressure, spasms, and coma, among others. Without appropriate medical attention, overdoses can result not only in serious, long-

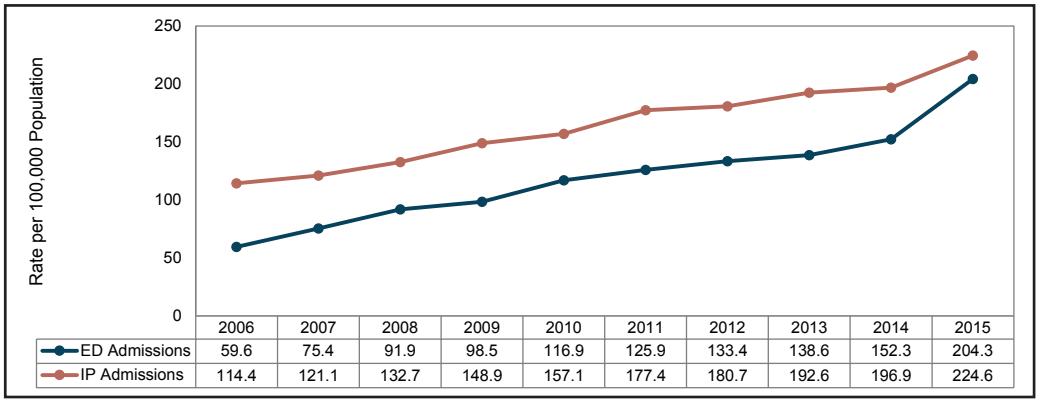
[1]Opiates/synthetics include the following drugs: buprenorphine, codeine, hydrocodone, hydromorphone, meperidine, morphine, opium, oxycodone, pentazocine, propoxyphene, tramadol, and any other drug with morphine-like effects

term medical consequences, but also death [13]. Because many people who experience an overdose and subsequently survive never seek medical attention, the actual number of nonfatal overdoses occurring annually is not known. Data from the Healthcare Cost and Utilization Project (HCUP) show that rates of both emergency department (ED) and inpatient (IP) hospitalizations involving opioid-related injuries have climbed steadily, increasing from 2006 to 2015 by 243% and 96% respectively [14], with the CDC reporting similar trends for 2016 through 2017 [15]. The Indiana State Department of Health (ISDH) indicates that the number of individuals admitted into Indiana's emergency departments specifically for opioid overdoses rose from 1,460 admissions in 2009 to 3,199 admissions in 2016, a 119% increase (see Figures 3 and 4).

Fatal Overdoses

The most extreme outcome from an overdose is death, primarily as a result of the severe respiratory depression that can be triggered by ingesting high levels of opioids [16]. The number of drug overdose deaths across the country has gone up over the past decade to the point that overdoses are now responsible for more deaths annually than automobile

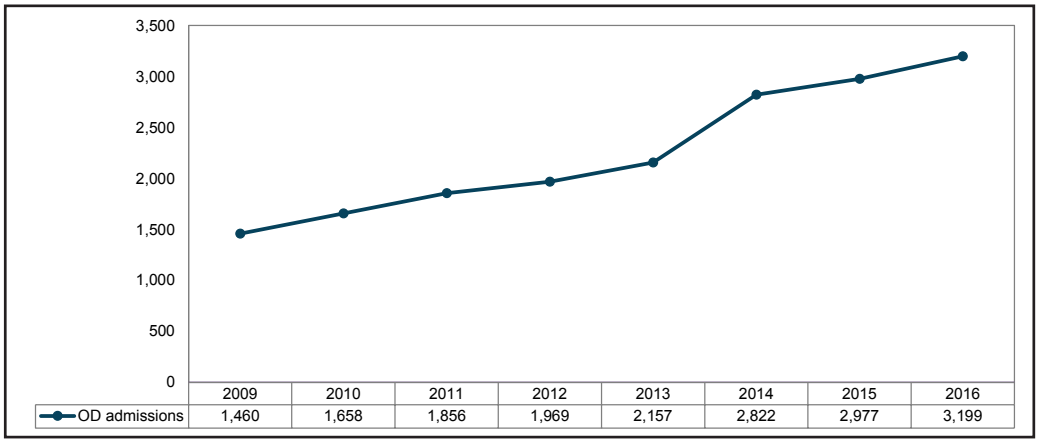
Figure 3. Rates Per 100,000 Population of Admissions to Indiana Emergency Departments (ED) and Inpatient (IP) Units for Opioid-related Injuries (AHRQ, 2006-2015)



	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
ED Admissions	59.6	75.4	91.9	98.5	116.9	125.9	133.4	138.6	152.3	204.3
IP Admissions	114.4	121.1	132.7	148.9	157.1	177.4	180.7	192.6	196.9	224.6

Source: Healthcare Cost and Utilization Project

Figure 4. Number of Admissions to Indiana Emergency Departments for Opioid Overdoses (ISDH, 2009-2016)



	2009	2010	2011	2012	2013	2014	2015	2016
OD admissions	1,460	1,658	1,856	1,969	2,157	2,822	2,977	3,199

Source: Indiana State Department of Health

accidents [1]. In 2016, a total of 63,602 U.S. citizens died from a drug-related overdose, representing a 77% increase in such deaths since 2007. Opioids are responsible for the majority of these deaths. In 2016, more than 42,000 deaths, or 66% of drug overdose deaths nationally, were due to opioids. Deaths due to heroin, synthetic narcotics (e.g., fentanyl), and other opioids (i.e., prescription opioids excluding methadone or synthetically produced narcotics) have risen annually since 2007. Until recently, prescription-type opioids were responsible for the greatest number of overdose deaths; however, by 2015, heroin accounted for more deaths than any other opioid; by 2016, synthetic narcotics accounted for more deaths than either heroin or other opioids [17] (see Figure 5).

Figure 5. Number of Overdose Deaths Attributable to Specific Opioids, U.S. 2007-2016

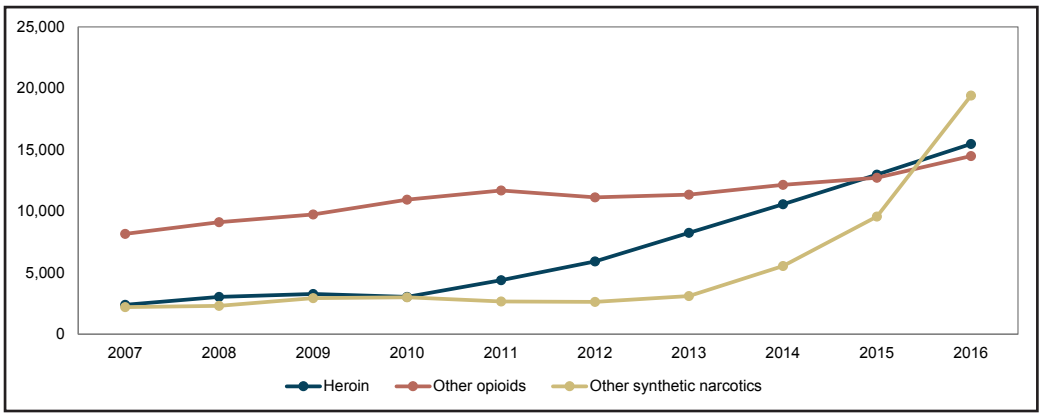
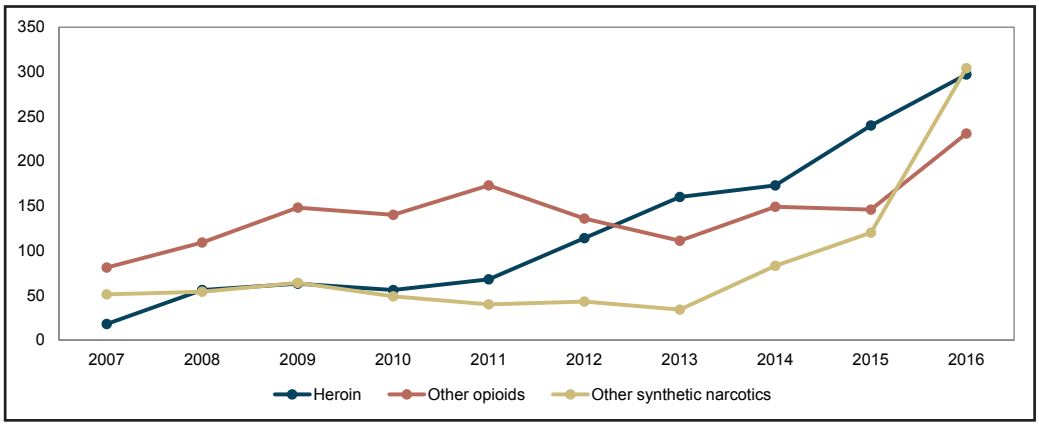


Figure 6. Number of Overdose Deaths Attributable to Specific Opioids, Indiana 2007-2016



Indiana has not been spared from the increase in overdose deaths. Comparably to what has occurred nationally, drug overdose deaths in Indiana have climbed annually from a low of 781 deaths in 2007 to a high of 1,526 deaths in 2016, a 95% increase. As is the case with the U.S., opioids are responsible for the majority of these deaths (54.5%). Prescription-type opioids were tied to more deaths than either heroin or synthetic opioids until 2013 when heroin

became responsible for more deaths. This pattern held until 2016 when more fatal overdoses were tied to synthetic narcotics than to either heroin or prescription-type opioids [17] (see Figure 6).

Demographic Composition of Fatal Opioid Overdoses in Indiana

The demographic makeup of Hoosiers who have died from any type of opioid overdose has changed little over time. Since 2007, men have accounted for a greater percentage of opioid overdose deaths than women. Opioid overdose deaths have increased sharply among both genders; between 2007 and 2016, the number of deaths rose 222% for men and 244% for women. Persons who have died from an opioid overdose were overwhelmingly white, accounting for over 90% of opioid overdose deaths during that 10-year period; though opioid overdose deaths increased for both White and Black Hoosiers. In terms of age, between 2007

Figure 7. Number of Opioid Overdose Deaths in Indiana by Gender, 2007-2016

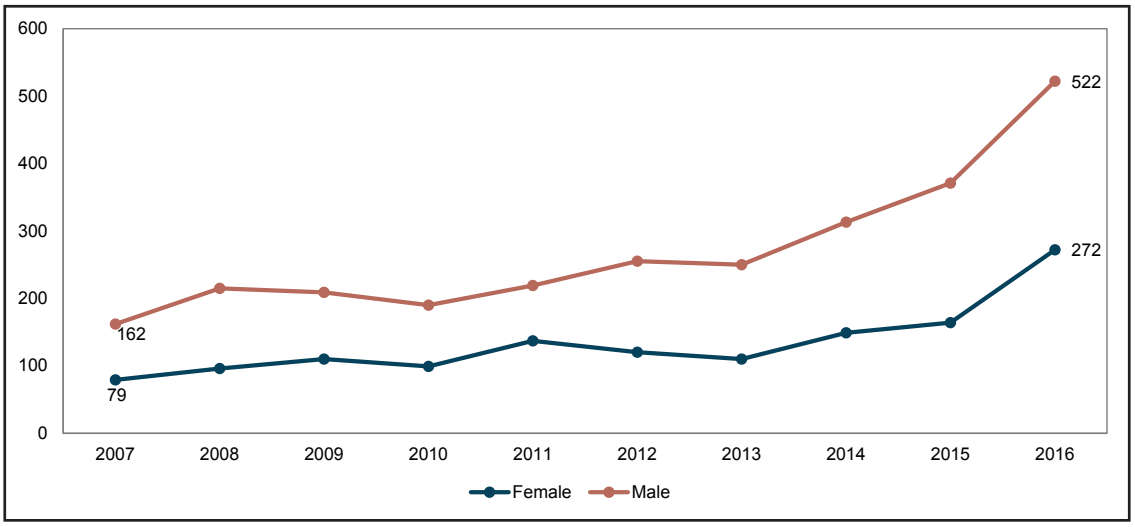


Figure 8. Number of Opioid Overdose Deaths in Indiana by Race, 2007-2016

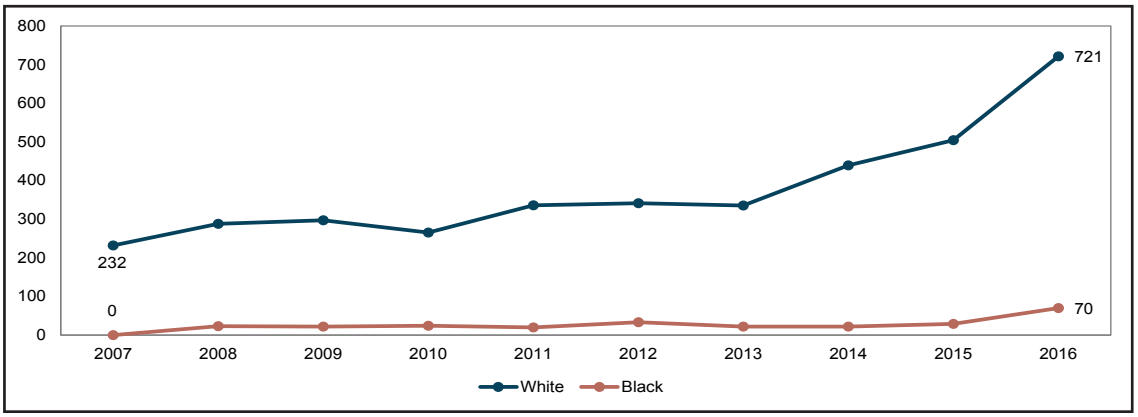
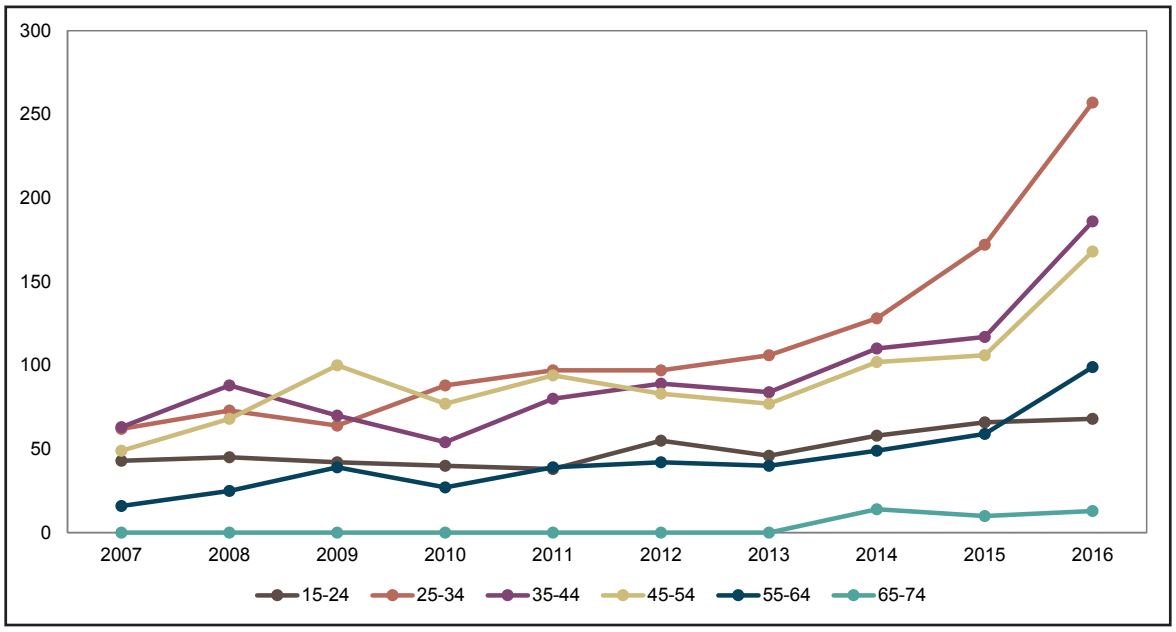


Figure 9. Number of Opioid Overdose Deaths in Indiana by Age Group, 2007-2016



and 2016, the majority of opioid overdose deaths occurred among persons between the ages of 25 to 54. Since 2010, individuals between the ages of 25 to 34 have accounted for the largest percentage of opioid overdose deaths in the state (see Figures 7-9).

We compared the demographic composition of Hoosiers who died from overdosing on heroin, prescription opioids, or synthetic narcotics in 2016. Although men accounted for the majority of deaths in each drug category, women were more strongly represented in deaths associated with prescription opioids. Whites composed the majority of overdose deaths in all opioid categories; however, the percentage of Blacks who overdosed was highest within the synthetic narcotic group. Deaths among younger individuals, those between ages 15 and 34,

Table 1. Number, Percentage, and Rate per 100,000 population of Opioid Overdose Deaths in Indiana, by Opioid Type and Demographic Characteristics, 2016

	Heroin			Other Opioids			Synthetic Narcotics		
	N	%	Rate	N	%	Rate	N	%	Rate
Gender									
Female	73	24.6	2.3	109	47.2	3.2	100	32.9	3.2
Male	224	75.4	6.9	122	52.8	3.8	204	67.1	6.6
Race									
Black	26	8.8	3.9	16	6.9	UR	40	13.2	6.0
White	270	91.2	5.1	214	92.6	3.8	263	86.5	5.0
Missing/suppressed	1	0.3	-	1	0.4	-	1	0.3	-
Age									
15-24	32	10.8	3.4	-		-	29	9.5	3.1
25-34	113	38.0	13.1	63	27.3	7.3	107	35.2	12.4
35-44	63	21.2	7.7	43	18.6	5.3	77	25.3	9.4
45-54	58	19.5	6.7	66	28.6	7.6	54	17.8	6.2
55-64	27	9.0	3.1	55	23.8	5.1	32	10.5	3.7
Missing/suppressed	4	1.3	-	4	1.7	-	5	1.6	-

Note: The CDC defines other opioids as any natural or semisynthetic opioid (e.g., morphine) and synthetic narcotics as synthetic opioids other than methadone (e.g., fentanyl).

were more prevalent among heroin and synthetic-narcotic-related overdoses, but overdose deaths linked to prescription opioids were more frequent among Hoosiers ages 45 and older (see Table 1).

RISK FACTORS FOR FATAL OPIOID OVERDOSES

General Risk Factors

The most significant risk factor for a fatal overdose, regardless of whether it was due to a prescription opioid or to an illicit opioid, is having a past history of nonfatal overdoses, with the risk rising in relation to the number of nonfatal overdoses [18-27].

A second risk factor for both fatal and nonfatal overdose is the concurrent use of opioids and benzodiazepines or other central nervous system depressants (e.g., alcohol or muscle relaxants), all of which can intensify the physiological effects of opioids [21, 23, 24, 26-35].

The risk of overdose is also increased among individuals who:

- use opioids and have chronic health conditions, especially those associated with chronic, non-cancer pain;
- are seropositive for hepatitis C (HCV) or HIV [19, 24, 29, 36];
- have a current or past history of substance use disorders, polysubstance use, or concurrent use or misuse of multiple opioids [20, 23, 26, 31, 32, 35];
- have a history of mental health problems, especially problems related to depression and/or anxiety [20, 23, 24, 27, 29, 31, 32, 35-37]; or
- have made a suicide attempt [23, 27].

Two groups who are at especially high risk for fatal and nonfatal overdoses are persons who are leaving incarceration or who have been discharged from an inpatient, abstinence-based detoxification facility. Persons in these situations are particularly vulnerable to overdose, especially within the first four weeks post-discharge, due to decreased physiological tolerance for opioids [21, 22, 34, 38, 39].

Substance-Specific Risk Factors

Some risk factors for overdose vary according to the particular opioid used. Among individuals who use prescription opioids, overdose is more likely to occur in those who receive prescriptions with higher morphine milligram equivalents (MME); the risk for overdose increases in relation to the MME prescribed [23, 28, 30-32]. Persons who receive prescriptions for multiple types of opioids [24, 32], who receive opioids from a physician with liberal opioid prescribing practices [40], and who receive opioid prescriptions from multiple prescribers (engaging in doctor-shopping) or fill opioid prescriptions at multiple pharmacies (engaging in pharmacy-shopping) are also at greater risk for experiencing an overdose. Demographically, persons who suffer fatal overdoses due to prescription opioids are typically male, 50 years of age or older, and White.

For persons who use heroin or other opiates, overdose risk is particularly high among those who engage in injection use. Large quantities of a drug can be administered in this fashion, and the physiological effects of the drug occur almost immediately [18-21, 24, 37]. Other factors associated with fatal and nonfatal heroin overdoses are injecting drugs alone, having disrupted life circumstances (e.g., homelessness, unemployment), experiencing conflicts in one's social network, and knowing someone or witnessing someone who has overdosed [20, 41]. Demographically, individuals who die from a heroin overdose are most often male, White, and between the ages of 25 to 34 [24, 27, 31, 41].

METHODS TO REDUCE FATAL OPIOID OVERDOSES

Reducing the prevalence of fatal opioid overdoses requires a multi-pronged approach to:

(1) Prevent or reduce exposure to opioids
(2) Reduce the risk of overdose among those who may be abusing opioids, through identification and provision of treatment, and
(3) Increase the chances of survival among those individuals who do experience an overdose.

The following strategies can assist in meeting the above mentioned goals.

Prescribing Guidelines

In 2016, the CDC released a set of prescribing guidelines to help medical providers understand the proper use of opioid medication [42]. When followed, the CDC's prescribing guidelines can serve as an overdose prevention tool by reducing the number of individuals who are exposed to opioid medication and, over time, decreasing the number of individuals who could potentially be at risk for overdose. For persons who are already taking opioids, the prescribing guidelines can lessen their risk of overdose by encouraging providers to use the lowest dose of opioids possible for symptom relief, to use safer opioid formulations, to limit the number of pills prescribed, to refrain from prescribing opioids and benzodiazepines together, and to regularly monitor patients on opioid medication for signs of abuse and arrange treatment if necessary [42]. With proper oversight, prescribing guidelines can bring about positive changes in opioid prescribing behaviors [43-46]. In at least one state, the guidelines helped reduce fatal overdoses [47].

Opioid Prescribing Laws

Prescription drug overdoses are generally driven by a small number of medical providers who prescribe and/or dispense a high volume of opioids inappropriately or for nonmedical reasons (i.e., "pill mills") [48]. Many states have enacted pain clinic laws as a way to control this type of improper prescribing. Implementation of such laws in Texas was associated with a decrease in the overall volume, strength, and monthly quantity of opioids dispensed [49] and in Florida with a significant drop in fatal opioid overdoses [50].

Prescription Drug Monitoring Programs

Prescription drug monitoring programs (PDMP) are another tool that can help reduce fatal overdoses. PDMPs are databases that collect information on dispensations of controlled substance medication, including opioids. The information gathered typically includes the name of the prescriber, details of the medication prescribed, the name, gender, and driver's license number of the person who filled the prescription; and the name and address of the pharmacy where the prescription was filled [51]. It is thought that PDMPs can be helpful in reducing overdose deaths by allowing prescribers and pharmacists to identify patients who may be at risk for overdose such as those who appear to be engaging in doctor or pharmacy shopping, who may be taking excessively large doses of opioids, or who may have been prescribed opioids and benzodiazepines. In instances where a risk is noted, a physician or pharmacist can then do further assessment to determine if the individual may need a referral to substance abuse treatment or a change to her or his medication regimen. From a regulatory perspective, PDMPs can be

> For persons who use heroin or other opiates, overdose risk is particularly high among those who engage in injection use.

used to monitor prescribing activity and alert law enforcement or professional oversight committees to physicians whose prescribing behaviors appear to consistently run counter to accepted guidelines or may indicate the operation of a "pill mill". At this time, the impact PDMPs have on reducing overdose deaths is unclear [52-55].

Medication Assisted Treatment

For individuals who have an opioid use disorder, medication assisted treatment (MAT) can be helpful in reducing the risk for fatal overdose [56]. Medication assisted treatment (MAT) uses FDA-approved medications to help individuals with opioid use disorders stop using opioids. The three drugs used for MAT are methadone, buprenorphine (Suboxone®), and naltrexone (Vivitrol®). Depending on the medication used, MAT works by reducing withdrawal symptoms and/or the euphoric effects associated with opioids, subsequently decreasing the need or desire to take opioid drugs and lowering the risk for overdose. Expanding the availability of MAT has been shown to reduce the rate of fatal overdoses at the community level. Similarly, providing MAT to persons in correctional facilities and to newly released persons can lessen the likelihood of overdose among this high-risk population [57-59].

Naloxone Distribution

For persons who are experiencing an overdose, administration of naloxone can reduce the likelihood that the overdose will be fatal. Naloxone (e.g., Narcan®) is an FDA-approved drug that can reverse the physiological effects of an opioid overdose by displacing opioids from the brain receptors to which they bind and restoring normal breathing. Naloxone has no abuse potential as it has neither euphoric nor analgesic properties [60]. Naloxone can be administered through intravenous or intramuscular injection or through an intranasal atomizer. Naloxone has been widely used in emergency departments for reversing opioid overdoses since 1971. With the increase of fatal opioid overdoses nationally, most states have developed programming to provide naloxone to first responders (e.g., EMTs, police) so that they can administer care more quickly. More recently, community organizations throughout the country have worked to make naloxone available to lay people and especially to people who use either prescription or illicit opioids and their family and friends, as these are the individuals most likely to be present in the event of overdose. Naloxone is typically distributed to these individuals through opioid overdose and naloxone distribution programs (OOND). Persons who receive naloxone through these programs are trained how to identify an overdose, how to properly administer naloxone, and what they should do post-administration. Evaluation of OOND programs indicates that they are effective in training individuals on when and how to properly use naloxone that people trained to use naloxone will use it, that in communities with widespread implementation, rates of overdose decrease, and that OONDs are cost-effective [58, 61-67]. The CDC reports that as of the end of 2014, over 150,000 laypeople had received naloxone kits and training in how to use them, with over 26,000 overdose reversals reported [68].

CONCLUSION

Neither Indiana's nor the nation's epidemic of death from opioid overdoses can be easily solved. Reduction in deaths can only be realized when policymakers, prescribers, pharmacists, mental health professionals, persons in recovery, and the public at large begin to work together to address the overall opioid epidemic through controlling access to both legal and illegal opioids; identifying and providing easily accessible, effective, and affordable treatment to persons who need it; and encouraging persons who have friends or loved ones who are using opioids to seek out naloxone and become familiar with how and when to use it.

Ultimately, all these groups need to work in tandem to address the social factors that lead to and often encourage all forms of substance use.

References

1. Rudd, R.A., Increases in drug and opioid-involved overdose deaths -- United States, 2010-2015. Morbidity and Mortality Weekly Reports, 2016. 65((50-51): p. 1445-1452.
2. O'Donnell, J.K., et al., Deaths involving fentanyl, fentanyl analogs, and U-47700 -- 10 states, July-December 2016. Morbidity and Mortality Weekly Reports, 2017. 66(43): p. 1197-1202.
3. Macmadu, A., et al., Prevalence and correlates of fentanyl-contaminated heroin exposure among young adults who use prescription opioids non-medically. Addictive Behaviors, 2017. 68: p. 35-38.
4. Council of Economic Advisers. Council of economic advisers' report: The underestimated cost of the opioid crisis. 2017; Available from: https://www.whitehouse.gov/briefings-statements/cea-report-underestimated-cost-opioid-crisis/.
5. Calcaterra, S., J. Glanz, and I.A. Binswanger, National trends in pharmaceutical opioid related overdose deaths compared to other substance related overdose deaths: 1999-2009. Drug & Alcohol Dependence, 2013. 131(3): p. 263-270.
6. Centers for Disease Control and Prevention. Opioid basics - understanding the epidemic. 2017; Available from: https://www.cdc.gov/drugoverdose/opioids.
7. Evans, W.N., E. Lieber, and P. Power, How the reformulation of OxyContin ignited the heroin epidemic. 2017, University of Notre Dame: Notre Dame, IN.
8. Carlson, R.G., et al., Predictors of transition to heroin use among initially non-opioid dependent illicit pharmaceutical opioid users: A natural history study. Drug and Alcohol Dependence, 2016. 160: p. 127-134.
9. Kertesz, S.G., Turning the tide or riptide? The changing opioid epidemic. Substance Abuse 2017. 38(1): p. 3-8.
10. Somerville, N.J., et al., Characteristics of fentanyl overdose -- Massachusetts, 2014-2016. Morbidity and Mortality Weekly Reports, 2017. 65(50-51): p. 1445-1452.
11. Substance Abuse and Mental Health Services Administration and Center for Behavioral health Statistics and Quality. National Survey on Drug Use and Health (NSDUH). 2017; Available from: https://www.samhsa.gov/

data/population-data-nsduh.
12. Substance Abuse and Mental Health Services Administration and Center for Behavioral Health Statistics and Quality, Treatment Episode Data Set- Admissions (TEDS-A). 2015.
13. U. S. Library of Medicine. Heroin overdose. 2015 1/5/2018; Available from: https://medlineplus.gov/ency/article/002861.htm.
14. Weiss, A.J., et al., Opioid-related inpatient stays and emergency department visits by state, 2009-2014. 2017, Agency for Healthcare Research and Quality: Rockville, MD.
15. Vivolo-Kantor, A.M., et al., Vital signs: Trends in emergency department visits for suspected opioid overdoses--United States, July 2016-September 2017. Morbidity and Mortality Weekly Reports, 2018. 67(9): p. 279-285.
16. White, J.M. and R.J. Irvine, Mechanisms of fatal opioid overdose. Addiction, 1999. 94(7): p. 961-972.
17. Centers for Disease Control and Prevention, Wide-ranging Online Data for Epidemiologic Research (WONDER) Multiple Cause of Death. 2018, Centers for Disease Control and Prevention (CDC): Atlanta, GA.
18. Britton, P.C., J. Wines, James D., and K.R. Conner, Non-fatal overdose in the 12 months following treatment for substance use disorders. Drug & Alcohol Dependence, 2010. 107(1): p. 51-59.
19. Caudarella, A., et al., Nonfatal overdose as a risk factor for subsequent fatal overdose among people who inject drugs. Drug & Alcohol Dependence, 2016. 162(51-55).
20. Coffin, P.O., et al., Identifying injection drug users at risk of nonfatal overdose. Academic Emergency Medicine, 2007. 14(7): p. 616-623.
21. Darke, S., Opioid overdose and the power of old myths: What we thought we knew, what we do know and why it matters, in Drug & Alcohol Review. 2014, Wiley-Blackwell. p. 109-114.
22. Dietze, P., et al., When is a little knowledge dangerous?: Circumstances of recent heroin overdose and links to knowledge of overdose risk factors. Drug & Alcohol Dependence, 2006. 84(3): p. 223-230.
23. Elzey, M.J., S.M. Barden, and E.S. Edwards, Patient Characteristics and Outcomes in Unintentional, Non-fatal Prescription Opioid Overdoses: A Systematic Review. Pain Physician, 2016. 19(4): p. 215-228.
24. Paulozzi, L.J., Prescription drug overdoses: A review. Journal of Safety Research, 2012. 43: p. 283-289.
25. Stoove, M.A., P. Dietze, and D. Jolley, Overdose deaths following previous non-fatal heroin overdose: Record linkage of ambulance attendance and death registry data. Drug & Alcohol Dependence, 2009. 28: p. 347-352.
26. Turner, B. and Y. Liang, Drug Overdose in a Retrospective Cohort with Non-Cancer Pain Treated with Opioids, Antidepressants, and/or Sedative-Hypnotics: Interactions with Mental Health Disorders. JGIM: Journal of General Internal Medicine, 2015. 30(8): p. 1081-1096.
27. Wines, J.D., et al., Overdose after detoxification: A prospective study. Drug & Alcohol Dependence, 2007. 89(2/3): p. 161-169.
28. Cochran, G., et al., An Examination of Claims-based Predictors of Overdose from a Large Medicaid Program. Medical Care, 2017. 55(3): p. 291-298.
29. Contreras, G.W., T.L. Bellomo, and L. Cichminski, Epidemic! Opioid overdose in America. Nursing Made Incredibly Easy, 2017. 15(2): p. 27-31.
30. Dasgupta, N., et al., Cohort study of the impact of high-dose opioid analgesics on overdose mortality. Pain Medicine, 2016. 17: p. 85-98.
31. Dilokthornsakul, P., et al., Risk Factors of Prescription Opioid Overdose Among Colorado Medicaid Beneficiaries. Journal of Pain, 2016. 17(4): p. 436-443.
32. Park, T.W., et al., Understanding Risk Factors for Opioid Overdose in Clinical Populations to Inform Treatment and Policy. Journal of Addiction Medicine, 2016. 10(6): p. 369-381.
33. Riley, E.D., et al., A longitudinal study of multiple drug use and overdose among young people who inject drugs. American Journal of Public Health, 2016. 106(5): p. 915-917.
34. Lake, S., et al., The effect of prescription opioid injection on the risk of non-fatal overdose among people who inject drugs. Drug & Alcohol Dependence, 2015. 156: p. 297-303.

35. Liang, Y., Models for women and men among opioid users with non-cancer pain. Pain Medicine. 17: p. 2268-2279.
36. Kelty, E. and G. Hulse, Fatal and non-fatal opioid overdose in opioid dependent patients treated with methadone, buprenorphine or implant naltrexone. International Journal of Drug Policy, 2017. 46: p. 54-60.
37. Binswanger, I.A., et al., Clinical risk factors for death after release from prison in Washington State: a nested case-control study. Addiction, 2016. 111(3): p. 499-510.
38. Binswanger, I.A., et al., Mortality after prison release: Opioid overdose and other causes of death, risk factors, and time trends from 1999 to 2009. Annals of Internal Medicine, 2013. 159(592-600).
39. Merrall, E.L.C., et al., Meta-analysis of drug-related deaths soon after release from prison. Addiction, 2010. 150: p. 1545-1554.
40. Dhalla, I.A., et al., Clustering of opioid prescribing and opioid-related mortality among family physicians in Ontario. Canadian Family Physician, 2011. 57: p. e92-e96.
41. Sherman, S.G., Y. Cheng, and A.H. Kral, Prevalence and correlates of opiate overdose among young injection drug users in a large U.S. city. Drug & Alcohol Dependence, 2007. 88(2-3): p. 182-187.
42. Centers for Disease Control and Prevention, Guideline for prescribing opioids for chronic pain. Morbidity and Mortality Weekly Reports, 2016. 65(1): p. 1-49.
43. Hill, M.V., et al., An educational intervention decreases opioid prescribing after general surgical operations. Annals of Surgery, 2018. 267(3): p. 468-472.
44. Howard, R., et al., Reduction in opioid prescribing through evidence-based prescribing guidelines. JAMA Surgery, 2018. 153(3): p. 285-286.
45. Osborn, S.R., et al., Changes in provider prescribing patterns after implementation of an emergency department prescription opioid policy. Pharmacology in Emergency Medicine, 2016. 52(4): p. 538-546.
46. Weiner, S.G., et al., The effect of opioid prescribing guidelines on prescriptions by emergency physicians in Ohio. Annals of Emergency Medicine, 207. 70(6): p. 789-808.
47. Cochella, S. and K. Bateman, Provider detailing: an intervention to decrease prescription opioid deaths in Utah. Pain Medicine, 2011. 12: p. S73-S76.
48. Malbran, P. What's a pill mill? 2007; Available from: http://www.cbsnews.com/news/whats-a-pill-mill.
49. Lyapustina, T., et al., Effect of a "pill mill" law on opioid prescribing and utilization: The case of Texas. Drug & Alcohol Dependence, 2016. 159: p. 190-197.
50. Kennedy-Hendricks, A., et al., Opioid overdose deaths and Florida's crackdown on pill mills. American Journal of Public Health, 2016. 106(2): p. 291-297.
51. Prescription Drug Monitoring Program Center for Excellence, Technical assistance guide: History of prescription drug monitoring programs, H.S.f.S.P.a. Management, Editor. 2018, Brandeis University.
52. Dowell, D., et al., Mandatory provider review and pain clinic laws reduce the amounts of opioids prescribed and overdose death rates. Health Affairs, 2016. 35(10): p. 1876-1883.
53. Li, G., et al., Prescription drug monitoring and drug overdose mortality. Injury Epidemiology, 2014. 1(9).
54. Nam, Y.H., et al., State prescription drug monitoring programs and fatal drug overdoses. American Journal of Managed Care, 2017. 23(5).
55. Patrick, S.W., et al., Implementation of prescription drug monitoring programs associated with reductions in opioid-related death rates. Health Affairs, 2016. 35(7): p. 1324-1352.
56. Volkow, N.D., et al., Medication-assisted therapies--tackling the opioid-overdose epidemic. New England Journal of Medicine, 2014. 370(22): p. 2063-2066.
57. Green, T.C., et al., Postincarceration fatal overdoses after implementing medications for addiction treatment in a statewide correctional system. JAMA Psychiatry, 2018.
58. Schwartz, R.P., et al., Opioid agonist treatments and heroin overdose deaths in Baltimore, Maryland, 1995-2009. American Journal of Public Health, 2013. 103(5): p. 917-922.
59. Lee, J.D., et al., Extended-release naltrexone to prevent opioid relapse in criminal justice offenders. New En-

gland Journal of Medicine, 2016. 374: p. 1232-1242.
60. Chamberlin, J.M. and B.L. Klein, A comprehensive review of naloxone for the emergency physician. American Journal of Emergency Medicine, 1994. 12: p. 650-660.
61. Bird, S.M., et al., Effectiveness of Scotland's national nalxone programme for reducing opioid-related deaths: a before (2006-10) versus after (2011-13) comparison. Addiction, 2015. 111: p. 883-891.
62. Clark, A.K., C.M. Wilder, and E.L. Winstanley, A systematic review of community opioid overdose prevention and naloxone distribution programs. Journal of Addiction Medicine, 2014. 8(3): p. 153-163.
63. Coffin, P.O., et al., Nonrandomized intervention study of naloxone coprescription for primary care patients receiving long-term opioid therapy for pain. Annals of Internal Medicine, 2016. 165(4): p. 245-252.
64. Enteen, L., et al., Overdose prevention and naloxone prescription for opioid users in San Francisco. Journal of Urban Health, 2010. 87(6): p. 931-941.
65. Giglio, R.E., G. Li, and C.J. DiMaggio, Effectiveness of bystander naloxone administration and overdose education programs: a meta-analysis. Injury Epidemiology, 2015. 2(10).
66. Kerensky, T. and A.Y. Walley, Opioid overdose prevention and naloxone rescue kits: What we know and what we don't know. Addiction Science and Clinical Practice, 2017. 12(4).
67. Walley, A.Y., et al., Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. British Medical Journal, 2013. 346(f174).
68. Wheeler, E., et al., Opioid overdose prevention programs providing naloxone to laypersons. Morbidity and Mortality Weekly Reports, 2015. 64: p. 631-635.

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